



**Rethinking the Practice of Community Engagement
in Health Research:
The Case of the Tenofovir Trials in Cambodia and Cameroon**

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Research project submitted in partial fulfilment of the requirements for the Master of Social Science (Health Research Ethics) in the School of Applied Human Sciences (Psychology) at the University of KwaZulu-Natal, Pietermaritzburg, South Africa.

March 2020

DECLARATION

I, Apungwa Cornelius Ntabe, declare that the thesis titled “Rethinking the Practice of Community Engagement in Health Research: The Case of the Tenofovir Trials in Cambodia and Cameroon”, which I hereby submit for the degree of Master of Social Sciences at the University of KwaZulu-Natal, Pietermaritzburg, is my original research aside from where otherwise indicated. I also declare that

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Apungwa Cornelius Ntabe

ACKNOWLEDGEMENTS

Supervisors

I am extremely grateful and indebted to my academic supervisor Dr. Heidi Matisonn for the excellent advice, support, mentorship and guidance and for her critical review of the project. I am most grateful for your great interest in my project, willingness to meet with me regularly and your constructive feedbacks. It was a great privilege to work under your leadership and I look forward to future collaborations.

I equally express my profound and sincere indebtedness and gratitude to Prof. Douglas Wassenaar who worked behind the scenes, providing oversight responsibility, thorough and critical review, comments and very useful suggestions on the three drafts of this thesis and ensuring that the conduct of research was carried out in accordance with the approved ethical clearance. His contribution significantly helped shaped this thesis.

Funding and academic support

My acknowledgements will be incomplete without mentioning that the research in this report was supported by the Fogarty International Centre of the National Institutes of Health (NIH) under award number 4R25 TW001599-14 to the South African Research Training Initiative (SARETI). The content of this thesis represents solely the opinion of the author and not necessarily that of the National Institutes of Health.

My sincere appreciation equally goes towards the SARETI staff and scholars of 2017 for their constant push on me and making me to believe in my abilities. I will forever remember this, for without you all, this would not have been feasible! I will miss you all and I wish you all the best of luck in all of your future endeavours. In addition, special gratitude goes to Mrs. Carla Pettit, Mrs. Nivedhna Singh and to Prof. Carel IJsselmuiden for their endless counselling and mentorship they provided to me during my stay in South Africa. My sincere thanks also goes to the Discipline of Psychology at UKZN (Pietermaritzburg), for granting me this exceptional platform to advance my career and education.

Friends and family

To my dear family and parents, for your love which conquers all especially to my late father, Mr. Apungwa Solomon Abie (Sunrise: 1952 and Sunset: 2018). May your soul rest in perfect peace. I will forever remember your parenting throughout my life. You were a great inspiration to me and hope to move to greater heights through this inspiration!

My sincere thanks equally goes to Dr. Leo Njock Ayuk for mentoring me through my career in health research and for assisting me successfully to pursue my studies in South Africa

right to the end. Ajeh Rogers, thank you for your encouragement and for helping me to find this opportunity and for helping me to carry out this research successfully to the end.

My dear Nsobahti Cameroon family at UKZN, thank you for our intellectually stimulating discussions and all the moral supports you provided me throughout this journey. I am very grateful to you all, for hosting me and bringing home very close to me and for the love you have extended to my entire family over the years.

My sincere thanks to the Cameroon Bioethics Initiative (CAMBIN) especially Prof. Godfrey Tangwa and Dr. Primus Chi Che for providing me this forum to widen my knowledge and understanding in completing this thesis and providing guidance and insightful comments throughout the completion of this thesis.

To all those whose names I cannot mention here individually, who all worked to facilitate my stay in South Africa, and SARETI in particular, and accompanied me throughout the period of my studies and research, accept all my total and infinite gratitude.

ABSTRACT

Recent developments in the governance of research have recognised the part that communities can and should play in emergent and inventive research. It is now widely agreed that community engagement is essential in certain kinds of research – indeed, an ethical prerequisite – and that it is indispensable to the success of many health research projects. Unfortunately, as an ethical requirement, community engagement has sometimes been seen as a hurdle to jump over rather than as an integral part of the research process. At times, inadequate attention has been paid to how and when community engagement should be implemented and on the need to engage the community meaningfully and genuinely throughout the research process. This is concerning given that researchers and sponsors invest large sums of money in the development of a product, training on clinical procedures, facility designing and building, etc., and yet seem to have repeatedly ignored the importance of meaningful community engagement processes, often at great cost.

The aim of this study was to demonstrate, using the tenofovir trials that were stopped in both Cameroon and Cambodia in 2005, that inadequate community engagement might lead to significant scientific losses, whereas early, sustained and meaningful community engagement could prevent this from occurring. The study involved no human participants and used a case study design approach that was based on the secondary data analysis. The cases (Cameroon and Cambodia) for the study were chosen for a number of reasons, but perhaps most significant of these was that the Good Participatory Practice (GPP/AVAC) guidelines which set standard practices for stakeholder's engagement in HIV vaccine trials, were established in response to the premature ending of the tenofovir trials in these two countries.

Several lessons were learned from this study: one of the major ones was that it is not sufficient for researchers to maintain high ethical and scientific standards in a study; in many cases, it is equally important and necessary for them to work very closely with the communities through various flexible mechanisms. Examples of such mechanisms include the community advisory boards (CABs), as well as the local ethical review boards (ERBs). In cases where community engagement is relevant, participation should commence from the very start of the protocol development. Participation should focus on the methodology, participant selection, the procedures for the study results disseminations at different points of the research and finally on enhancing informed participation. Any consultation with the community after the protocol is developed may be regarded as cosmetic rather than as genuine community engagement.

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LIST OF ACRONYMS

AIDs	Acquired immunodeficiency syndrome
ACT UP	AIDS Coalition to Unleash Power
ARV	Antiretroviral
CAB	Community advisory boards
CAG	Community advisory groups
CE	Community engagement
CDC	Centers for Disease Control and Prevention
CIOMS	Council for International Organization of Medical Sciences
CRS	Chemokine receptor status
CXCR4	Chemokine receptor type 4
DNA	Deoxyribonucleic acid
FDA	Food and Drug Administration
HAART	Highly active antiretroviral therapy
HIV	Human immunodeficiency viruses
HPTN	HIV Prevention Trials Network
ICH	International Council for Harmonisation
IRB	Institutional review board (often also referred to as REC outside of the US)
NCB	Nuffield Council on Bioethics
NCHADS	National Centre for HIV/AIDS, Dermatology and STDs
NIH	National Institutes of Health
NRTIs	Nucleotide/Nucleoside Reverse Transcriptase Inhibitors
OHRP	Office of Human Research Protections
PrEP	Pre-exposure prophylaxis
REDS	Réseau Éthique Droit et Santé
SA	South Africa
SARETI SIV	South African Research Ethics Training Initiative Simian immunodeficiency virus
TFV	Tenofovir
UK	United Kingdom
UKZN	University of KwaZulu-Natal
US	United States of America

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CHAPTER ONE

INTRODUCTION

1.1 Background to the study

Globally, there are wide disparities in economic development in terms of the burden of diseases and health outcomes (Evans, 2001), and there is a high probability that, without the necessary precautions and human rights protections, the continuously accelerating trends towards globalisation will only make these health inequalities worse. Health can be regarded as wealth and thus the bedrock and foundation of development: “Good health is a cornerstone of economic progress ... and indeed the primary objective of development” (Chen & Berlinguer, 2001).

In order to improve and develop health care in terms of health care delivery, services, programmes, treatments and techniques, research is very important. In the absence of research, we will not progress and we will have no empirically tested body of knowledge underpinning our service, practices or commissioning. In other words, in the absence of research, we would neither move forward nor would we be able to evaluate the efficiency and effectiveness of what we do now since only research can tell us that.

Health research is well known to be the main route in establishing the causes of sickness and discovering new approaches in treating and alleviating pain or illnesses. It generates a wealth of data that leads to the enhancement of the quality of human life. Many diseases, known to have caused high mortality and morbidity rates in the world in the past (e.g. diarrhoea, measles, tuberculosis, HIV/AIDS, etc.), have now been contained through different preventive, diagnostic, treatment, and public health policies and methods which have been developed through health research.

Because of research, many health professionals can now enjoy the excitement and challenge of a variety of research-related careers. However, it is important not to overlook the relevance and role of research participants in this research success. Contributions from research participants include offering their time voluntarily, often without any gains to themselves, and often under the most trying of personal circumstances; for these, and other reasons, appropriate respect for and protection of their interests are essential.

While research is important for the improvement and development of effective health care services, it may also involve an element of risk since it often necessitates trying something new. It is imperative that any risks involved in the research be minimised and that the dignity,

rights, safety and well-being of those consenting to take part in the research are not compromised (Department of Health (UK), 2011). The respect for ethical research practices is central to attaining this objective.

Violations of the rights of participants in health research aimed at advancing medical knowledge have occurred in the past, leading to the creation of guidelines to avoid re-occurrence. The abominable acts carried out by the Nazi research physicians that were exposed at the Nuremberg trials after World War II, resulted in the creation of the Nuremberg Code for regulating experimentation on human subjects (Nuremberg Code, 1949). Similarly, the Tuskegee Syphilis study (1932-1972) led to the publication of the Belmont Report (1978). Three principles that came out of this publication were 'respect for persons', 'beneficence' and 'justice'. These principles dominated research ethics for the latter part of the twentieth century.

More recent developments in the governance of research have recognised the part that communities can and ought to play in emergent and inventive research studies. The Council for International Organizations of Medical Science (CIOMS), the Declaration of Helsinki, the UK Nuffield Council on Bioethics, the US National Bioethics Advisory Commission and the National Institute of Allergy and Infectious Diseases, as well as other research institutions such as the National Institutes of Health and the Centers for Disease Control and Prevention, have all recognised the importance of increased involvement from the community in the research process. In 2004, Emanuel and colleagues (Emanuel, Wendler, Killen, & Grady, 2004) recommended eight ethical principles with accompanying benchmarks for the conduct of research, among which was collaborative partnerships/community engagement.

A key consideration in ethical research is in the recognition that research is done *with* people and not *to* them (Emanuel, Wendler, & Grady, 2000). When researchers collaborate with participants in research, it helps to guard against exploitation, as participants help design fair and just study practices. In addition, such collaboration helps in ensuring that the proposed research meets the community's needs and expectations (Emanuel, 2011).

The concept of community engagement (CE) originates from the works of Paulo Freire who argued for the encouragement of education of communities so that they might be empowered to act as agents of change (Freire, 1994). CE can lead to a population that is more informed, since engagement with the community will necessitate discussions and explanations of the research. These meetings for discussions serve as a great opportunity for potential participants to be informed and educated about the research. They also help to provide a platform to raise pertinent questions or concerns that participants might have about the research.

In medical research, CE came to the fore with the initiation of HIV research, and this was principally in the 1980s during the activism about access to HIV treatment. The relevance of CE was unambiguously noticeable during the tenofovir trials, which failed because of inadequate CE. These trials tested for the safety and efficacy of oral pre-exposure prophylaxis for the prevention of HIV transmission (Staunton & Moodley, 2016).

CE has been practiced in a variety of health-related research studies such as in the Navrongo Community Health and Family Project (CHFP) in Kassena-Nankana, Ghana (Binka, Nazzar, & Phillips, 1995), the Majengo Observational Cohort Study (MOCS) studying disadvantaged female sex workers in Nairobi, Kenya (Bandewar, Kimani, & Lavery, 2010), an epidemiological investigation of some 7-12 year olds in South Korea, and an Autism Spectrum Disorder (ASD) detection programme for 18-36-month-old Zulu-speaking children in South Africa (Grinker et al., 2012).

It is now widely agreed that CE is an ethical requirement for some research and that it is indispensable to the success of a health research project; as a result of this, CE as a theme has been welcomed by researchers, sponsors and pharmaceutical industries. Regrettably, CE as an ethical requirement has at times been considered by researchers as an ethical procedure to be respected and followed (thus as a hedge), instead of as an integrated element of the research process. Due to this, insufficient consideration has been given to how and when CE should be undertaken and on the need for meaningful and genuine CE throughout the research process. This has led to CE being regarded as ‘pulling wool over the eyes’, something to be ticked off a list with the intention of gaining an advantage, when, in reality, it is not being taken too seriously.

This is of great concern, since researchers and sponsors invest huge sums of money in product development, training on clinical procedures, facility designing and building, etc., and hitherto continuously neglect the relevance of meaningful CE processes. CE can help avoid or reduce conflicts and problems that might lead to the premature ending of research. There is no gain to any stakeholder in research when a trial is halted or closed for reasons which are non-scientifically related. As demonstrated by the tenofovir trials, the failure to engage with the community adequately can come at substantial scientific cost.

Several projects implementing CE continues to fail thus leaving one with the impression that, CE has not being very effective whereas it could be the absent of a meaningful and genuine CE at fault. The recently early closed down Ebola vaccine trial in Cameroon in 2016 (Quinn, 2004b) was a quick reminder to the researcher about what happened in the Tenofovir trial in 2005 which had some of the major stakeholders in health research engaged but still had the

study closed down. Despite engaging with different stakeholders like the Ministry of Public Health, the different Regional Public Health Delegations and the health practitioners in the different regions, the Ebola study still experience an early shutdown just like the Tenofovir study. So looking at this situation and several more, the researcher thought that there was need to rethink the current practices of CE in a way to avoid several other studies from shutting down probably as a result of glitches that could otherwise occur as a result of the absence of meaningful and genuine CE.

It is the researcher's hope that meaningful CE rather than just 'mechanical' CE will be embraced by researchers as one possible avenue to increase trial successes.

1.2 Structure of the dissertation

This dissertation is structured into six chapters. The first chapter is the introduction, which presents the historical evolution of the concept of health research ethics and community engagement. The second chapter presents the different literature reviews that were relevant to the subject matter. The third chapter deals with the methodology of the study. The fourth chapter presents the case studies. The fifth chapter discusses the findings, while the last chapter addresses the possible measures that could be used to resolve some of the concerns and problems regarding inadequate CE raised during the tenofovir trials in Cameroon and Cambodia.

CHAPTER TWO

LITERATURE REVIEW

2.1 What is research ethics?

Research ethics refers to the moral principles that inform and guide research practices. These have a specific focus on ethical issues that may be encountered when enrolling humans in a study as research participants. Several research ethics codes do exist, and most are largely concentrated on the following key principles: participant protection, conducting research of a high standard, planning and executing research with ethical honesty and trustworthiness, such as the informed consent process, protection of confidentiality and risk management, and guaranteeing transparency of the entire process of the research.

When people think of the word ‘ethics’, they tend to think of a set of rules that distinguish between wrong and right. Example of such rules include the Golden Rule (“Do unto others as you would have them do unto you”) (Etzioni, 1996); codes of professional conduct like the Hippocratic Oath (“First of all, do no harm”) (Jonsen, 1978); the religious creeds like the Ten Commandments (“Thou shalt not kill.”); or a wise adage like the wise words of Confucius.

For this thesis, ethics is understood as the science of principles, standards and tenets for human action and conduct that seek to address philosophical questions about morality. Ethics is involved in reflections and analyses of morals regarding whether an act is bad or good and how it influences our fundamental quest for meaning. It also involves our pursuit for the well-being of humankind and our effort to construct a humane society, having as goal the safeguarding of human dignity and the promotion of truth, equality, trust and justice. In essence, ethics entails a critical reflection on morality (Benatar et al., 2007).

2.2 Community engagement

2.2.1 Why is community engagement important?

The term ‘community’ can refer to a group of persons living in the same local geographical location or having some other non-spatial common social identity. This social identity may include a similar trade or group membership. For this study, the term ‘community’ will be understood as group of persons with a mutual social identity, as defined by Kathleen MacQueen (MacQueen, Bhan, Frohlich, Holzer, & Sugarman, 2015). The term ‘engagement’ will indicate some form of relationship between a community and the research body.

The idea of community engagement (CE) as an ethical requirement for research that involves human participants, mainly marginalised populations, has made its way into many (international) guidelines on research ethics. Several reasons account for this valuing of CE in health research, as can be found below.

Firstly, CE can improve the impact, quality and significance of a research study (Cargo & Mercer, 2008; Israel, Schulz, Parker, & Becker, 1998a), and cooperation with community members and their representatives has given researchers, often from diverse cultures and socio-economic backgrounds, new points of view and respect for a community's values and interests from the perspective of the study participants. This has helped to improve study designs and methods and also increase study participant recruitment and retention. It has also increased consent and study enrolment, and led to the production of valid and more significant results (O'Fallon & Deary, 2002).

CE has been recognised as an essential activity that can be used for promoting the ethical conduct and successful implementation of research. This is done by ensuring that research conducted is locally relevant to the host community and that viewpoints of the local populations are integrated into the research design during the conduct of the study (Dickert & Sugarman, 2005; Emanuel et al., 2004).

CE is also important in that it helps to extend the ethical principle of 'respect for persons' to the entire community. This may avoid exploitation and build confidence between researchers and the communities taking part in the research (Lakes et al., 2014; Tindana et al., 2011).

CE permits members of the community to express their concerns, priorities or reservations about the research. It also permits researchers to identify vulnerable populations (groups of persons incapable of fully protecting their own interests). Engagement may also facilitate the identification of potential consequences of, or implications for, the research that might not have been anticipated by the researcher. Furthermore, CE permits the community, as a group, and the individual potential research participants, to think about the risks and benefits involved in participation and to assess the defined protections put in place for them.

CE assists in creating beneficial, collaborative and transparent relationships between potential researchers and the communities with which they might work to conduct the research (UNAIDS/AVAC, 2007). This is very important since favourable relationships between researchers and communities can promote trust in scientific research, as well as lead to greater recognition of scientific results. These relationships could equally lead to the identification of potential future research endeavours that might be beneficial to the community.

Involving community members and representatives in conducting the research also helps to increase awareness and knowledge amongst the community. Participation can also help create trust between the communities and the researchers, and this will help to increase the probability that community members will be aware and take advantage of any benefits that may emerge from the research (2011) .

CE helps to ensure that communities more prone to shouldering the burdens of research unequally have fair access to the benefits of the research, as the principle of justice requires. Engaging the community in the protocol planning, participant recruitment and research results dissemination can provide a great opportunity for communities to identify groups that might need specific consideration. Identifying these sets within the population may help prevent either overburdening such groups or forgetting them from the final dissemination of the research outcomes.

More generally, Dickert and Sugarman (2005) have identified four main values of CE. These are protection enhancement, enhancement of benefits, creation of legitimacy and sharing responsibilities; these are facilitated by the integration of the opinions of the community and its participation in research (Dickert & Sugarman, 2005).

At all levels, there is a blurred difference between “CE” and “stakeholder engagement”. Depending on the definition of community that is adopted, any interactions with research stakeholders, such as the media, policy makers, ethics committees, Ministries of Health, international organizations and universities, could be regarded as a form of CE. Linking the term ‘community’ to ‘engagement’ serves to shift the focus from the individual to the collective, with a focus on inclusion of diverse stakeholders within any community. The term stakeholder could be understood as individuals or organisations with a specific stake in the outcome of a decision to the impact of a policy, project or proposition sufficient to justify engagement but who may or may not have geographic proximity to potential research project sites (Kolopack & Lavery, 2017). Hence stakeholders can be part of your community, or your community members can be stakeholders

2.2.2 Challenges of community engagement

A key challenge emerging in discussions of CE relates to the understanding of the term “community” (Ernst & Fish, 2005a; Q. Karim et al., 2006). Defining and understanding what a community is, constitutes a great challenge since it is only through an adequate definition of what this entails can engagement begin. What constitute a community seems to be evolving in this time of globalisation and this poses a great challenge to researchers as their lack of

understanding of what a community is makes them to leave out certain important communities in the engagement processes which always come at considerable cost to them in the future.

The next challenge revolves around lack of funding from funders (Swainston & Summerbell, 2008). This is seen to be the biggest challenge as without such funding allocation, CE activities cannot be carried out by researchers. So the lack of CE or inadequate CE could be link to funders/sponsors and not entirely blamed to researchers as it has been seen most often. There is need for funders to understand the relevance for CE activities and make considerable funds available for its activities.

Another challenge with CE has been the power struggle between stakeholders (Swainston & Summerbell, 2008). This is a big challenge mostly in very big projects as the different stakeholders fight to position themselves; due to their societal influence and status; to imposed their decisions or override the decisions of other stakeholders. This is very costly to the overall success of the project as it gives room for personal interest and ego over collective interest and overall goal of the project. This constitute a big challenge for CE in research projects and calls for an urgent need to harmonise every stakeholders effort into archiving the common goal designed for the given project.

Lastly, another challenge that could be noticeable in CE is that associated with certain cultural practices and social settings as in some societies, it would be considered culturally inappropriate for researchers to ask individuals to participate in research without consulting the community or obtaining permission from community leaders. Thus it is important to understand these challenges and identify solutions to overcome them prior to the commence of the research study.

2.2.3 Types of community engagement

CE can be and is applied in several ways and to different extents, and the level of engagement covers a broad spectrum, depending on the kind and intricacy of the project(s) involved (Fleischman, 2007). These are discussed below.

2.2.3.1 Traditional research: This type of research method marks the ‘lowest’ end of the CE spectrum. This is so because, historically, research has been driven mainly by prior experimental data and funding priorities. Protocol designs by researchers in traditional research do not seek inputs from participants or the community at large on the scientific methods, ethical

requirements, and feasibility of the study throughout the research process. Participant recruitment is classically centred on scientific criteria that are specific to the protocol, and researchers figure out the best ways to reach out to the members of the community for the purpose of recruitment. In this type of research, researchers are linked to the community only through the research project and nothing else. In this research method, researchers do all the work such as collecting, analysing, and interpreting data, reporting results, and publishing findings on their own while the members of the community typically have no role to play in the research, beyond being research participants.

2.2.3.2 Community-engaged research: This type of research method extends through the biggest part of the CE spectrum, and the inputs of members of the community are sought in identifying relevant issues for the study, creation of culturally suitable study designs, or in identifying and incorporating ethical considerations into the design of the study and the strategies for the recruitment of participants. The establishment of community advisory boards (CABs) for consultation with researchers is a popular method that visibly indicates that researchers value the inputs of the community. However, this approach is limited in that community representatives are not considered as full partners in the research endeavour. Usually, every partner in the research process carries equal weight in every research-related process of making decisions; however, this is not the case for the CABs, as they are limited to providing information whilst having no power to make final decisions. Members of the community might be involved at times during the collection and analysis of data, and this analysis, interpretation, and dissemination of results is shared openly with the community.

Along the community-engaged research spectrum, the degree of engagement and collaboration between researchers and members of the community could be depicted as outreach, consultation, involvement, collaboration and shared leadership as shown in Figure 1 (2011)

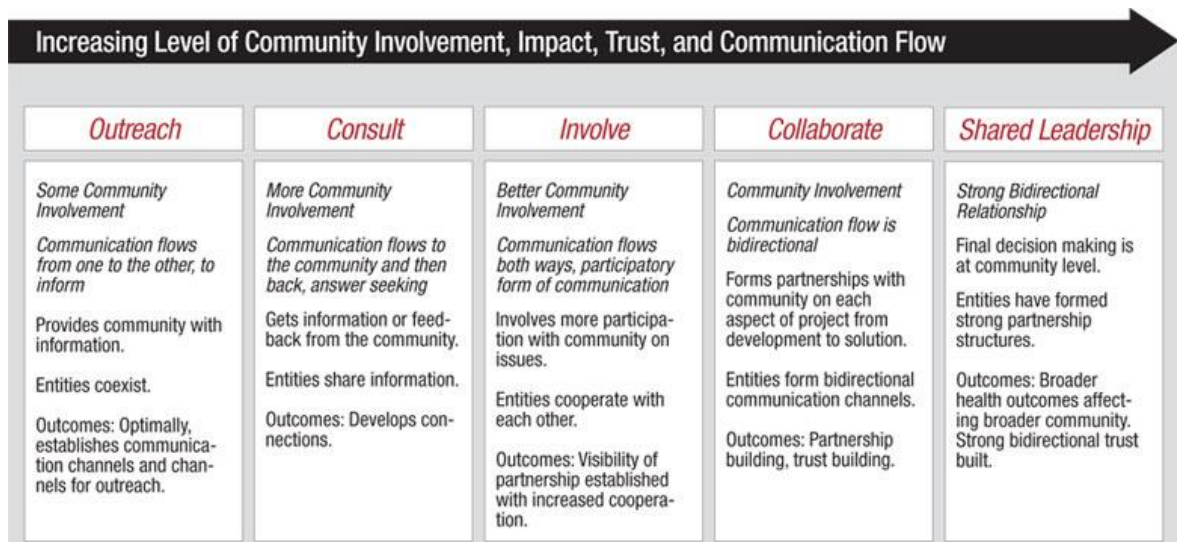


Figure 1: Continuum of community engagement mechanisms.

Source: Clinical and Translational Science Awards Consortium and Community Engagement Key Function Committee Task Force on the Principles of Community Engagement. (2011). *Principles of community engagement* (2nd ed.). Bethesda, MD: National Institutes of Health, p.8.

2.2.3.3 Shared leadership model: This type of research method represents the maximum level of community participation in research. In this model, members of the community function as full partners in the research study. The communities assist in identifying the topics or issues for study based on their priorities. These communities actively participate in designing the study and providing guidance to the researchers concerning the recruitment and retention of participants. Community members are also involved in collecting data – data that is shared with the community and the researchers in collaboration with the members of the community, who normally work to analyse and interpret these data.

Researchers do not only share the results with the community, but the community members themselves assist in disseminating the research results to the public. This research method stresses capacity building, for example, the involvement of the local community in the research process with the aim to strengthen skills, competencies, and at times infrastructure, so as to deal with prevailing social and/or economic hurdles within the community. This approach is the best and the approach that is recommended for every researcher/investigator to implement in their health research projects requiring CE.

2.3 Theories upon which thesis will be based

CE has been linked to development practices which came into global health research in reaction to calls to see much greater research community representation and participation, especially from vulnerable persons (MacQueen et al., 2015).

The establishment of different international ethical guidelines has facilitated the protection of research participants in research. These guidelines include: the Nuremberg Code established in 1947; the Declaration of Helsinki, with the first version in 1964 and the most recent in October 2013; the Belmont Report of 1979; the Council for International Organizations of Medical Sciences (CIOMS) ethical guidelines, with the first version in 1982 and the most recent in 2016; the International Council for Harmonisation (ICH) Good Clinical Practice guideline issued in 1996; and the UNAIDS/AVAC Good Participatory Practice (GPP) guidelines, with the first version in 2007 and the most recent in 2011. Drawing from the different international guidelines, Emanuel et al. (2004) proposed eight ethical principles, with accompanying benchmarks, for the conduct of research; among these was collaborative partnerships/community engagement.

Hashagen (2002) argues that the use of the word ‘engagement’ means that those in charge of community planning should think properly about the communities they intend to work with. This is to enable them to understand the community’s culture and history, an array of local needs and matters, and how they are perceived, the nature of local community networks and organisations, the strengths and assets of the community that they might capitalise on and, finally, the nature of prevailing dialogue and community participations.

Aslin and Brown (2004) articulate that CE is not something to be done once and forgotten about but rather a continuing process, with the goal of “engaging the community to take action” (p. 3). Furthermore, these authors stress that the CE process does not stand alone but rather forms a part of another process known as “decision-making for a particular purpose” (p. 3). These two authors emphasise that engagement “... goes further than participation and involvement and it involves capturing people’s attention and focusing their efforts on the matter at hand ... Engagement implies commitment to a process that has decisions and resulting actions meaning that it is possible to consult people, get them to participate, to be involved even, but not engaged” (Aslin & Brown, 2004, p. 5). Of utmost significance to this explanation are the commitments by the participants – both the researchers and the communities – for without commitments, there is not likely to be any sustained and meaningful engagement.

Two schools of thought can be applied to the concept of CE (Brunton et al., 2017). They include the utilitarian and the social justice perspectives. These two perspectives often appear

in CE literature. Health researchers and authors take different positions regarding these two perspectives and, depending on their perspective, may approach CE quite differently. Researchers from a utilitarian perspective consider research to be good or bad for the community based on the consequences or outcome of the research to the community. In theory at least, this means that if a community benefits from research, even without being engaged with in the research process, the research is ‘good’.

From the social justice perspective, less emphasis is placed on the instrumental usage of CE to attain a certain end (as with the utilitarian perspective), than to the development and empowerment of the community itself. The ladder of citizen participation by Arnstein (1969) is the oldest and probably best-known model centred on social justice. This method of participation ranges from non-participating methods of manipulations, via ‘tokenistic’ placation, informing and consultations, to ‘power-sharing strategies’ of partnership and power delegation. With the use of this model, CE procedures near the foot of this ladder of participation might comprise information dissemination about the planned research, while research mechanisms at the topmost part of the ladder can provide lawfully established representatives as veto powers in relation to the proposed research. This study will focus on the social justice perspective, which is founded on empowerment of the community members, which is required for genuine and meaningful engagement.

According to MacQueen and colleagues (MacQueen, Eley, Frick, & Hamilton, 2018), the numerous gaps in and challenges with CE are a reflection of the outlier status of CE to (some) stakeholders. This means that CE is often regarded as an auxiliary to trials rather than as an integral element, with equivalence to the regulatory, laboratory, clinical, laboratory and statistical elements. This problem – where engagement is viewed myopically as an instrument or procedure for buttressing clinical trials – has profound repercussions. Pantelic and colleagues argued that engagement ought not to be regarded as a *method* but rather as an *orientation* that needs to be incorporated into the designed and tried intervention (Pantelic, Stegling, Shackleton, & Restoy, 2018). These authors made the case to shift the nature and focus of HIV-prevention research towards the individual’s needs and interests. They proposed that obstacles to improving and incorporating knowledge about CE in research be addressed through community-based participatory and person-centred research techniques.

Despite the fact that CE is relevant for the ethical conduct of research, it cannot be implemented in all kinds of research situations (Weijer & Emanuel, 2000). This is because there do exist differences in cultural and social norms, goals, values, resources and technological understandings between researchers and typical community participants; these must be taken

into consideration, if research is to be conducted successfully right to the end (Doumbo, 2005; Leach & Fairhead, 2011; Mitchell, Nakamanya, Kamali, & Whitworth, 2002; Molyneux, Wassenaar, Peshu, & Marsh, 2005). Weijer and Sharp's analysis stating that prospective systems of engagement are based on particular community attributes offered a useful conceptual framework for this study (Sharp & Foster, 2000; Weijer & Emanuel, 2000; Weijer & Miller, 2004).

Possibly the best-known mechanism for CE in international research has been the use of community advisory boards (CABs). CABs are defined as "being composed of committee members who share a common identity, history, symbols and language, and culture" (Strauss et al., 2001, p. 15). Marshall and Rotimi describe CABs as an example of an approach of "safeguarding the interests of local populations, through the establishment of a solid foundation that supports a relationship based on trust and engagement with community members" (Marshall & Rotimi, 2001, p. 243). A strong CAB is one which is established based on a stronger relationship with the researcher and is sustained over time, usually longer than the lifespan of any particular research study.

CABs are now generally accompanied by and balanced with other forms of engagement and participation so as to bring diverse community voices, viewpoints and worries to the fore. These forms of engagement include the use of traditional community assemblies (Vreeman et al., 2012), qualitative research as was for the case of Cameroon (MacQueen et al., 2007), and deliberative engagement processes (Lemke, Halverson, & Ross, 2012). One of the issues debated by CABs has been the quality of care to be offered to participants. Experiences in the field demonstrate that research participants cherish the high quality care they get at research sites (MacQueen et al., 2007; Ramjee et al., 2010). Offering high quality care is regarded as a means of 'giving back' to communities that have offered an accommodating environment for research in an effort to advance science. Participants find this experience extremely advantageous (Dawson, Klingman, & Marrazzo, 2014).

The debate has raged over whether the level of care being offered should be equal to that available in the home country of the sponsor of the trial or be comparable to the best standards of care obtainable within the country where the trial is taking place, though not necessarily within the actual location of the trial (MacQueen et al., 2007). In terms of HIV research, many commentators are of the opinion that researchers have some positive responsibilities to assist those trial participants who seroconvert during the study (MacQueen, Karim, & Sugarman, 2003). Unfortunately, it has been recognised that even in the presence of state-of-the-art technologies for testing the intervention, 'offshore' trials cannot deliver the

same quality of care as is obtainable in the country of the trial sponsor (Craddock, 2004; Kalipeni, Craddock, Opong, & Ghosh, 2004; MacQueen et al., 2007).

There has also been wide debate on the associated ethical challenges in HIV research regarding prevention and treatment, both at the national and international levels (Lurie & Wolfe, 1997; K. MacQueen, Shapiro, Karim, & Sugarman, 2004; Rennie, Muula, & Westreich, 2007). One of the challenges centres on the much greater distance existing between the theoretical ideal and the reality of individual understanding in circumstances where participants might lack proper education. Not only do several languages not have words for fundamental terms such as ‘hypothesis’ or ‘research’, ‘false positives’, ‘placebo’ and ‘randomization’ (Ekunwe & Kessel, 1984; K. MacQueen et al., 2004; Molyneux, Peshu, & Marsh, 2004; Moodley, 2002), they may even lack corresponding concepts. Comprehension of the information discussed during the consenting process may well be improved by way of counselling and consultation with cultural authorities and/or local cultural representatives, (Fitzgerald, Marotte, Verdier, Johnson Jr, & Pape, 2002; K. MacQueen et al., 2004; Marshall & Rotimi, 2001; Strauss et al., 2001; Woodson & Karim, 2005), hence the need for CABs.

A key challenge for CABs has been to identify stakeholders who have legitimate and genuine interests. By this is meant identifying stakeholders who will avoid politicisation and will reliably represent their communities (Dickert & Sugarman, 2005; Foster et al., 1999; Marshall & Rotimi, 2001; E. J. Mills et al., 2005; Sharp & Foster, 2000). Another challenge has been that there has been no instruction (either uniform or adapted to local contexts) regarding what indicators should be used in addressing ethical issues raised by the use of CABs or regarding how they might best be used to improve post-trial benefits and reduce potential community exploitation (MacQueen et al., 2015). Also another challenge of CABs resides on whether CAB members should be compensated financially for the work they do since most at time individuals available to participate in CAB’s activities may be unemployed and therefore have challenges meeting their daily needs (Manda-Taylor, 2013; Morin, Maiorana, Koester, Sheon, & Richards, 2003a). While it could be justify that there is a strong positive relationship between compensating CAB members for their time and with their greater commitments to the CAB’s activities (Mott, Crawford, & Group, 2008), the problem associated with this approach comes when this compensation is being provided for by the research group. If the research group provides for the compensation, then there is a possibility that the CAB members may be influenced in their decision making in favour of the research team (Israel, Schulz, Parker, & Becker, 1998b; Lo & Bayer, 2003; Quinn, 2004b). Lastly, both scientists and CAB members have raised the issue of insufficient power being given to community representatives and of

their actions being largely limited to advising and giving feedback to researchers (Lwin et al., 2014; Manda-Taylor, 2013; Pratt et al., 2015).

A power shift is needed in which CABs can assume a more *intrinsic* role. This would include, for instance, participating in setting the study agenda with researchers and evaluating the appropriateness and relative priority of future studies (MacQueen et al., 2015). This is in contrast to having a purely *instrumental* role, such as providing guidance in the wording of the informed consent form or helping with recruitment and enrolment (MacQueen et al., 2015). Thus it is important for CE strategies to be informed by local advisors and occasionally re-evaluated for results (MacQueen et al., 2015). In the absence of this, a well-intended proposal to engage specific communities might encounter obstacles that are well beyond the scope of any particular clinical trial and consequently make a generally ‘good practice’ non-effective.

In addition to these challenges by CABs are debates on: how the term community ought to be defined (Ernst & Fish, 2005b; UNAIDS, 2006); debate on the harmonisation of compensations and ensuring the independence of members (Morin, Maiorana, Koester, Sheon, & Richards, 2003b); debate on the need for resources for the training and sustainability of CABs’ activities; and lastly debates on the resolution of disputes resulting from individual- and community-level decisions (Quinn, 2004a; Sharp & Foster, 2000). Given the relevance of principal researchers in dispute resolution through negotiations, the efficacy of CABs has been tied to the connection between the principal investigator and the community (Sharp & Foster, 2000).

Several reasons account for why things might go wrong with a CE process. These reasons include poor planning, lack of commitment, lack of resources or interest from one or more stakeholders, bad timing, and so on. Dare and colleagues (Dare, Schirmer, & Vanclay, 2008) advised that it is important not to abandon a process or ignore any problem but rather to identify the causes of these problems in the process and (attempt to) fix them.

In light of the above, the researcher tried to identify what exactly went wrong with the CE process during the tenofovir trials in both Cameroon and Cambodia. In looking at these trials, the study aimed to propose a way forward for other researchers who will be implementing the concept of CE in similar situations in the future, so as to avoid the mistakes made in those trials.

2.4 History and development of tenofovir

The life cycle of the HI virus provides numerous specific goals for ARVs, and there are many classes of ARV microbicides that are now under development. Two of these are entry inhibitors and reverse transcriptase inhibitors (Garg, Nuttall, & Romano, 2009). Entry inhibitors can operate in different ways, with some impeding the binding of the HI virus to CD4 receptors and CCR5/CXCR4 co-receptors, hence hindering entry into target cells (Shattock & Moore, 2003), while others interact with the gp120 on the HI virus. For this thesis, attention will be on the nucleotide/nucleoside reverse transcriptase inhibitors (NRTIs), which irreversibly and allosterically combine to reverse transcriptase and thus prevent HIV duplications (Q. A. Karim et al., 2010). Reverse transcriptase (RT) is a viral enzyme used for the conversion of viral mRNA into double-stranded viral DNA. This can then be integrated into the host cell chromosome, thus permitting host duplication of the virus (Sarafianos et al., 2009). Consequently, RT is essential for HIV duplication and spread (Sarafianos et al., 2009), and inhibiting RT can potentially prevent infection.

In practice, NRTIs have proven to be highly efficient in blocking the action of RT. NRTIs were the first class of antivirals approved by the FDA for HIV treatment (Young, 1988). All NRTIs are activated to triphosphate analogues by cellular kinases (Furman et al., 1986; Hart et al., 1992; Mitsuya, Matsushita, Yarchoan, & Broder, 1984; Mitsuya et al., 1985). NRTIs represent the pillar of highly active antiretroviral therapy (HAART) for the clinical management of HIV infection, hence this ARV class is important to the development of microbicides. This class is relevant because it can sustain ample anti-HIV activity all through the interval between when it is applied to the vagina or rectum and when the semen is deposited (Karim et al., 2010; Shattock & Moore, 2003). Amongst this ARV class is tenofovir (TFV), which is an acyclic nucleotide which speedily changes over within cells from TFV monophosphate to its active form TFV-diphosphate (TFV-DP) (Birkus et al., 2007; Herman & Sluis-Cremer, 2012; Q. A. Karim, 2013).

ARV drugs are proven to be efficient in the control of HIV for persons already infected. The biggest question surrounding ARVs has been to find out if it is possible for antiviral treatment to reduce the risk of the transmission of HIV, if it is taken as a form of prophylaxis prior to exposure to the virus; this marks the beginning of the tenofovir story. As discussed above, tenofovir is a long-acting ARV drug of the RT inhibitor class; it can be consumed once daily and has fewer side effects than several older agents. In ground-breaking research, it was ascertained by scientists that TFV administered immediately after a monkey's exposure to SIV, a simian virus like the HIV, could prevent infections to the monkeys (Black, 1997; Tsai et al.,

1998). This result buttressed the notion that TFV could be used as a post-exposure prophylaxis for humans, and maybe as a pre-exposure prophylaxis in high-risk HIV-negative populations for infection prevention.

The foundation for preventing sexual HIV acquisition with pre-exposure use of ARV drugs originates from the demonstration that ARVs prevent HIV transmission from an infected mother to her infant and from a study on animals. ARVs are the foundation for the prevention of mother-to-child HIV transmission, which was first demonstrated with peripartum zidovudine (Connor et al., 1994). More recent studies have equally proven that post-natal ARVs, which are offered to infants with continuing exposure to HIV via breastmilk, can considerably assist in HIV-risk reduction (Chasela et al., 2010). Therefore, these infant studies provided proof-of-concept that ARV prophylaxis could be extremely effective in the context of HIV exposures that were known and ongoing (Mofenson, 2010).

This form of chemoprophylaxis, pre-exposure prophylaxis (PrEP), is an approach for the prevention of HIV, in which an individual who is not infected with HIV is administered an oral or topical formulation of an anti-HIV drug to protect themselves against HIV infection (Van Rompay, Johansson, & Karlsson, 1999). It refers to the taking of daily medications by persons at very high risk of HIV infection, so as to reduce their risks of infection (Centers for Disease Control and Prevention, 2019).

Currently, the only FDA-approved formulation of PrEP is Truvada, an oral co-formulation of the nucleoside/nucleotide RT inhibitors TFV and emtricitabine (Barry et al., 2014; Meesters et al., 2011). Approval was issued in October 2004 for HIV treatment in adults, based on its efficacy and safety data (Louie et al., 2003; Schooley et al., 2002; Squires et al., 2003; Staszewski et al., 1996). PrEP is believed to be a very promising approach to prevention.

TFV is approved for usage as part of combination ARV therapy in the treatment of HIV infection for children two years and older, adolescents, and adults. Its high effectiveness and opposition to resistance, and its once-daily and single pill administration, has led to TFV being one of the favourite drugs for individuals with HIV infection (Aurpibul & Puthanakit, 2015; Lyseng-Williamson, Reynolds, & Plosker, 2005).

2.5 An overview of a clinical trial

Clinical research is an important element of health care systems and contributes to the development of new therapeutic agents and interventions, and it improves existing clinical practices; at times, it exposes the inadequacies of health care systems (Friedman, Furberg, DeMets, Reboussin, & Granger, 2010). Clinical research is carried out using different methods;

nevertheless, clinical trials are currently the leading method of clinical research (Friedman et al., 2010; Piantadosi, 2005).

The term ‘clinical trial’ was first used in the early 20th century by the British Medical Research Council (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), June 10, 1996; Lefebvre, Eisinga, McDonald, & Paul, 2008). The term ‘trial’ comes from the Anglo-French ‘*trier*’, which means to try. The term ‘clinical’ comes from ‘clinic’, from the French word ‘*clinique*’ and the Greek word ‘*klinike*’ – both referring to the practice of caring for the sick at the bedside. Thus a clinical trial could narrowly be regarded as the action or process of putting something to a test or proof at the bedside of the sick. Broadly, it could refer to any testing done on human beings with the aim of determining the value of a treatment for the sick or for preventing disease or sicknesses.

A well-designed clinical trial involves a particular kind of method that permits researchers to test an intervention, idea or drug. The advent of ‘clinical trials’ as a process for testing the efficiency of drugs developed accidentally. Surgeon Ambroise Paré is known to have carried out the first documented clinical trial of a novel therapy in the 1500s. He did this when he treated wounded soldiers with an alternative to the standard-of-care treatment, due to the low supply of the standard treatment and, in great surprise, this alternative treatment appeared to be more effective than the standard treatment (Bhatt, 2010)

Some scientific research studies which compared treatments were carried out in the 18th and 19th centuries, and these included studies on smallpox and cholera. The most prominent intervention trial carried out was that by James Lind. Lind was a surgeon, and the trial was conducted in 1747, involving twelve sailors who had scurvy (Lilienfeld, 1982). Lind divided them into six groups of two and assigned each group a different existing treatment (Bhatt, 2010). According to (Chalmers, 2003):

In Lind’s opinion, one reason for the prevailing confusion about the diagnosis, prevention and cure of scurvy was that ‘no physician conversant with this disease at sea had undertaken to throw light upon the subject’. He set about filling this gap, with a clear commitment to base his work on “‘Observable facts’ rather than the theories of medical decision-making at that time”(p. 1).

This comparison by Lind became the first documented ‘prospective controlled trial’.

The UK Medical Research Council (MRC) planned and executed the first known double-blind controlled clinical trial of the patulin drug in 1946; this was designed in response to public pressure. The public wanted to know whether patulin, a product purportedly

discovered by a group in the Royal Navy and anticipated to be better than penicillin in the fight against the common cold, was in fact, more effective. The members of the trial committee chosen by the MRC comprised biostatisticians and physicians, making this a 'rigorously controlled trial' (D'Arcy Hart, 1999). The first true randomised clinical trial was carried out by the British Medical Council in 1948. This trial involved 100 patients and studied the effects of streptomycin on tuberculosis treatment (Medical Research Council, 1948).

The broad definition of 'clinical trial' comprises explanations that allow for the use of the term in reference to studies which involve a single treatment (for example, most phase I trials and some phase II drug trials) and for trials that involve the use of an external control (for example, studies that involve historical controls) (Meinert, 2012). In this research, the term will be used for referring to trials that involve two or more treatment groups consisting of persons who are enrolled, treated and followed up over a specific period of time.

Research with human participants is currently regulated in several ways and at different levels. Clinical trials are guided and implemented according to a clinical trial protocol, which contains information on scientific evidence supporting the trial and on how the trial will be carried out, including its design, eligibility criteria of the participants and the outcomes to be measured. Protocols of clinical trial are sent to regulatory bodies such as clinical trials registries and ethics committees for review and approval (Kerr, Knox, Robertson, Stewart, & Watson, 2008).

Funders and sponsors of clinical trials research range from pharmaceutical companies, national research bodies, charitable foundations to private donations. Trials are carried out in private clinical laboratories, universities, medical centres, hospitals and research facilities, with persons from different fields taking part in the design, conduct and management of the studies. The research team is made up of, but not limited to, nurses, medical practitioners, scientists and other health care professionals, ethics committee members, the sponsor organisation, statisticians, epidemiologists, and carers and patients (Kerr et al., 2008). Clinical trials are carried out in a broad range of clinical and disease contexts, and differ in their aims, objectives, purposes and designs. That said, five broad categories that relate principally to the objective of the clinical studies, are commonly used for categorising clinical trials. These classifications are summarised in Table 1.

Table 1: Categories of clinical trials research (Sateesh, 2008)

Treatment trials	New drug combinations, new methods of radiation therapy or surgery, test experimental treatments
Prevention trials	Evaluate approaches for the prevention of diseases in persons who have never had the disease or the prevention of a disease from coming back; such methods may include vaccines, minerals, medicines, vitamins, medicines or lifestyle changes.
Diagnostic trials	Carried out to discover better processes or investigations for diagnosing specific conditions or diseases.
Screening trials	Testing the best ways for detecting certain health conditions or diseases.
Supportive care trials or quality of life trials	Exploring ways of improving the quality of life and comfort for persons with chronic illnesses.

Generally, clinical trials are carried out in four phases, with each phase having a different purpose designed to help the investigators to answer different questions (see Table 2). Phase I clinical trials are often comprised of tests with small groups (20-80) of human participants. Tests here are geared at determining the safety of the drug in terms of most common side effects and metabolism in humans and, at this phase, enrolled participants are mostly healthy volunteers. Research results here are deemed successful if the level of toxicity is judged acceptable.

Between phase I and II trials proof-of-principle studies are at times carried out on humans so as to get supplementary indications of efficacies prior to going to phase II. A phase II clinical trial may begin after suitable IRB/REC approval. Phase II clinical trials are conducted on larger groups (amounting to some 300 participants) and are aimed at evaluating the efficacy of the drug in humans. Phase II clinical trials usually involve comparing the investigational drug to either a placebo (a substance that is inactive) or another drug. Phase III trials may only commence if the phase II trials ended on a positive note in terms of the drug's effectiveness, and here the objective is to assess further the safety and efficacy of the drug in 300 to 3,000 or more participants. Participants here are principally persons with conditions related to the drug being tested, and such trials are always carried out in multiple sites and are accomplished by: testing the drug in diverse populations; testing varying doses of the drug; and probably using it in combination with other drugs.

After successfully completing phase III clinical trials, the pharmaceutical company may submit a New Drug Application (NDA) which, if approved, would result in permission being granted to bring the new drug onto the market. The process of NDA review entails reviewing both animal and human testing data by an expert team. This team of experts reviews the proposed information to be put on the drug labels and inspects the facilities for the drug's manufacture. The phase IV clinical trials are carried out after a drug has been approved for marketing and aims to find supplementary data "about a drug's safety, efficacy or optimal use" (Lada, 2016, p. 30).

Table 2: Clinical trial development phases I-IV (Sateesh, 2008)

Phase	Description	Example of study population
Phase I	Researchers testing an investigational treatment or drug within a small group of persons for the very first time. Test here is geared at evaluating the drug's safety, determining a safe dosage range, and identifying side effects of the drug.	20-80 persons, usually healthy volunteers or persons with disease of interest
Phase II	The investigational study treatment or drug is administered to a larger group of persons with the disease of interest. The aim here is to find out if the drug is effective, and to further assess its safety.	100-300 people
Phase III	The investigational study treatment or drug is administered to large groups of persons to confirm its effectiveness and to monitor its side effects. In addition, it is given to compare the study drug or treatment to generally used treatments or placebo in a randomised controlled study design. It also collects information that will permit the investigational treatment or drug to be used safely.	301-3,000 or more people
Phase IV	Post-marketing studies geared at gathering supplementary information such as the drug's benefits, risks and best use.	General population

In spite of the above-mentioned range of clinical contexts, objectives and trial types, there are shared characteristics of clinical trials that differentiate this research methodology from other approaches. First of all, a clinical trial is a potential study design where participants are

monitored in time from a clear distinctive instant, where they are identified, selected and tested from the initiation point (Friedman et al., 2010). Also, clinical trials are carried out in settings which allow for the control of main variables like the measurement and intervention initiation of confounders and covariates, which helps in minimising bias (Piantadosi, 2005).

Clinical trials are the backbone of modern-day medicines and, since the Lind scurvy trial, clinical trials have evolved into a standardised procedure with focuses on scientific assessment of efficacy and patient safety guardians. As the field of the development of drugs continues to be improved by innovative technologies and therapies, there will always be an ongoing exigency to balance patient safety and medical progress. As scientific developments continue, so will there be new ethical and regulatory challenges. These challenges will require dynamic updating in the legal and ethical frame of reference of clinical trials in order for them to be sufficiently addressed.

CHAPTER THREE

RESEARCH METHODOLOGY

Research has been defined as a systematic method of collecting and logically analysing data for a particular objective (McMillan & Schumacher, 2010). Research methods have been established in order to acquire knowledge reliably and validly. A research method is focused and systematic, aimed at yielding data for a specific research problem (McMillan & Schumacher, 2010). This chapter will introduce and explain the rationale for the research methodologies chosen for the study. It begins by stating the aim of the research, providing the research questions and describing the research design. The chapter also includes a discussion about the reason for the choice of the case studies, the method of data collection, ethical considerations and the issues of validity and reliability as they relate to the research.

3.1 Study aims

The aim of this study was to demonstrate how inadequate CE might come at considerable scientific cost, whereas early, sustained and meaningful CE could contribute greatly to research. The researcher used the case of the tenofovir trials that were prematurely ended in both Cambodia and Cameroon in 2005 to draw lessons for future researchers.

3.2 Main objective

The main objective of this study was to understand the root causes of the early stopping of the tenofovir trials in both Cameroon and Cambodia in 2005, and with reference to the different international guidelines, to propose solutions for researchers embarking on similar research in the future.

3.3 Research questions

To address this research objective, the following research questions were posed:

- ❖ How did the researchers understand the term ‘community’ during the tenofovir trials?
- ❖ How were communities engaged during the tenofovir trials in Cameroon and Cambodia?
- ❖ What lessons can be learnt from the tenofovir trials with respect to community engagement, especially with respect to the concept of ‘meaningful community engagement’?

3.4 Research design

Heppner, Kivlinghan and Wampold (1992) describe a research design as a structure or plan for an experiment or a list of requirements and procedures used for the conduct and control of a study. Simply put, a research design is a master plan indicating the strategies for carrying out the study.

Who, what, where, how and why are typical research questions (Yin, 2003). The form a research question takes can suggest the most suitable investigation strategy. The ‘how’ and ‘why’ questions can best be answered by case studies since this method allows for careful observation of the problem in question (Kothari, 2004). The study approach is termed a qualitative inquiry strategy, and it offers a learning method about a complex situation by way of a broad description and circumstantial analysis (Yin, 2003).

Mitchell (1983) defines a case study as a “detailed examination of an event (or sequence of connected events) which the researcher thinks reveals (or reveal) the procedure of some recognised general theoretical principles” (p. 192). According to Gomm and colleagues (Gomm, Hammersley, & Foster, 2000), detailed research of peculiar occurrences in case studies can truly portray causative processes in context, which permits the analyst to appreciate which theoretical point of view offers the best explanations. According to another author (Stoecker, 1991), a case study is able “to explain idiosyncrasies, which make up the ‘unexplained variance’” (p. 94).

Qualitative research designs can be classified by: (a) focusing on personal lived experiences, such as in case study grounded theory, phenomenology and some critical studies; and (b) focusing on society and culture, as established by ethnography and some critical studies (McMillan & Schumacher, 2010). The researcher chose to use the qualitative research design type (a), which involves a case study approach, for the purpose of this study. This decision was triggered by the desire of the researcher to appreciate the relevance of meaningful community engagement in health research in the 21st century and, for that to be done, it required an in-depth examination of the two case studies (Cameroon and Cambodia).

3.5 Selection of the study materials

The specific method used in collecting data/information for this research was collective review. Cooper (1998) suggests that a literature review provides the potential to propose much-needed research in specific areas. Furthermore, he points out that theses with a focus on

literature review produce a wealth of data, which can then serve as the academic core for studies to be carried out in the future by identifying gaps and weaknesses in published knowledge.

For this study, the stages of review advanced by Petticrew and Roberts (2006) were used for collective reviewing. Petticrew and Roberts (2006) summarised the stages of carrying out the review as such: the first stage is defining the study type (i.e., the literature review); the second stage is delineating the process for selection of literature to be included in the review, thereby applying the search strategy (Higgins & Green, 2008). For this research, electronic databases available to students of the University of KwaZulu-Natal, Google Scholar, and personal contacts and experts in the field for relevant authors were used to source literature. During the third stage, the researcher screened the material based on a structured classification system in order to structure and refine the literature review. Once the process of gathering and describing the research was completed, the researcher began the fourth stage of the review, which was assessing and synthesising the data. This involved appraising the quality and relevance of the data; synthesising the results of the studies; drawing conclusions; developing recommendations; and writing the final report (Major & Savin-Baden, 2010).

Through this review, the researcher established the strength of assertions made in the literature. Firstly, the researcher reflected on the credibility, feasibility, coherence, intelligibility, and effect of the claims. Secondly, the primary literature researched was reviewed against its evidence. The researcher, in view of this, also considered aspects of reliability, reproducibility as well as significance. Thirdly, the researcher focused on data relating to the information concern. Subsequently, the merits of information were extremely important.

Nevertheless, it should be noted that, only literature that could be verified by formal avenues was included in the review itself. The restricted focus implied by limiting the literature review to published literature did not indicate an absence of the researcher's personal imagination, as implied by Cooper, as that could be vigorously noticed during the stages where sense-making (Abolafia, 2010) was applied to the data, and explicitly when correlated conceptions were analysed in the literature. What hopefully becomes apparent during the review analysis is that the collective results of reviewed literature are usually more combined in nature (analysis is on combined results from the different case studies and not just one) than taken into consideration in a separate study (as done on a case-by-case basis), and import is thus more powerful.

Higgins and Green (2008) point out that, while this methodology might seem slightly simplistic, this process is rigorous and laborious since the researcher systematically employs a range of theoretical and scientific opinions to establish the significance of the data.

3.6 Selection of cases

In order to conduct this research, it was necessary to identify clinical research studies that failed because of poor CE. Thus, in the selection phase, clinical studies that had failed because of reasons other than poor CE were excluded. Inclusion criteria consisted of the following: the study had to be a clinical trial, secondly, this clinical trial had to have been stopped prematurely, and lastly, the reason for the premature end had to be as a result of poor CE. Through this search, the Cameroon and Cambodia studies were identified as best fit for the study. Cameroon and Cambodia were chosen for convenience, availability of information, similarity and uniqueness in the cause-effect relationship (Blanche, Blanche, Durrheim, & Painter, 2006). In addition, a factor that contributed to the selection was that the major reason for the establishment of the Good Participatory Practice (UNAIDS/AVAC, 2007) guidelines, which set standard practices for stakeholder engagement in HIV vaccine trials, was the failure of these two trials.

3.7 Data collection and procedure

Secondary data was obtained from the internet and the UKZN library. Different articles published online, text books, journals, reports, newspapers, and research dissertations were searched for on Google.com, Google Scholar.com and from the UKZN campus and online library. On the UKZN online library, platforms such as the EBSCOhost and SABINET were used for the search of current articles. Key words searched for included community engagement, tenofovir trials, clinical trials, health research, and Emanuel et al. eight benchmarks. The references cited in the different books and articles already published also served as a means for locating other articles for review.

3.8 Ethical considerations

This study involved no human participants as research was done reviewing secondary (existing) data. However, this study obtained an Exemption from Ethics Review (BREC Ref No: EXM538/18) from the Biomedical Research Ethics Committee (BREC) of the University of KwaZulu-Natal prior to the start of the study.

3.9 Reliability and validity

Reliability is a problem in the social sciences since human behaviours are under no circumstances fixed; this concept is founded on the hypothesis that there is a single reality and that repeatedly studying it will generate similar outcomes. This is in contrast with qualitative case study research, since researchers here strive to describe and explain the world as it was experienced by those in the world (Merriam, 2009). As there are several understandings of what is occurring, there is no standard means by which to determine reliability in the traditional sense; thus, the more essential problem for qualitative research is whether the results are consistent with the data collected. Consequently, the terms ‘consistency’ or ‘dependability’ are used.

In this study, the researcher used the review of existing documents as the primary means of data collection. The reliability of the research results can be evaluated by the number of documents that were reviewed in order to establish the facts of the cases presented. The reliability of results can also be weighed through triangulation. This is the use of more than one method to research a problem. Triangulation aims to increase faith in the results through the validation of a proposal with the use of two or more independent procedures (Heale & Forbes, 2013). Combining results from two or more painstaking methods offers a more complete image of the results than when only a single method is used (Teddlie & Tashakkori, 2003).

External validity is the question of whether the empirical findings could be generalised (Calder, Phillips, & Tybout, 1982). As ascertained, the aim of case study research is to create profound understandings of the phenomena under investigation; this means it does not have as its aim the generalisation of the findings to other circumstances (Hammersley, Foster, & Gomm, 2000). Thus, for this study, the external validity will be low. However, it is vital that a study is internally valid (Calder, Philips, & Tybout, 1983). Internal validity is concerned with the degree to which research results correctly reflect the phenomenon under study (A. C. Burns & Bush, 2003), and to which they can be applied to other situations (Merriam, 2009). Simply put, internal validity refers to the degree to which the results match reality (Ong, 2012).

CHAPTER FOUR

CASE STUDIES

4.1 Presentation of the tenofovir trials in both Cambodia and Cameroon

Information for the two case studies reported on this chapter is largely summarised from two case reports published under the auspices of The Global Campaign for Microbicides titled “Preventing Prevention Trial Failures: A Case Study and Lessons for Future Trials from the 2004 Tenofovir Trial in Cambodia” and “Research Rashomon: Lessons from the Cameroon Pre-exposure Prophylaxis Trial Site”. Some additional sources were obtained from 9 peer reviewed articles (Cáceres et al., 2015; Folygon, Peterson, & Kombe, 2015; Mack, Robinson, MacQueen, Moffett, & Johnson, 2010; E. Mills et al., 2005; E. J. Mills et al., 2005; Nyika et al., 2010; Singh & Mills, 2005; Slevin, Ukpong, & Heise, 2008; Tangwa & Munung, 2011), 1 PhD thesis (Bridget Gabrielle Haire, 2013) and a book (Brizi, Filibeck, Kangaspunta, & O’Neil, 2009).

Methods for the prevention of HIV infection have been amongst the most pressing needs of global public health (A. UNAIDS, 2004), and one innovative technique used in clinical trials is pre-exposure prophylaxis with the ARV drug tenofovir, which is a proven drug used for the treatment of AIDS. The tenofovir drug was produced by Gilead Sciences in the United States. Gilead conducted trials to establish whether tenofovir could work as a prophylactic with the main purpose of testing the safety and efficacy profile of tenofovir for humans. The test procedure entailed the administration of a daily oral dose of either placebo or tenofovir to sex workers who had tested HIV negative at screening and then comparing the number of sex workers who took the oral tenofovir and seroconverted in the course of the trial to the number who seroconverted in the control group getting the placebo.

Trials were stopped in Cambodia and Cameroon partly because of inadequate CE that led to misunderstanding and miscommunication. Other reasons for the early stopping of the trial included: unethical study design, study protocol concerns, inadequate access to care for participants who seroconverted, inadequate prevention counselling, and the lack of medical insurance for trial-related injuries, among others. Most of the controversies in the trials arose from failures to obtain appropriate consent, failures to engage with local research actors, and failures to provide tangible benefits to host communities.

4.1.1 Cambodia

The Kingdom of Cambodia, also known as the Khmer Empire, obtained independence from France in 1953. It is located in the southern portion of the Indochina Peninsula and is bordered by Thailand in the west/northwest, Gulf of Thailand in the west, Vietnam in the east and southeast, and Laos in the north and northeast. About 75% of central Cambodia is covered by a level basin that is bordered by the Mekong River and the Tonle Sap Lake. To the southwest of the basin, the Cardamom and Dangrek Ranges are located, with the last being a famous and well known slope that runs through the Thai border to the north. The coastline has a small plain faced by several offshore islands. Cambodia has a population of more than 15.8 million people (Japan, 2016). The main ethnic majority are the Khmer, who account for about 94% of the population, 3% are Chinese and 2.3% are Cham-Malays, while the rest are a mixture of small ethnic minorities such as Lao, Kola, Thai and Vietnamese. Cambodia's official language is Khmer and the entire native population speaks it, even though the population equally speak some French and Chinese

In November 27, 2001, the Bill and Melinda Gates Foundation held consultations on the proposal for a test of oral tenofovir in phase III trials in four countries including Cambodia, presented by Family Health International (FHI). In January 2003, the University of California, San Francisco (UCSF), provided a one-week training programme in Phnom Penh on "Ethical issues in research: Human subjects". The Ministry of Health stakeholders, members of the Ethical Review Board of Cambodia, some sex workers and non-governmental groups attended this training. On February 28, 2003, the UCSF's Committee on Human Research Institutional Review Board gave a one-year approval of the protocol. On 1 July 2003, the Cambodian Ethical Review Board gave a one-year approval of the preliminary protocol. On July 23, 2003, trial staff held their first community information session about the trial. On the March 4, 2004, they held their second Cambodia Community Advisory Forum.

Starting in July 2004, growing pressure from activist-affiliated non-governmental organisations and activist groups influenced the Prime Minister of Cambodia, Hun Sen, to end the clinical trial preparations on August 13, 2004 (Forbes & Mudaliar, 2009). The Prime Minister said that "Cambodian people are not waste, and Cambodia is not a waste bin", and that researchers should to take their trial somewhere else (Bridget G Haire, 2011). The spectacular protest against the Cambodian trial at the XV International AIDS Conference in Bangkok, Thailand, caught the attention of the world's media (Chase & Naik, 2004).

The Women's Network for Unity (WNU), the union of Cambodian sex workers, led these protests. The WNU, which was launched in June 2000 by a group of sex workers, is a

union of Cambodian sex workers, which functions as an autonomously registered non-governmental organisation (NGO). The WNU “provides a foundation for support and builds solidarity and self-empowerment among sex workers. The network provides a space for women to come together, share ideas and discuss the collective challenges they face” (Forbes & Mudaliar, 2009) . The network consist of more than five thousand general members from the sex worker population in Cambodia (Forbes & Mudaliar, 2009). In July, some WNU members attended the 2004 International AIDS Conference held in Bangkok and, for the first time, they were introduced to ACT-UP Paris (an international AIDS activist group that is stationed in many countries). On 14 July, during a Gilead-sponsored satellite session on antiretroviral, ACT-UP (AIDS Coalition to Unleash Power) Paris and members from different sex worker advocacy organisations supported the WNU to put up an extremely visible protest against Gilead Sciences (the manufacturer of tenofovir). This massive protest brought tenofovir to the front of the public’s attention, with some key reasons for the protest cited as the following:

- ***Purported insufficient prevention counselling offered to participants by the investigators of the study.*** This insufficient prevention counselling was regarded by the activists as a move by the researchers to allow research participants to become HIV positive during the trial since it was impossible for researchers to assess the impact of the test intervention without having a given number of participants becoming HIV positive during the trial.
- ***The partial participation of the targeted communities in the design of the trial protocol.*** A preliminary protocol was submitted to the Ethical Review Board of Cambodia in March 2003; this was subsequently approved. It was only after the approval was obtained that the local population and different stakeholders were involved to help in the design of the different parts of the study (beside the protocol), such as the participant recruitment strategy. With this approval, the team was able to start formative research for the trial. They started employing staff and building the trial’s clinic and laboratory capacity. They equally began deliberating on the protocol in focus groups and interviews with stakeholders, made up of potential participants, local government officials, police and brothel owners.

Dr. Margery Lazarus (a medical anthropologist at the University of California’s San Francisco campus) started the social research phase of the trial by carrying out detailed assessment of the risk behaviours, working conditions, demographics, and sexual and economic networks of the female sex workers in Phnom Penh. She also assembled a team of bilingual Cambodian staff, with selection criteria principally

based on their communication and qualitative research skills. Through her work with them, she assessed promising locations for the clinic site, designed and assessed the lucidity of informed consent materials and established a recruitment strategy for potential participants. Conclusively, the local population and different stakeholders were not involved in the design and conception of the study protocol, but were involved only after the study approval on aspects such as the design and development of participant recruitment strategy (Ahmad, 2004; Cohen, 2004; Forbes & Mudaliar, 2009; James, 2004).

- ***The limited community involvement in designing the study.*** The University of California, San Francisco, and the University of New South Wales, in order to carry out this trial, sub-contracted the Cambodian National Centre for HIV/AIDS, Dermatology and STDs (NCHADS), and Dr. Ly Penh Sun of NCHADS served as co-principal investigator for the trial. Several foreign and local staff at NCHADS played key roles in the design of the trial. Dr. Ly Penh Sun and Dr. Vonthanak Saphonn led the NCHADS trial team. Dr. Mean Chi Vun, who served as the director of NCHADS, was very instrumental to the development of the trial. Conclusively, only staff at NCHADS participated in the design of the study protocol, while the rest of the participant community and different stakeholders such as the activists were never involved (Forbes & Mudaliar, 2009).
- ***The non-provision of medical services and insurance to those who seroconverted in the course of the study or who suffered adverse events that were connected to the trial drug*** (Ahmad, 2004). Research participants, together with the activists, called for long-term insurance against possible trial-related side effects. This was based on the fact that the impact of tenofovir on HIV-negative people, especially over the long term, was unknown; thus, activists thought it wise that the risk taken by participants be offset by some kind of long-term insurance protection. Activists demanded 20-30 years of medical coverage for all expenses produced by the possible side effects of tenofovir. Unfortunately, the NIH funding guidelines permits but does not require the use of NIH funds to cover insurance and medical insurance to treat participants suffering from trial-related adverse events and, in cases where this is allowed, then such insurance must end at the close of the trial. This NIH policy prohibition for health insurance coverage brought frustration to the research participants and the activists, and they perceived this refusal as a tacit admission that tenofovir might have serious and lasting health implications and thus triggered an end to the study.

- ***Compensation to research participants.*** Above all, the subject of compensation was exceptionally problematical as US law does not permit research sponsors to offer free medical care or compensation to research participants harmed in clinical research studies (Steinbrook, 2006). Though medical care was to be provided to participants from the research facility, for the duration of the trial only, it was never clear whether potential participants comprehended this and, at the end, there was no delivery of medical care after the trial, besides the access to ART for seroconverts through the then-fledgling national programme. It was unclear whether the preferential access to ART for trial participants was well understood by the trial participants, as access to ART was mentioned as a main matter by the activists. Adverse effects of the study drug, particularly potential severe long-term ones, became a very important centre of interest for the potential study participants. This was so because most of these participants were the main source of income for their families, who depended on the fitness of the commercial sex workers for work (Bridget G Haire, 2011).

4.1.2 Cameroon

Cameroon is a former German colony (1884–1914), which later became a United Nations mandated territory with part trusted to France and the other part to Great Britain. The territory of Cameroon covers approximately 475,650 km², with the country having close to 4,591 km of land borders and 590 km of coastline along the Atlantic seaboard. Land borders include Chad in the northeast, Gabon and Equatorial Guinea in the south, Nigeria in the west, the Central African Republic in the east, and Congo (World Health Organization (WHO), 2016). The country is multi-ethnic, multi-cultural and multi-lingual, with English and French (dominant in eight out of ten regions) being the official languages. Cameroon has an estimated population of 22 million inhabitants (BUCREP, 2015)

On September 8, 2001, FHI was visited by Gilead Sciences to discuss the role of tenofovir in a research study on HIV prevention and on October 6, 2001, FHI and Gilead visited the Bill and Melinda Gates Foundation to share their interest in conducting a tenofovir PrEP trial. On November 27, 2001, the Gates Foundation held an ethical consultation with experts on the proposal by FHI to test oral tenofovir in a phase III trial in Cameroon, (McGrory, Irvin, & Heise, 2009) and in October 2002, one year after the initial PrEP proposal was submitted to the Gates Foundation, the sum of US\$6.5 million was awarded by the Gates Foundation to FHI. This award was a three-year grant for a multinational clinical trial to evaluate the efficacy and safety of tenofovir as a method for the prevention of HIV.

In January 23, 2003, the Minister of Public Health in Cameroon authorised FHI to carry out the tenofovir trial in Cameroon, and in September 2003, formative research began in Douala. Specifically, this formative research had three main objectives:

- **Site preparation assessment:** This involved the preparation of the site for the implementation of the clinical trial and this comprised five components:
 - To identify areas with high HIV transmission and assess the cohesiveness of the targeted population of the community,
 - Assess options for community consultations,
 - Assess the processes of informed consent and the approach to be used to ensure that the words used in the informed consent booklets were suitable to the local language(s). They also had to identify proper communication strategies for the explanation of complicated concepts in the consent form (e.g. the use of a placebo) and to explore strategies for the evaluation of participants' understanding,
 - Verify whether FHI's assumptions about care and treatment were compatible with the values upheld by the stakeholders of the community. Identify available resources for HIV care and potential referral sites for participants and their families. Obtain communities' input on how to address broader access to care issues,
 - Assess the degree to which stigma was a problem, and its potential consequences, and to develop a strategy to decrease the risk of stigmatisation. Devise strategies to monitor for social harms throughout the trial and evaluate the existing prevention programmes, HIV-risk behaviours and unmet HIV-prevention requirements, to inform the guidelines for HIV-risk reduction counselling.

'Community' in this context was defined as persons associated with the 'high-transmission areas' in Douala, where the research was to be conducted, and it included potential trial participants and partners of potential trial participants. It also included local HIV-prevention and care providers and community gatekeepers.

- **Acceptability assessment:** This entailed assessing the suitability of tenofovir as an HIV-preventive intervention amongst potential participants for the trial, their spouses, potential clients, providers and stakeholders of the community.

- **Research outcomes assessment:** This entailed identifying obstacles and facilitators to the conversion of the results of the trial for use in HIV-prevention programmes (McGrory et al., 2009).

Starting from late September 2003, FHI first held an expert meeting with members of the community, with professionals working in the HIV field and with at-risk populations. Anecdotal information obtained here was combined with epidemiological information to ascertain potential areas of high transmission. Next, the formative research team studied 25 sites in six areas of high transmission and then carried out 53 detailed interviews. The study conducted five focus groups discussions with women at high risk for HIV; community members; people living with HIV; health care providers; public health officials; and NGOs working with women's issues or HIV, or both. The same research team embarked on collecting onsite participant remarks to find out more about the health beliefs, knowledge of HIV/AIDS, the community, past experience with research, attitudes toward prevention research, level of comprehension and to substantiate information from the expert meetings (Nyama, Mack, MacQueen, Guest, & Namey, 2006).

The Protection of Human Subjects Committee, which is the FHI's IRB, initially approved the study in August 2003, requiring a yearly renewal. On December 16, 2003, the Cameroon National Ethics Committee approved the study protocol for one year and this committee later renewed its approval on December 11, 2004. On April 22, 2004, the study was authorised to be carried out in Douala by the Littoral Provincial Delegation of the Ministry of Public Health, and the trial commenced enrolment in July 2004 (McGrory et al., 2009). The trial was stopped by the Minister of Public Health, Urbain Olangena Awono, in February 2005, spurred on by protests both from within and outside the country.

The protests were driven by ACT-UP Paris, who collaborated with Réseau Éthique Droit et Santé (REDS), an AIDS activist group that is based in Cameroon. These protesters underscored their worries with how the study was conducted. Specifically the activists were concerned with:

- ***The level of HIV prevention counselling offered to participants.*** They complained that there were only five counsellors available to counsel a total of 400 women.
- ***The absence of the provision of female condoms (the trial provided only male condoms).*** Participants (sex workers) were provided only with male condoms; it was not always easy for them to negotiate with and convince their clients to use them.

- ***Purported inadequate preparation for the provision of ART.*** In fact, the informed consent documents unequivocally indicated that the trial would not offer ART to seroconverts. This position was taken based on the notion that offering ART in a context where it was not generally obtainable would represent an undue inducement (McGrory et al., 2009). Trial seroconverts were to be sent to existing NGO sources for treatment; the ACT-UP Paris activist group portrayed these as overburdened with the provision of treatment for 10,000 persons, while 40,000 persons were already in need (ACT-UP Paris, 2008).

Besides these essential worries, Mills and colleagues (E. J. Mills et al., 2005) reported extensive, incorrect allegations that the investigators were intentionally injecting participants with HIV, and or that the tablets themselves contained the HI virus. These allegations came from a claim advanced by the ACT-UP Paris activist group, that the offering of insufficient counselling for HIV prevention to participants was a back-door approach for augmenting the infection of HIV in the cohort. Activists alleged that the FHI investigators deliberately let participants become infected and equally offered insufficient counselling, as the 400 participants were being counselled by only five counsellors (UN Integrated Regional Information Networks, 2005). In addition, activists alleged that the volunteers were vulnerable participants whose rights were being exploited and that the participants in the trial were not fully informed of the risks involved in the trial.

Another important issue raised was that the majority of these sex workers were uneducated and did not have a good mastery of the English language and could only understand a small amount of French. Despite this, informed consent forms and protocol documents were provided only in English, only one of the two official languages of Cameroon. In addition, participants mistook the drug for a vaccine against AIDS and thus became more careless in their behaviour and thus more susceptible to the disease.

Activists and ethicists also argued about the controversial subject of the standard of care in randomised trials (Singh, 2004); according to the protocol of FHI, participants who seroconverted in the course of the trial were to be offered state-of-the-art ARV therapy, with the likelihood of continuing treatment after the close of the trial. The activist groups argued that treatment ought to be offered in a similar way as would be offered in developed countries

Activists argued that, if the primary endpoint of the trial was infection, then counselling participants on safe sexual behaviour lessens the probability of discovering an effect. As a result

of this, activists alleged that investigators had a conflict of interest between attaining the standards of human rights and acquiring scientific data

Undesirable and incorrect messages were reiterated, and on several occasions, overstated in various media spaces. For example, a radio programme reported that the research team was giving money “to young girls on tenofovir in an operation (surgery) that will last for two hours” (Mack et al., 2010).

Finally, activists in general supported a wider conception of the term ‘the community’ than the FHI understood it during this trial. A wider range of international and national civil society groups today regard themselves as stakeholders in the research business. For example, activists were amazed to learn that national and local associations of persons living with HIV and AIDS were not consulted and were not aware of the ongoing research (McGrory et al., 2009).

As a response to these allegations, the government of Cameroon created an independent committee of inquiry to look into the trial, and finally, the Public Health ministry decided that the trial could not continue in the absence of frequent reporting and an official authorisation of the satellite trial clinic as a study site (Atatah, 2005, February 24). The committee of inquiry later proposed that the trial be resumed after the administrators of the trial had addressed the issue of reporting and equally obtained site authorisation. However, in July 2005, FHI announced that the suspension was too long to permit the trial to continue and hence decided to close the trial. In August 2005, FHI announced its decision to close down the Douala study site, justifying the decision on the basis that the participants had been off the study drug for such a lengthy period that any scientific outcomes produced would have been considered invalid.

CHAPTER FIVE

RESULTS AND DISCUSSION

Human participants are frequently involved in health research and because of this, it is very important to respect the safety, rights and well-being of these participants, thus ensuring that the research is carried out within the best possible scientific rigour so as to generate reliable data to inform policies in health. In response to this call, numerous guidelines have been established to foster good research practices. Some of these guidelines include: the Declaration of Helsinki, the guidelines of the Council for International Organizations of Medical Sciences (CIOMS) and the World Health Organization (WHO), and the International Council for Harmonization (ICH) Good Clinical Practice (GCP) guidelines. This chapter presents, among the different international guidelines, those that discuss the issue of CE, since the focus of this thesis is on CE in health research. The chapter further pinpoints within the different international guidelines the approaches that were being implemented during the tenofovir trial and those that were not being implemented.

5.1 Existing international guidelines and their position on CE

5.1.1 Nuremberg Code

The Nuremberg Code, made up of ten principles, was one of the first ethical guidelines on ethical research to be produced. The code was primarily written by jurists in 1947 as a result of the Nuremberg trials in which Nazi physicians were accused of shockingly cruel research on prisoners in concentration camps in the course of the Second World War. Between November 1945 and October 1946, an American military tribunal was assembled to listen and examine the charges against 23 administrators and physicians of German nationality (Bloxham, 2013). During the period of the “Doctors’ trial”, as it was commonly referred to, eyewitnesses presented situations of dreadful medical research involving participants involuntarily, the greatest number of whom were imprisoned Poles, Jews, Roma and Russians. These participants were exposed to exceedingly merciless research, which led to many of them dying, while survivors were left with severe scars and other malformations. The judgement decision (August 19, 1947) comprised a part titled “Permissible Medical Experiments” which became known as the ‘Nuremberg Code’ (Nuremberg Code, 1949) and addressed fundamental issues involving human participants in medical experimentation. The Nuremberg Code is the basis for many successive endeavours for defining and codifying protections for human participants in medical

experimentations. The Nuremberg Code does not address the issue of community participation/engagement.

5.1.2 Declaration of Helsinki

The World Medical Association (WMA) recommendations that guide medical practitioners in biomedical research involving human participants were received at the 18th World Medical Assembly in Helsinki, Finland, in June 1964 (Rickham, 1964); these are commonly referred to as the Declaration of Helsinki. This declaration has undergone seven revisions, with the most recent at the October 2013 General Assembly. The document, produced by physicians as opposed to jurists (who drafted the Nuremberg Code), is in some ways an enhancement of the Nuremberg Code in that it provides more details on the principles listed in the Nuremberg Code and offers practical guidelines for carrying out experimentation with humans. It also brings a balance between people's concerns and the benefits to the general public (LaFrance, 2007). The Declaration of Helsinki stipulates the information that researchers must give to participants prior to obtaining consent. This information includes all anticipatable benefits and risks, information that the participant may pull out of the study at any given time and lastly, a comprehensive literature of the protocol of the research.

The Declaration of Helsinki acknowledges the possibility for unintentional compulsion that might result from the investigator/participant relationship and suggests that under such conditions, an investigator aside from the principal investigator should obtain the consent of the participant. One of the key necessities postulated in the Declaration of Helsinki was the appointment of independent committees for reflection, observations and guidance on research protocols (Basic principle 2) (World Medical Association (WMA), 1964) and, ever since, research ethics committees have been set all up over world and remain a key authority instrument for human participant research. The Declaration of Helsinki does not address the issue of community participation/engagement.

5.1.3 Belmont Report

In 1974, the US Congress established the National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research in response to the Tuskegee Syphilis study. This commission was created to identify the fundamental ethical principles which should guide research with human participants and to create guidelines that would ensure that research was carried out in conformity with the principles. The National Commission met at the Smithsonian Institution's Belmont Conference Centre in 1976 and from there, successive

discussions arose, the end product of which was the creation of a document entitled *Ethical principles and guidelines for the protection of human subjects of research*. This document has three sections and is usually referred to as the ‘Belmont Report’(1978) .

The first section details the limits between research and medical practices. The next section institutes three fundamental ethical principles: ‘respect for persons’, ‘beneficence’ and ‘justice’. The third section offers three requirements for applying the general principles to research conduct. These include informed consent, risk and benefits assessment and participant selection. The Belmont Report does not address the issue of community participation/engagement.

5.1.4 Council for International Organizations of Medical Sciences (CIOMS)

In understanding of the situations of developing countries with respect to the application of the Nuremberg Code and Declaration of Helsinki, in 1982, the Council for International Organizations of Medical Sciences (CIOMS) and the World Health Organization (WHO) issued the *Proposed international guidelines for biomedical research involving human subjects* (2016) . These guidelines recognise the supremacy of local concerns in the evaluation of the research protocol objectives. For the very first time in an international guideline, the issue of compensation being required for persons injured in the course of the research is dealt with. The CIOMS guidelines also draw attention to the issue of community engagement in health research, denoting in Guideline 7 that research activities must be centred on a continuous commitment to sustain community engagement. The focus is on communication of the research purpose, design and possible risks and benefits to the individuals and the society as a whole, as well as the elicitation of the concerns and preferences of the community.

5.1.5 Federal Regulations – Office for Human Research Protections (OHRP)

Since 1966, the National Institutes of Health (NIH) has had a policy concerned with protecting human participants in research. That policy did not, however, have any regulatory standing until 1974 when the National Research Act (NRA) became operational. Research ethics committees were created as part of the NIH policy. The NRA created the commission which established the Belmont Report and in reaction to suggestions in this report, in 1981, passed legislation codifying the Department of Health and Human Services rules and regulations on biomedical research with human participants. The regulations by NIH appeared in Title 45, Part 46 of the Code of Federal Regulations (45 CFR 46), with amendments in 1983 and 1991 (Office for Human Research Protections, 2014). All rules which were approved in

1980 pertaining to clinical trials are regulated by the Food and Drug Administration (FDA) in 21 CFR Parts 50 and 56. The Office for Protection from Research Risks (OPRR) was established inside NIH as part of NRA. In 2000, the OPRR was restructured as a Health and Human Services department-level agency, with a new name: the Office for Human Research Protections (OHRP).

The regulations (45 CFR 46) consist of four parts. A is entitled the ‘Common Rule’ and consists mostly of the regulatory facets of protecting research participants, defining research as “a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalisable knowledge” (Federal Register, 1991).

The core components of the Common Rule include: requirements for assuring compliance by research institutions; requirements for researchers obtaining and documenting informed consent; requirements for institutional review board (IRB) membership, function, operations, review of research, and record keeping (Code of Federal Regulations, 2009).

Parts B, C and D of 45 CFR 46 are designed specially to protect pregnant women, research with foetal tissue, children and prisoners. Institutional review boards reviewing studies that involve these particular participants must pay due consideration to whether they are really needed for the research. Unless their involvement is highly relevant to the study, these participants will normally be exempted from participating. All grants awarded by the Department of Health and Human Services require compliance with 45 CFR 46 or 21 CFR 50 from the receiving institution. Neither the Common Rule (part A) nor parts B, C or D address the issue of community participation/engagement.

5.1.6 The Nuffield Council on Bioethics (NCOB)

The Nuffield Council on Bioethics is a self-governing organisation that was created in 1991 for the examination of ethical issues that arise from developments in biomedicine and biology with a focus on supporting the development of public policies and promoting public knowledge. When the NCOB identifies an aspect of key ethical concern, it forms a multidisciplinary working party, with members who have the relevant know-how to scrutinise and report on the concern. Since 1991, the NCOB has been one of the United Kingdom’s leading bioethics advisory organisations. It has released more than a dozen reports and discussion papers on the ethical scope of several medical and biological technologies. These reports have been very influential in shaping public policies and bioethical debates, both within and outside of the UK.

The NCOB 2002 report does address the issue of community participation/engagement. It emphasises the relevance of involving and consenting with the community in the conduct of research in developing countries. Paragraph 6.19 states that, “[i]n some societies, it would be considered culturally inappropriate for researchers to ask individuals to participate in research without consulting the community or permission from community leaders” (Nuffield Council on Bioethics, 2002). Paragraph 6.20 further cautions that “to seek consent from an individual without seeking assent from leader(s) of the community, or creating public acceptance of research, may be considered disrespectful and may harm the relationships within that community and between a community and researchers” (Nuffield Council on Bioethics, 2002).

5.1.7 International Council for Harmonisation (ICH) – Good Clinical Practice (GCP) guideline (1996)

The ICH GCP E6 guideline (ICH GCP) was issued in 1996 (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), June 10, 1996) and was established by the WHO after consulting with the national drug regulatory agencies in developed countries. Its goal was to set internationally acceptable principles that can be applied to clinical trials. This is to help provide shared acknowledgement of data between concerned countries, which then contributes to the harmonisation process of results. The ICH GCP guideline, which is intended to be relevant to all phases of the development of a drug, can equally apply to the concept of biomedical research. The ICH GCP guideline does not address the issue of community participation/engagement.

5.1.8 Other guidelines positions on community engagement

In 2000, UNAIDS put forward a complete set of guidelines for HIV vaccine trial implementation, which referenced the participation of the community. Guidance point 5 states that: “Community representatives should be involved in an early and sustained manner in the design, development, implementation, and distribution of results of HIV vaccine research” and this includes the establishment of “a continuing forum for communication and problem-solving” (UNAIDS, 2000)p. 19). In the revised and enlarged 2007 *Ethical considerations in biomedical HIV prevention trials*, the language was altered with the need for CE to gain increased attention:

Guidance point 2: Community participation

To ensure the ethical and scientific quality and outcome of proposed research, its relevance to the affected community, and its acceptance by the affected community, researchers and trial sponsors should consult communities through a transparent and meaningful participatory process which involves them in an early and sustained manner in the design, development, implementation, monitoring, and distribution of results of biomedical HIV prevention trials (UNAIDS/WHO, 2007).

Also in 2007, UNAIDS and AVAC (a global advocacy organisation that is involved in HIV-prevention research) co-authored the *Good participatory practice guidelines for biomedical HIV prevention trials* (GPP-HIV) (UNAIDS/AVAC, 2007). The GPP-HIV were updated in 2011 and include guiding principles for the implementation of stakeholder and community engagements (UNAIDS/AVAC, 2011). The Community and Stakeholder Engagement Workgroup of the Critical Path to TB Drug Regimens (CPTR) worked in partnership with AVAC in adapting the GPP-HIV for tuberculosis (TB) research. This collaboration led to the releasing of the *Good participatory practice guidelines for TB drug trials* (GPP-TB) in 2012 (Boulanger et al., 2013; Critical Path to TB Drug Regimens (CPTR/AVAC), 2012). The importance of CE as a cross-cutting ethical issue for TB, malaria and HIV vaccine trials was highlighted in a report from a consultation meeting in 2009, a meeting funded by the Ethics, Law and Human Rights Collaborating Centre of the WHO/UNAIDS African AIDS Vaccine Programme (Mamotte, Wassenaar, Koen, & Essack, 2010).

Also in 2009, the HIV Prevention Trials Network's (HPTN) ethical guidance on research (Rennie, Sugarman, & HPTN Ethics Working Group, 2009) in Guidance point 3, openly addressed CE as an ethical obligation: "In order to ensure that HPTN research is appropriate as well as scientifically and ethically sound, relevant communities will be engaged in a meaningful process that will help guide the research from protocol development to dissemination of results".

CE has been clearly integrated into some national guidelines broadly, as well as specifically for clinical research and HIV research, respectively. One of such national guidelines has been the South Africa's National Health Research Ethics Council's *Guidelines for good practice in the conduct of clinical trials involving human participants* (Department of Health, 2006). These guidelines recommend that ethics committees require investigators to provide plans on consulting with the representatives of the community and also expect communities to be involved during the research and in the dissemination of research results. The guidelines also remark on the relevance of engaging communities in research, especially

when they are considered ‘vulnerable’, and they explicitly demand CE in population-focused HIV-prevention research design and conduct (Department of Health, 2006). The guidelines further recommend that funders create community advisory groups (CAGs) for research conducted at the level of the community (e.g. vaccine trials) as a way to “ensure adequate consultation with civil organisations that may exist within affected communities at all phases of the trial” (Department of Health, 2006)29).

Due to some deficiencies related to the application of these existing guidelines, in 2004, Emanuel and colleagues at the US National Institutes of Health (NIH), drawing on the different guidelines and principles, proposed an ethical framework for minimising exploitation and promoting collaborative partnerships as indispensable to the ethical justification of research in low- and middle-income countries (LMICs). Some of these deficiencies included the fact that some ethical guidelines could be interpreted in multiple ways, while others appeared paradoxical or relied on unspecified but debatable ethical principles (Emanuel et al., 2004).

This Emanuel et al. (2004) ethical framework consists of eight key principles/benchmarks for the planning and review of biomedical research in LMICs, and these have now become accepted and used worldwide. While the different existing guidelines appear as official documents for reference in the conduct of biomedical research, it should be known that the ethical framework by Emanuel et al. is non-official although it assists researchers in the research process. These eight principles/benchmarks include:

1. ***Collaborative partnership/community engagement:*** Collaborative partnerships have to be established between the researchers and the community in which the research is being carried out as this collaboration will help in ensuring that the research conducted is acceptable, offers valuable benefits to the community and is responsive to the actual health problems of the community.
2. ***Social or clinical significance:*** All research should be carried out with the sole purpose of providing responses to one or more questions of potential social/clinical significance, since any research which lacks value provides no basis for the justification of risks to the participants.
3. ***Scientific merit:*** Research must be designed and carried out with adequately meticulous methods if such research is to be scientifically validated. Planned studies that lack scientific validity are unethical. This is because they expose participants to risk in research having no potential to generate generalised knowledge.

4. ***Fair selection of study participants:*** Research participants must be fairly selected in accordance with the scientific goals of the study, avoiding redundant involvement of vulnerable groups.
5. ***Favourable risk-benefit ratio:*** All research must have a favourable risk-benefit ratio that minimises risks to participants and aligns the risks to the potential benefits for participants and the value of the obtainable knowledge from the research.
6. ***Informed consent:*** Eligible adults must not be enrolled in research studies if they have not been sufficiently informed about the study and they have accepted to take part. For research involving incompetent adults and children, informed permission by parents or other substitute decision makers, is imperative.
7. ***Independent ethical review:*** To ensure participant protection and public accountability, all research studies must obtain eventual and continuous protocol review by a committee that is comprised of individuals who are independent of the research.
8. ***Respect for recruited study participants and study population:*** Research must be carried out in a way which respects the rights and protects the welfare of enrolled participants.

Collaborative partnership is ascertained as the main factor in the ethical framework for multinational research developed by Emanuel and colleagues. The respect of a “community’s values, culture, traditions, and social practices” is regarded as an important aspect in building successful partnerships. Table 3 presents a tabular representation of the different international guidelines and their positions on CE.

Table 3: The positions of the different international guidelines on CE

Source	Reference to community engagement (CE)	Cameroon	Cambodia
Council for International Organizations of Medical Sciences (CIOMS, 2016)	“The process must be completely collaborative and transparent and should involve a wide variety of participants such as patients and consumer organisations, community leaders and representatives, relevant NGOs and advocacy groups, regulatory authorities,	This was not applied here as the was no CAB creation as well as advocacy groups as required.	This was not applied here as the was no CAB creation as well as advocacy groups as required

government agencies and community advisory boards.”		
“The community should participate when feasible in the actual discussion and preparation of the research protocol and documents.”	Members were never involve in the preparation of the study protocol	Members were never involve in the preparation of the study protocol
“Engagement at the earliest opportunity. Before a study commenced, the community from which participants will be recruited should, when feasible, be consulted about their research priorities, preferred trial designs, willingness to be involved in the preparation and conduct of the study.”	Members were only engaged after the study protocol and designed had been agreed upon by the research team.	Members were only engaged after the study protocol and designed had been agreed upon by the research team.
“Community engagement should be an ongoing process, with an established forum for communication between researchers and community members.”	The community was only engaged once during formative research and not continuous as recommended	The community was only engaged once during formative research and not continuous as recommended
“Community members should be invited to assist in the development of the informed consent process and documents to ensure that they are understandable and appropriate for potential participants.”	Members never involved in the development of any working document for the study with the informed consent inclusive	Members never involved in the development of any working document for the study with the informed consent inclusive
“Any disagreements that may arise regarding the design or conduct of the research must be subject to negotiation	This was not the case as concerns with regards the research design	This was not the case as concerns with regards the research design

	between community leaders and the researchers.”	could not be adjusted as the study protocol had already been agreed upon	could not be adjusted as the study protocol had already been agreed upon
Ethics of research related to healthcare in developing countries (Nuffield Council on Bioethics, 2002)	“Consultation is required with the community before individuals are approached about research.”	Community members were consulted through formative research prior to project commencement	Community members were consulted through formative research prior to project commencement
	“Permission from the leader(s) of the community is required before any research is discussed with the community or individuals.”	During formative research, permission were obtained from the community leaders prior to project commencement	During formative research, permission were obtained from the community leaders prior to project commencement
	“A comprehensive care package should be agreed upon through a host/community/sponsor dialogue, which reaches consensus prior to initiation of a trial.”	A comprehensive care package was never agreed upon given room for misunderstanding on what this ought to be.	A comprehensive care package was never agreed upon given room for misunderstanding on what this ought to be.
Ethical considerations in HIV-preventive vaccine research (UNAIDS, 2000)	“To ensure the ethical and scientific quality of proposed research, its relevance to the affected community, and its acceptance by the affected community, community representatives should be involved in an early and sustained manner in the design, development, implementation, and distribution of results of HIV vaccine research.”	Community members were not involved in an early and sustained manner as they were only involved after protocol design had been done and the absence of CABs implied the was no sustainably engaged.	Community members were not involved in an early and sustained manner as they were only involved after protocol design had been done and the absence of CABs implied the was no sustainably engaged.

	<p>“Involvement of community representatives should not be seen as a single encounter, nor as one-directional. The orientation of community involvement should be one of partnership towards mutual education and consensus-building regarding all aspects of the vaccine development programme. There should be established a continuing forum for communication and problem-solving on all aspects of the vaccine development programme.”</p>	<p>Communities were only engaged once as against the continuous approach recommended</p>	<p>Communities were only engaged once as against the continuous approach requested</p>
	<p>“Members of the community who may contribute to a vaccine development process include representatives of the research population eligible to serve as research participants, other members of the community who would be among the intended beneficiaries of the developed vaccine, relevant non-governmental organisations, persons living with HIV/AIDS, community leaders, public health officials, and those who provide health care and other services to people living with and affected by HIV.”</p>	<p>None of the community members were destined to benefit from the developed vaccine as it was never disclosed or any formal agreement upon</p>	<p>None of the community members were destined to benefit from the developed vaccine as it was never disclosed or any formal agreement upon</p>

	<p>“To ensure the ethical and scientific quality and outcome of proposed research, its relevance to the affected community, and its acceptance by the affected community, researchers and trial sponsors should consult communities through a transparent and meaningful participatory process which involves them in an early and sustained manner in the design, development, implementation, and distribution of results of biomedical HIV prevention trials.”</p>	<p>Community members were never consulted in a sustained manner and were never also engaged early in the design and development of the study protocol as recommended</p>	<p>Community members were never consulted in a sustained manner and were never also engaged early in the design and development of the study protocol as recommended</p>
<p>Ethical considerations in biomedical HIV-prevention trials (UNAIDS/WHO, 2007)</p>	<p>“The nature of community involvement should be one of continuous mutual education and respect, partnership, and consensus-building regarding all aspects of the testing of potential biomedical HIV prevention products. A continuing forum should be established for communication and problem-solving on all aspects of the HIV prevention product development programme”</p>	<p>The engagement process was never continuous given the absent of CABs which a great structure for sustainable engagement.</p>	<p>The engagement process was never continuous given the absent of CABs which a great structure for sustainable engagement.</p>
	<p>“As more groups and people define themselves as part of the interested community, the concept needs to be broadened to civil society so as to include advocates, media, human rights organisations, national institutions and governments, as well as researchers and community representatives from the trial site”</p>	<p>The aspect of community here appeared very limited as it did not include civil societies and activist groups.</p>	<p>The aspect of community here appeared very limited as it did not include civil societies and activist groups</p>

HIV Prevention Trials Network (HPTN) Ethics Guidance for Research (Rennie & Sugarman, 2009)	“In order to ensure that HPTN research is appropriate as well as scientifically and ethically sound, relevant communities will be engaged in a meaningful process that will help guide the research from protocol development to dissemination of results.”	Community were never engaged from the protocol development as the community was only engaged after the protocol development	Community were never engaged from the protocol development as the community was only engaged after the protocol development
Guidelines for good practice in the conduct of clinical trials in human participants in South Africa (DOH, 2006)	“Studies require active community participation in both the design and the monitoring of the intervention is to be applied to a population.”	Community were never engaged in the design of the study	Community were never engaged in the design of the study

From Table 3, it can be noticed that there is no reference to the Nuremberg Code, the Declaration of Helsinki, the Belmont Report, the Federal Regulations – Office for Human Research Protections (OHRP) and the ICH-GCP guideline (1996). This is because nothing is mentioned in these guidelines about the concept of community engagement in research. Secondly, the table does not mention the Emanuel et al. (2004) guidelines which specifically address the issue of CE. This is because the table seeks to capture just pertinent guideline phrases that give specific instructions on how community engagement should be implemented throughout the conduct of a study, which was not the case for Emanuel et al. guidelines.

Out of all the current guidelines, the CIOMS guidelines offer the clearest directives, as far as implementing CE is concerned. Many guidelines require that representatives and leaders of communities, advocacy groups and relevant NGOs be included in the CE process (CIOMS, 2016; UNAIDS, 2000; UNAIDS/WHO, 2007). Noteworthy from the tenofovir trials in Cambodia and Cameroon was that this requirement was not taken into consideration, as can be seen from the protests that led to the closure of the two sites: activist groups who complained (amongst other things) of having been left out in the process.

Many of these guidelines recommend that the community partake in the discussion, preparation and design of the protocol of the research (CIOMS, 2016; DOH, 2006; Rennie & Sugarman, 2009; UNAIDS, 2000; UNAIDS/WHO, 2007) but again this was never done in Cambodia and Cameroon; the communities were consulted only after the study protocol had

been designed and ethical clearance had been obtained for the study. In addition, it is also required that the community should be engaged at the earliest opportunity during the conduct of the study (CIOMS, 2016; UNAIDS, 2000; UNAIDS/WHO, 2007), but this was not the case for either study.

The guidelines also recommend that CE should be an ongoing process (CIOMS, 2016; UNAIDS, 2000; UNAIDS/WHO, 2007). In the tenofovir trials, FHI never set up a CAB or any other structure for ongoing community involvement. CIOMS (2016) advises that any disagreement that may arise with regard to the research design or conduct must be subjected to negotiation between community leaders, but this was not done, as disagreements between researchers and potential participants were never addressed prior to the commencement of the study.

Finally, while the NCOB (2002) requires that the ‘care package’ be agreed upon prior to initiation of a trial, this appeared not to have been fulfilled, as this was one of the reasons for the protest by the activist groups in both countries. It should be noted, however, that the requirement that consultation with the community before engaging with the individuals and obtaining permission from community leaders prior to the commencement of the study (NCOB, 2002) was very much respected on both sites.

5.2 Concerns about how community engagement is practiced in some cases/projects

In spite of very clear objectives directed to the production of socially responsible knowledge, CE practices are not yet innately democratising, as engagement in health research is at times used for instrumental gains – ensuring smooth research operations, increasing consent and study enrolment, gaining community buy-in – instead of achieving a wider revolution in the politics and power dynamics of research.

The researcher included this section in the research so as to demonstrate that poor CE is not only noticeable in the tenofovir trials but that it cuts across most health-related research studies requiring CE. Below are some shared characteristics and concerns in the way community engagement is practiced in some cases.

The first concern centres on the late engagement of the community in research projects. Most researchers only engage the community after the ethical and administrative clearance for the study have been obtained. International guidelines from CIOMS, the Nuffield Council on Bioethics and the National Institute of Allergy and Infectious Diseases have all emphasised the

significance of early CE, as this permits the local population to express their views on the research and facilitates the researcher to develop culturally appropriate policies geared towards the study.

Community engagement requires a broad dialogue with main stakeholders that should commence long before the implementation of the research study, and discussions with community leaders and members should dwell on topics such as the protocol formulation, design of the study, methodology of the study, timelines and plans for the implementation of the study, and the potential risks for participants.

This form of community dialogue is very important for several reasons:

- First, it provides communities with the opportunity to share opinions on the design of the study. Sharing their perspectives helps to reduce the challenges that might be related to the recruitment and retention of study participants (2012).
- It facilitates the community's ownership of the processes of the research and its outcomes. This helps to expedite the translation of research findings into action, a regular challenge affecting several research ventures (Barkin & Schlundt, 2011).
- It promotes the comprehension of the research concepts and lessens myths and therapeutic misconceptions centred around the research (Folayan, Mutengu-Kasirye, & Calazans, 2009; Miller et al., 2010).
- It reinforces the process of informed consent via the dissemination of information on research risks, benefits and goals.
- It equally helps to inculcate the respect of social norms and practices of potential volunteers (Kamuya, Marsh, Kombe, Geissler, & Molyneux, 2013; UNAIDS/AVAC, 2011).
- Finally, in some circumstances, community dialogues are required to negotiate and reach consensus on the standard-of-care and prevention packages for participants of the study. This is so because, most times, views about these may differ between trial volunteers and researchers (Strauss et al., 2001).

When researchers carry out community dialogues, they should expect that some elements of the design of the study might be considered undesirable or unethical by members of the community and thus be ready to negotiate and correct any potential differences that dissatisfy members of the community. One of the key motives for the early stopping of the tenofovir trials was that such discords between the potential participants and researchers were never resolved. This process of active CE before, during and after research helps in promoting respect for the

community, and in strengthening credibility and trust of researchers (Diallo et al., 2005; Kamuya et al., 2013); furthermore, it gives the community a sense of ownership and augments their interest in the process of the research (Kamuya et al., 2013). Early engagement is a vital component if one wants to achieve meaningful engagement.

The next concern raised in the way community engagement is done in some cases is that, even after the researchers engage very early with the community on the conception of the protocol, the inputs of the community members are not often taken into consideration or inserted into the protocol design. Limiting engagement to an exercise of consultation without the concession of power to lay people, ‘tokenism’ on the part of researchers, or failure to act on the community’s propositions means that engagement can prove a disheartening encounter for certain members of the community and might eventually result in participation withdrawal. Evidence from a number of studies (Bickerstaff & Walker, 2005; Chau, 2007; Cole, Hickman, & McCoulough, 2004) thus suggests that people are less likely to find CE a positive practice where consultation is the principal approach used by experts. This is because, in this method, no real power to effect change is relinquished to the members of the community.

Another concern in the way community engagement is done in some cases is that the community is only engaged during the early stages of the study and, as the research continues, there is no further discussion and engagement with the community members. Communities need to be engaged throughout the life of a research study and not only during community meetings when participant recruitment is ongoing, and then again during results dissemination, as this does not constitute meaningful CE.

Moreover, there is concern about the nature of stakeholders included during community engagement. Many times, the government is left out in this very important exercise, and the researchers focus just on the community of concern. Government appears to be the least engaged and least informed though it plays a vital part in regulations. The engagement of the national government facilitates consultations about the design and protocol of the research. Negotiations between the sponsor and the government are also critical in ensuring future access to developing therapies at affordable prices, when needed (Milstien & Kaddar, 2006), and such negotiations are properly made during the design of the study through the memoranda of understanding signed between the both parties.

Another key concern in the way community engagement is done in some cases is at the level where research protocols are conceptualised. In the discipline of international research, it has been shown that the conceptions for research are mostly established by the partners from the north, with partners of the south only acting as collaborating investigators. These southern

partners are engaged as an effort to “build their capacity to learn something useful to science and/or practice in the north” (Engel & Keijzer, 2006, p. 16).

Finally, a concern with the way community engagement is done in some cases is that most research studies engage the community in a rush and do not give ample time for the community to receive and assimilate the information they are given by the researcher; the researchers also do not give the community enough time to reflect on the information and give their feedback and proposals on certain modifications to the protocol at the time of conception. This has many potential repercussions.

There are several studies that have ended in failure, like the ones on the tenofovir trials in Africa and Southeast Asia, as a result of rushing the CE process. The community initially agreed to participate but then realised as the study progressed that the explanation was not very clear at the beginning, which means there was not enough time invested in engagement with the community. Community engagement is often a very lengthy process that can be influenced by time constraints, finances, and resources (Israel et al., 2006). Researchers most often only start to engage the community after they have obtained approval for the study to begin. Sometimes, the time between obtaining ethics committee approval for the protocol of the research and commencing the implementation of the research is too limited; this may render impracticable and unattainable the extensive community consultation required to constitute reasonable dialogue between the communities and researchers.

5.3 CE as practiced by both trials: Deviating from the international guidelines requirements

FHI was under serious pressure from the public health and scientific communities to start the trials quickly, as a mutual sense of urgency existed to look for a strategy for HIV-infection prevention in women. Some FHI researchers agreed that the relative speed with which the research was designed and developed had an impact on the degree of community preparation and the degree to which formative research findings could be integrated into the processes of the trial (McGrory et al., 2009). A wide range of organisations and persons with different standpoints remarked that the process of developing and implementing the tenofovir PrEP trials was hasty (McGrory et al., 2009). The urgency to start the trial was motivated at least partially by the potential that tenofovir appeared to have to provide another method for the prevention of HIV infection. The need for a new method for HIV prevention was critically important given that the development of the other biomedical interventions for HIV prevention, like the

microbicides and vaccines, were experiencing some challenges. Nevertheless, this sense of urgency reduced the time to properly prepare, consult and involve the community before the commencement of the clinical trial (McGrory et al., 2009).

The approach by FHI to community consultation in Cameroon entailed the carrying out of qualitative research in the community of the trial site. FHI defined the ‘community’ as the women who were potential participants in the trial and the main actors around them such as their families and partners, policymakers, and AIDS and health care providers in the Douala areas where the women worked and lived. This approach was intentionally designed by FHI and its partners to allow them get, first hand, the points of view of the actual and potential trial participants.

However, this approach had a problem because, in this situation, these women at high risk for HIV were never well ‘structured’ or represented (in terms of in a recognised and registered legal organisation or association), and other organisations which might have represented the interest of the women did not surface throughout the preparatory work. The researchers used this approach because they thought that it was wise for these potential female participants to speak for themselves and that they could act as their own activists. It was later acknowledged by one of the researchers that this might have been very unrealistic (McGrory et al., 2009) . Thus, it is noted that FHI never engaged in a wider civil society or stakeholder consultative process and never put in place a CAB or other framework for continuous community involvement in the trial implementation.

Another issue raised by the tenofovir trials was: What comprises an appropriate and meaningful community involvement and consultation? The decision by FHI to use formative research as their only form of community consultation in the trial proved to be problematic. While formative research might have offered a methodological technique into gaining understanding of the preferences and views of the potential participants, it was incapable of meeting the wider community’s need for dialogue or provision for an assembly for addressing the problems raised. The total absent of CABs, or other official structures, implied that no system was put in place for continuous discussion or resolution of conflicts when hurdles emerged. Furthermore, since FHI prioritised data integrity, and had guaranteed participants of confidentiality during the formative process, they were unable to disclose to the activists who had and had not been consulted in this process. This made the activists question the process even more.

In the two trial countries, the processes of community consultation and outreach were undertaken after the development of the protocol and the decision to carry out the research had

been reached. Community consultation was conceived as a dialogue on how to carry out the research rather than on where or whether to do the research in the first instance. The activists alleged that the organisation of community ‘consultation’ or ‘advisory’ processes after the development of the research protocol was not meaningful, as this runs contrary to the various established international guidelines on health research.

From our findings above, it could be observe that the study based her argument on the theory of social justice using the ladder of citizen participation by Arnstein (1969). From the findings it is illustrated that the types of engagement used here were those identified by Arnstein to be near the foot of this ladder (weaker forms of citizen engagement) of participation which comprises information dissemination about the planned research. The researcher’s interest here was to advocate on the social justice perspective, which is founded on empowerment of the community members, which is required for genuine and meaningful engagement and which could be obtained at the topmost part of the ladder.

CHAPTER SIX

CONCLUSION: LESSONS LEARNT FROM THE TENOFOVIR TRIAL

In the Cameroon case, the criticisms raised during the tenofovir trial comprised of: insufficient numbers of study staff; the provision inadequate information about risks to participants; insufficient access to care for seroconverts; and an unethical design of the study, where participants “were being used as guinea pigs to promote the interest of the drug’s manufacturers” (Stone, Stones, Saxena, & Chandhiok, 2005, December 5-6). In particular, the inadequate community involvement was emphasised.

In the Cambodia case, advocates contend that it was improper for western interests to take advantage of commercial sex workers for an investigational drug trial, particularly in a poor country like Cambodia. They went further to ask why they could not conduct the trial in high-risk populations in Europe and the US. Activists even blamed the researchers for providing insufficient HIV-prevention counselling in order for the study to attain good results. The use of placebo pills created some misunderstanding and misrepresentation, as the researchers were criticised for giving ‘dummy pills’ to some women. Activists demanded medical insurance coverage to trial participants for trial-related injuries. This insurance coverage was to span between 30 and 40 years. Lastly, activists highlighted the inadequate involvement of the community in the planning of the study. Properly involving the community would indeed have been one tool which, used effectively and efficiently, may have been capable of resolving most or even all of the problems noted (Stone et al., 2005, December 5-6).

Given this missed opportunity, this chapter discusses some of the lessons that can be learned from the premature closure of the tenofovir trials that could help other trials to do better next time.

6.1 Involve stakeholders in the development of the protocol

In both countries, community outreach and consultations only took place after the protocol development and the decision to conduct the study had been made. The first lesson is that researchers should involve community and national stakeholders in the development of the protocol. They should seek critical inputs during the trial design, a stage where changes could still be incorporated. Consulting with civil societies after the protocol has been developed will be regarded as cosmetic.

6.2 Expand outreach efforts

Outreach efforts have to go beyond the immediate geographic surrounding of the trial, to involve provincial, national and perhaps international collaborators. Activists were shocked to know, for instance, that local and national organisations of persons living with HIV and AIDS were not aware of the research and were never consulted (Forbes & Mudaliar, 2009; McGrory et al., 2009).

6.3 Consultation rather than formative research

While very important, it was not right for FHI to substitute other open processes of consultation with formative research. They included substantial formative research as a means of systematically gathering community inputs in order to help inform the design of the trial, and more significantly, to inform how the results of the trial could contribute to effective and adequate prevention interventions. Rather, they should have gone for a consultative process with the local organisations, civil societies, targeted community and potential participants, which entailed gathering all the elementary materials required for the design of the study protocol. It should be known, however, that this consultative process is seen to have taken place between FHI and the Bill and Melinda Gates Foundation on the designing of the proposal and also with the Gates Foundation and experts on the ethics of the proposal by FHI. The intention of the researcher here is not to discard formative research as a tool for engaging the community but rather to acknowledge the tool and point to its limitation of meeting the wider community's need for dialogue or provision for an assembly for addressing the problems raised by the community

6.4 Mechanisms for dealing with issues

Trials need specific procedures and processes for dealing with enquiries, queries and grievances. Ideally, this mechanism should involve an informed impartial actor who has sufficient facts, documentation, and access, for instance, a CAB or community liaison. This structure could receive and elevate the community concerns, as well as facilitate communication to ensure that questions and concerns raised by the community members are adequately responded to, and in a timely manner. It is noted from the study that the absence of an appropriate platform where disagreements between researchers and potential participants could be discussed and resolved was highlighted as one of the main reasons for the ending the tenofovir trials. Events in both countries highlighted the crucial importance of researchers

heeding the inputs obtained from members of the community, participants and other stakeholders, in order to deal with their trial-related concerns. The experience made clear that controversy in the community undermines a trial as surely as scientific setbacks.

6.5 Create mutual frameworks

It is also learned from this study that there is a need for researchers, activists and governments to create a mutual framework for future collaboration, acknowledged standards and practical methods for engaging the community. The Good Participatory Practice guidelines developed by UNAIDS and AVAC provide a worthy initial step, and efforts to establish whether these guidelines could be made prescriptive for HIV-prevention trials ought to be encouraged.

6.6 Educate communities on research processes

Mechanisms should be put in place for ensuring that communities obtain a broad understanding on what clinical trials are and on the different processes involved. This would permit community members to be well informed to participate in dialogue and negotiations about a particular trial. Communication strategies should be designed with the main intention of gaining a mutual comprehension between the communities and the researchers, each of whom might differ in interpretations and expectations. These strategies must clearly acknowledge that the usage of scientific language is not always the ‘right’ way to discuss research. More so, being uneducated/illiterate should not equate to an incapability to understand and criticise scientific procedures.

Trials with greater success rates, for example, the Navrongo Community Health and Family Project (CHFP) in Kassena-Nankana Ghana (Binka et al., 1995), the Majengo Observational Cohort Study (MOCS) based on disadvantaged female sex workers in Nairobi, Kenya (Bandewar et al., 2010), an epidemiological investigation of some 7-12 year olds in South Korea, and an Autism Spectrum Disorder (ASD) detection program for 18-36 month old Zulu-speaking children in South Africa (Grinker et al., 2012), are those that permit both community stakeholders and researchers to share ideas amongst themselves on prime research concerns, as well as on how best to carry out the trials. The community that is treated and respected as a partner, instead of as a ‘research participant’ supplier, is likely to be more supportive of a planned research study.

Although the process of CE cannot absolutely guarantee a collaboration that is free of disagreement or free of substantial differing opinions (Newman, 2006), it has been proven that productive discussions with community stakeholders can lead to benefits for both the researcher and the communities. Examples of this come from a study on the locally appropriate standard of care in the context of a phase III vaginal microbicide trial in Mwanza City, northwest Tanzania (Vallely et al., 2009), a multicentric clinical trial in Mexico to evaluate the efficacy of the Human Papilloma Virus (HPV) vaccine in young men who have sex with men (MSM) (Gutiérrez-Luna et al., 2009), and the breastfeeding, antiretroviral, and nutrition (BAN) study which is an unblinded clinical trial in Lilongwe, Malawi, focusing on the safety and efficacy of antiretroviral and nutritional interventions to reduce mother-to-child transmission of HIV during breastfeeding (Corneli et al., 2007).

Discussing with the community stakeholders can help in refining the procedures for the study to suit the local situation. This will go a long way towards maximising the research results (Corneli et al., 2007; Gappoo et al., 2009; Gutiérrez-Luna et al., 2009; Vallely et al., 2009) and may lead to more effective participant recruitment and enrolment approaches, enhanced rates of retention and sturdier adherence to the study. CE necessitates broad discussion with important stakeholders and should commence before the implementation of the trial. Discussion should focus on issues like the design of the study, how the therapies or vaccines should be handled, plans and timelines for the implementation of the study, potential risks to the participants of the trial, as well as on how state powers could be involved in the designing and execution of the trials in a manner that protects the study participants' rights (Folayan et al., 2015).

6.7 Use flexible means to work with communities

Another important lesson from these tenofovir trials is that, besides the respect for the highest ethical and scientific standards, it is also very important for researchers to work directly with the community through various flexible means like the local ethical review boards and the CABs, which work as a surrogate for the community. The absence of CABs in both studies accounted for a great loss in terms of the potential success of the studies, despite their scientific validity.

6.8 Allow sufficient time for community engagement

Another important lesson learnt is that researchers should provide sufficient time and resources for CE, as engaging with community stakeholders in an iterative and collaborative way entails a significant investment. Talking about the priorities of a research study and trying to determine the best strategies needs time, effort and financial support, and so institutions and sponsors must be ready to finance activities that can develop the conduct of a trial and lay the foundation for constructive partnerships in the future (Miller et al., 2010). The urgency of the HIV-prevention research must be continually balanced against the apparent cost-cutting measure of proceeding too quickly. HIV-prevention trials demand substantial and prolonged engagement with the community and national stakeholders prior to the initiation of a trial (Forbes & Mudaliar, 2009) .

CE is gradually being acknowledged as an important constituent of the ethical conduct of biomedical HIV-prevention trials, and the *Good participatory practice guidelines in biomedical HIV prevention trials (GPP)* (UNAIDS/AVAC, 2007) provide the primary series of global guidelines to outline in-depth steps to ensure appropriate CE within the framework of biomedical HIV-prevention trials. The GPP guidelines are designed for implementers and trial funders, and they pinpoint key principles for the basis of relationships between community stakeholders and trial entities; for example, they include principles such as transparency, research literacy, respect, and ethical and scientific integrity. The GPP guidelines are sufficiently broad to deal with the differences in trial sites around the world but explicit enough to provide an appropriate outline to ease successful implementation of main activities (Miller et al., 2010)

The GPP are based on the same ethical principles of transparency, accountability, respect and beneficence that underlie all good clinical practice; however, a distinctive feature of the GPP guidelines is that they can be used as an instrument for assessing efficient collaborative procedures by trials sponsors, researchers and community stakeholders (Miller et al., 2010).

The speed and the level of sponsoring at which research is presently carried out preclude most research associations from having either the resources or the time to participate in training activities. However, developing the host community's research literateness, (typically from the base up) is very important in ensuring their capacity to engage efficiently with the process of the research (Forbes & Mudaliar, 2009). As the GPP guidelines point out, devoting the effort and time needed to engage the trial host community “through genuine, transparent, meaningful

participatory processes” is not only an ethical obligation but also an essential contributor to the research quality (UNAIDS, 2007).

6.9 Plan for adequate funding

Another important lesson is that sponsors and funders of projects should allocate adequate funding for intensive community engagement activities, as it is very costly to properly engage the community in every stage of the project. The more time it takes to engage with the community, the more cost this entails (D. Burns, Heywood, Taylor, Wilde, & Wilson, 2004). Most funders shy away from meaningful CE because of this additional cost involved.

6.10 Need for continued engagement between all stakeholders

Lastly, the PrEP trials in both countries are case studies of clinical trials that were reviewed and approved by several ethics committees, but later found undesirable by certain community stakeholders (Miller et al., 2010). Experiences from these trials advise that it can no longer be assumed that all planned research studies that require wide-ranging community recruitment should be executed exactly as established by both the researchers and IRB, with the exclusion of the community in concern. The right case scenario will be for the communities, together with the researchers and IRBs, to work together to determine whether a specific study is suitable or not at a certain time and location.

6.11 Conclusion

In conclusion, the cost of the lack of CE in the tenofovir trials was both financial and in terms of lost opportunity. Limited resources for exceedingly costly public-interest health research were wasted, and reputations of individuals, organisations and institutions were damaged. Other independent observers and researchers even interrogated the trustworthiness and rightfulness of research on new HIV-prevention technologies itself, and animosity was fostered among AIDS community stakeholders, all of whom express a profound pledge to work to end the epidemic. In addition, the early stopping of the trials was a strong message conveyed to potential government allies that backing for clinical trials could be scandalous and might even be an incitement for political disaster. Moreover, maybe most embarrassingly, the research company lost credibility among trial participants and communities who had every historic motive to be cynical about drug research studies and their benefits, yet at the same time badly needed the new HIV-prevention approach.

Maybe the most significant lesson to be acquired from these experiences is that government authorities, study community members, activist groups, investigators, sponsors and participants must enthusiastically and genuinely engage at all trial stages. This is to ensure that the study is carried out in a way that is respectful and beneficial to the participants without taking away the scientific validity of the study.

Given these developments, it is hoped that researchers will embrace this new direction (meaningful community engagement rather than just superficial community engagement) as one potential way to enhance trial successes and improve the ethical conduct of their research.

It will be wrong to conclude from this research that genuine and meaningful CE may altogether totally address the concerns raised during the two trials and that CE is the only remedy required for hitch-free clinical trials. Conversely, what this research seeks to demonstrate or argue is that, CE could go a very long way towards averting several of the probable glitches that could otherwise occur without meaningful and genuine CE measures and mechanisms being put in place. It appears curious to an independent observer that researchers and funders are willing to spend millions of dollars on the protocol design, building of facilities, clinical training, product development, etc., but leave the core processes of CE mainly to trial and error.

CE must be regarded not only as an ethical requirement but also as a prerequisite, which helps to avoid future conflicts and problems that might lead to early closure of a trial. It should be known that nobody wins when a trial is discontinued for reasons that are non-scientific. For everyone to win in a research study of this magnitude, the researcher suggests that such regrettable situations in research studies could be prevented if all research stakeholders spend the appropriate resources and time required to develop the kind of common trust on which collaborative partnerships can be founded. As established by the tenofovir trials, failure to genuinely and meaningfully engage with the community might come at significant scientific cost, but early and continued CE can stop this from occurring.

From the above analysis, the researcher's quest to demonstrate how inadequate CE might come at considerable scientific cost, whereas early, sustained and meaningful CE could contribute greatly to research through the understanding of the root causes of the early stop of the trials through the answering of three main questions proof useful in addressing the great concern of rethinking CE in health research. Specific questions aimed at understanding the complexity that surrounds the concept of "community", the detailed procedures used for engaging the different populations helped in generating useful insights and lessons for future

researchers and every stakeholder in the research domain on the appropriate approach to adopt and avoid with regards to CE in health research.

REFERENCES

- Abolafia, M. Y. (2010). Narrative construction as sensemaking: How a central bank thinks. *Organization Studies*, 31(3), 349-367.
- ACT-UP Paris. (2008). Act Up-Paris and treatment activism. Retrieved from <http://www.actupparis.org/article3482.html>
- Ahmad, K. (2004). Trial of antiretroviral for HIV prevention on hold. *Lancet. Infectious Diseases*, 4, 597.
- Arnstein, S. (1969). A ladder of citizen participation. *Journal of the American Institute of Planners*, 35 (34), 216-224.
- Aslin, H., & Brown, V. (2004). Towards whole of community engagement: A practical toolkit. Retrieved from <https://www.mdba.gov.au> › default › files › archived › mdbc-S-E-reports
- Atatah, C. (2005, February 24). Douala AIDS drug controversy: Medical council says trials violated ethical norms. *The Post*. Retrieved from http://www.postnewsline.com/2005/02/strongdouala_ai.html
- Aurpibul, L., & Puthanakit, T. (2015). Review of tenofovir use in HIV-infected children. *Pediatric Infectious Disease Journal*, 34(4), 383-391.
- Bandewar, S. V., Kimani, J., & Lavery, J. V. (2010). The origins of a research community in the Majengo Observational Cohort Study, Nairobi, Kenya. *BMC public health*, 10(1), 630.
- Barkin, S., & Schlundt, D. (2011). The challenge facing translation of basic science into clinical and community settings to improve health outcomes. *Environmental Health Perspectives.*, 119(10), a418.
- Barry, J. A., Robichaud, G., Bokhart, M. T., Thompson, C., Sykes, C., Kashuba, A. D., & Muddiman, D. C. (2014). Mapping antiretroviral drugs in tissue by IR-MALDESI MSI coupled to the Q Exactive and comparison with LC-MS/MS SRM assay. *Journal of the American Society for Mass Spectrometry*, 25(12), 2038-2047.
- Benatar, S., Bhoola, K., Cleaton-Jones, P., de Klerk, W., du Toit, D., Herman, A., . . . Van Wyk, C. W. (2007). *Guidelines on ethics for medical research : General principles (4th ed) Book 1: General Principles including research on children, vulnerable groups, international collaboration and epidemiology*: Cape Town Medical Research Council.
- Bhatt, A. (2010). Evolution of clinical research: A history before and beyond James Lind. *Perspectives in Clinical Research.*, 1(1), 6-10.
- Bickerstaff, K., & Walker, G. (2005). Shared visions, unholy alliances: Power, governance and deliberative processes in local transport planning. *Urban Studies*, 42(12), 2123-2144.
- Binka, F. N., Nazzar, A., & Phillips, J. F. (1995). The Navrongo community health and family planning project. *Studies in Family Planning.*, 26(3), 121-139.
- Birkus, G., Wang, R., Liu, X., Kutty, N., MacArthur, H., Cihlar, T., . . . McDermott, M. (2007). Cathepsin A is the major hydrolase catalyzing the intracellular hydrolysis of the antiretroviral nucleotide phosphonoamidate prodrugs GS-7340 and GS-9131. *Antimicrobial agents and chemotherapy*, 51(2), 543-550.
- Black, R. J. (1997). Animal studies of prophylaxis. *American Journal of Medicine*, 102(5), 39-44.
- Blanche, M. T., Blanche, M. J. T., Durrheim, K., & Painter, D. (2006). *Research in practice: Applied methods for the social sciences*: Juta and Company Ltd.

- Bloxham, D. (2013). From the international military tribunal to the subsequent Nuremberg proceedings: The American confrontation with Nazi criminality revisited. *History*, 98(332), 567-591. doi:10.1111/1468-229X.12024
- Boulanger, R. F., Seidel, S., Lessem, E., Pyne-Mercier, L., Williams, S. D., Mingote, L. R., . . . Lavery, J. V. (2013). Engaging communities in tuberculosis research. *Lancet Infectious Diseases*, 13(6), 540-545.
- Brizi, A., Filibeck, U., Kangaspunta, K., & O'Neil, A. L. (2009). Biomedical Research in Developing Countries: The Promotion of Ethics, Human Rights, and Justice.
- Brunton, G., Thomas, J., O'Mara-Eves, A., Jamal, F., Oliver, S., & Kavanagh, J. (2017). Narratives of community engagement: a systematic review-derived conceptual framework for public health interventions. *BMC Public Health*, 17(1), 944.
- BUCREP. (2015). Bureau Central de Recensement et d'Etude de la population au Cameroun. Retrieved from <https://www.osidimbea.cm/entreprises/a-capitaux-publics/bucrep/>
- Burns, A. C., & Bush, R. F. (2003). Marketing research—online research applications (4th ed.): Upper Saddle River, NJ: Prentice Hall.
- Burns, D., Heywood, Taylor, M., Wilde, P., & Wilson, M. (2004). *Making community participation meaningful: A handbook for development and assessment*. Bristol: Policy Press.
- Cáceres, C. F., Koechlin, F., Goicochea, P., Sow, P. S., O'Reilly, K. R., Mayer, K. H., & Godfrey-Faussett, P. (2015). The promises and challenges of pre-exposure prophylaxis as part of the emerging paradigm of combination HIV prevention. *Journal of the International AIDS Society*, 18, 19949.
- Calder, B. J., Philips, L. W., & Tybout, A. M. (1983). Beyond external validity. *Journal of Consumer Research*, 10(1), 112-124.
- Calder, B. J., Phillips, L. W., & Tybout, A. M. (1982). The concept of external validity. *Journal of Consumer Research*, 9(3), 240-244.
- Cargo, M., & Mercer, S. L. (2008). The value and challenges of participatory research: Strengthening its practice. *Annual Review of Public Health*, 29, 325-350.
- Centers for Disease Control and Prevention. (2019, 20- February). CDC/HIV PrEP. Retrieved from <https://www.cdc.gov/hiv/basics/prep.html>
- Chalmers, I. (2003). The James Lind initiative. *Journal of the Royal Society of Medicine*, 96(12), 575.
- Chase, M., & Naik, G. (2004). Key AIDS study in Cambodia now in jeopardy. *Wall Street Journal*. Retrieved from <https://www.wsj.com/articles/SB109225657391788941>
- Chasela, C. S., Hudgens, M. G., Jamieson, D. J., Kayira, D., Hosseinipour, M. C., Kourtis, A. P., . . . Ahmed, Y. I. (2010). Maternal or infant antiretroviral drugs to reduce HIV-1 transmission. *New England Journal of Medicine*, 362(24), 2271-2281.
- Chau, R. C. (2007). The involvement of Chinese older people in policy and practice. *Aspirations and expectations*. York, UK: Joseph Rowntree Foundation.
- Chen, L., & Berlinguer, G. (2001). *Health equity in a globalizing world: Challenging inequities in health: From ethics to action*. New York, NY: Oxford University Press.
- Clinical and Translational Science Awards Consortium Community Engagement Key Function Committee Task Force on the principles of community engagement (CTSA). (2011). *Principles of community engagement* (2 ed.). Bethesda, MD: National Institutes of Health.
- Code of Federal Regulations. (2009). Federal policy for the protection of human subjects ('Common Rule'). Retrieved from <https://www.hhs.gov/ohrp/regulations-and-policy/regulations/common-rule/index.html>
- Cohen, J. (2004). Cambodian leader throws novel prevention trial into limbo. *Science*, 305(5687), 1092-1093.

- Cole, I., Hickman, P., & McCoulough, E. (2004). *The involvement of NDC residents in the formulation of strategies to tackle low demand and unpopular housing*: Sheffield: Centre for Regional Economic and Social Research, Sheffield Hallam University.
- Connor, E. M., Sperling, R. S., Gelber, R., Kiselev, P., Scott, G., O'Sullivan, M. J., . . . Jacobson, R. L. (1994). Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. *New England Journal of Medicine*, 331(18), 1173-1180.
- Cooper, H. M. (1998). *Synthesizing research: A guide for literature reviews* (3rd ed. Vol. 2). Thousand Oaks, CA: Sage.
- Corneli, A. L., Piwoz, E. G., Bentley, M. E., Moses, A., Nkhoma, J. R., Tohill, B. C., . . . Duerr, A. (2007). Involving communities in the design of clinical trial protocols: the BAN Study in Lilongwe, Malawi. *Contemporary Clinical Trials*, 28(1), 59-67.
- Council for the International Organizations of Medical Sciences (CIOMS). (2016). *International ethical guidelines for biomedical research involving human subjects*. Geneva, Switzerland. Retrieved from <https://cioms.ch> > wp-content > uploads > 2017/01 > WEB-CIOMS-Ethical...
- Craddock, S. (2004). *AIDS and ethics: Clinical trials pharmaceuticals and global scientific practice*.
- Critical Path to TB Drug Regimens (CPTR/AVAC). (2012). *Good participatory practice guidelines for TB drug trials*. Retrieved from <https://www.cptrinitiative.org> > resources > GPP-TB Oct1 2012 FINAL
- D'Arcy Hart. (1999). A change in scientific approach: From alternation to randomised allocation in clinical trials in the 1940s. *BMJ*, 319(7209), 572-573.
- Dare, M., Schirmer, J., & Vanclay, F. (2008). *A brief guide to effective community engagement in the Australian plantation sector*. Hobart: Cooperative Research Centre for Forestry. Retrieved from <http://www.crcforestry.com.au/publications/downloads/TR181-Dare-community-engagement.pdf>
- Dawson, L., Klingman, K., & Marrazzo, J. (2014). Addressing standards of care in resource-limited settings. *Journal of Acquired Immune Deficiency Syndromes*, 65(0 1), S10-S14.
- Department of Health. (2006). *Guidelines for good practice in the conduct of clinical trials with human participants in South Africa*. Pretoria: Department of Health.
- Department of Health (UK). (2011). *Research governance framework for health and social care*. Retrieved from <https://assets.publishing.service.gov.uk> > uploads > attachment_data > file
- Diallo, D. A., Doumbo, O. K., Plowe, C. V., Wellems, T. E., Emanuel, E. J., & Hurst, S. A. (2005). Community permission for medical research in developing countries. *Clinical Infectious Diseases*, 41(2), 255-259.
- Dickert, N., & Sugarman, J. (2005). Ethical goals of community consultation in research. *American Journal of Public Health*, 95(7), 1123-1127.
- Doumbo, O. K. (2005). Global voices of science: It takes a village: Medical research and ethics in Mali. *Science*, 307(5710), 679-681.
- Ekunwe, E. O., & Kessel, R. (1984). Informed consent in the developing world. *Hastings Center Report*, 14(3), 22-24.
- Emanuel, E. J. (2011). An ethical framework for biomedical research *Oxford textbook of clinical research ethics*, (pp. 123-135). Oxford, UK: Oxford University Press.
- Emanuel, E. J., Wendler, D., & Grady, C. (2000). What makes clinical research ethical? *JAMA*, 283(20), 2701-2711.

- Emanuel, E. J., Wendler, D., Killen, J., & Grady, C. (2004). What makes clinical research in developing countries ethical? The benchmarks of ethical research. *Journal of Infectious Diseases*, 189(5), 930-937.
- Engel, P., & Keijzer, N. (2006). *Research partnerships: Who decides? Review of a design process*. German Development Institute. Retrieved from https://www.die-gdi.de/uploads/media/studie_naar_research_partnerships.pdf
- Ernst, A. A., & Fish, S. (2005a). Exception from informed consent: viewpoint of institutional review boards—balancing risks to subjects, community consultation, and future directions. *Academic Emergency Medicine*, 12(11), 1050-1055.
- Ernst, A. A., & Fish, S. (2005b). Exception from informed consent: Viewpoint of institutional review boards balancing risks to subjects, community consultation, and future directions. *Academic Emergency Medicine*, 12(11), 1050-1055.
- Etzioni, A. (1996). *New golden rule*. New York, NY: HarperCollins Publishers.
- Evans, T. (2001). *Challenging inequities in health: from ethics to action*. Oxford, UK: Oxford University Press.
- Federal Register. (1991). *Federal Register: 56 Fed. Reg. 27889 (June 18, 1991)*. Retrieved from <https://cdn.loc.gov/service/ll/fedreg/fr056/fr056117/fr056117.pdf>.
- Fitzgerald, D. W., Marotte, C., Verdier, R. I., Johnson Jr, W. D., & Pape, J. W. (2002). Comprehension during informed consent in a less-developed country. *Lancet*, 360(9342), 1301-1302.
- Fleischman, A. R. (2007). Community engagement in urban health research. *Journal of Urban Health*, 84(4), 469-471.
- Folayan, Mutengu-Kasirye, L., & Calazans, G. (2009). Participating in biomedical research. *JAMA*, 302(20), 2200-2202. doi:10.1001/jama.2009.1720
- Folayan, Peterson, K., & Kombe. (2015). Ethics, emergencies and Ebola clinical trials: The role of governments and communities in offshored research. *The Pan African Medical Journal*, 22(Suppl 1), 10. doi:10.11694/pamj.suppl.2015.22.1.6216
- Forbes, A., & Mudaliar, S. (2009). Preventing prevention trial failures, A case study and lessons for future trials from the 2004 Tenofovir trial in Cambodia. *Washington, DC: Global Campaign for Microbicides*.
- Foster, M. W., Sharp, R. R., Freeman, W. L., Chino, M., Bernsten, D., & Carter, T. H. (1999). The role of community review in evaluating the risks of human genetic variation research. *American Journal of Human Genetics*, 64(6), 1719-1727.
- Freire, P. (1994). *Pedagogy of hope* (transl) New York, NY: Continuum.
- Friedman, L. M., Furberg, C., DeMets, D. L., Reboussin, D. M., & Granger, C. B. (2010). *Fundamentals of clinical trials* (Vol. 4). New York, NY: Springer.
- Furman, P. A., Fyfe, J. A., St Clair, M. H., Weinhold, K., Rideout, J. L., Freeman, G. A., . . . Mitsuya, H. (1986). Phosphorylation of 3'-azido-3'-deoxythymidine and selective interaction of the 5'-triphosphate with human immunodeficiency virus reverse transcriptase. *Proceedings of the National Academy of Sciences*, 83(21), 8333-8337.
- Gappoo, S., Montgomery, E. T., Gerds, C., Naidoo, S., Chidanyika, A., Nkala, B., & Ramjee, G. (2009). Novel strategies implemented to ensure high participant retention rates in a community based HIV prevention effectiveness trial in South Africa and Zimbabwe. *Contemporary Clinical Trials*, 30(5), 411-418.
- Garg, A. B., Nuttall, J., & Romano, J. (2009). The future of HIV microbicides: Challenges and opportunities. *Antiviral Chemistry and Chemotherapy*, 19(4), 143-150.
- Gomm, R., Hammersley, M., & Foster, P. (Eds.). (2000). *Case study method: Key issues, key texts*. London: Sage.
- Grinker, R. R., Chambers, N., Njongwe, N., Lagman, A. E., Guthrie, W., Stronach, S., . . . Chhagan, M. (2012). "Communities" in community engagement: Lessons learned

- from autism research in South Korea and South Africa. *Autism Research*, 5(3), 201-210.
- Gutiérrez-Luna, A., Angeles-Llerenas, A., Wirtz, V. J., Del Río, A. Á., Zamilpa-Mejía, L., Aranda-Flores, C., . . . Lazcano-Ponce, E. (2009). Strategies and ethical considerations for the recruitment of young men who have sex with men: Challenges of a vaccination trial in Mexico. *Clinical Trials*, 6(4), 365-372.
- Haire, B. G. (2011). Because we can: Clashes of perspective over researcher obligation in the failed PrEP trials. *Developing World Bioethics*, 11(2), 63-74.
- Haire, B. G. (2013). Good, better or best: A study of standards of prevention and care in HIV prevention trials.
- Hammersley, M., Foster, P., & Gomm, R. (2000). *Case study and generalisation*.
- Hart, G., Orr, D., Penn, C., Figueiredo, H., Gray, N., Boehme, R., & Cameron, J. (1992). Effects of (-)-2'-deoxy-3'-thiacytidine (3TC) 5'-triphosphate on human immunodeficiency virus reverse transcriptase and mammalian DNA polymerases alpha, beta, and gamma. *Antimicrobial agents and chemotherapy*, 36(8), 1688-1694.
- Hashagen, S. (2002). *Models of community engagement*. Glasgow : Scottish Community Development Centre. Retrieved from <https://www.lcsansw.org.au> > documents > item
- Heale, R., & Forbes, D. (2013). Understanding triangulation in research. *Evidence-based Nursing*, 16(4), 98. doi:10.1136/eb-2013-101494
- Heppner, P. P., Kivlinghan, D.M. & Wampold, B.E. (1992). *Research design in counselling psychology*. Belmont, CA: Brooks Cole.
- Herman, B. D., & Sluis-Cremer, N. (2012). Molecular pharmacology of nucleoside and nucleotide HIV-1 reverse transcriptase inhibitors *Pharmacology*: IntechOpen.
- Higgins, J. P., & Green, S. (2008). Cochrane handbook for systematic reviews of interventions. doi:10.1002/9780470712184
- International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). (June 10, 1996). *ICH harmonised tripartite guideline for good clinical practice E6(R1)*. Retrieved from <https://www.ich.org> > Guidelines > Efficacy > E6 > E6_R1_Guideline
- Israel, B. A., Krieger, J., Vlahov, D., Ciske, S., Foley, M., Fortin, P., . . . Tang , G. (2006). Challenges and facilitating factors in sustaining community-based participatory research partnerships: Lessons learned from the Detroit, New York City and Seattle Urban Research Centers. *Journal of Urban Health*, 83(6), 1022-1040.
- Israel, B. A., Schulz, A. J., Parker, E. A., & Becker, A. B. (1998a). Review of community-based research: Assessing partnership approaches to improve public health. *Annual Review of Public Health*, 19(1), 173-202.
- Israel, B. A., Schulz, A. J., Parker, E. A., & Becker, A. B. (1998b). Review of community-based research: assessing partnership approaches to improve public health. *Annual review of public health*, 19(1), 173-202.
- James, J. S. (2004). Cambodia stops important tenofovir prevention trial. *AIDS Treatment News*.(403), 4-5.
- Japan, S. (2016). *Population projections for Cambodia, 2008--2030*. Retrieved from <https://www.stat.go.jp> > info > meetings > cambodia > pdf > rp12_ch10
- Jonsen, A. R. (1978). Do no harm. *Annals of Internal Medicine*, 88(6), 827-832.
- Kalipeni, E., Craddock, S., Oppong, J. R., & Ghosh, J. (2004). *HIV and AIDS in Africa: beyond epidemiology*: Blackwell Publishing.
- Kamuya, D. M., Marsh, V., Kombe, F. K., Geissler, P. W., & Molyneux, S. C. (2013). Engaging communities to strengthen research ethics in low-income settings: Selection and perceptions of members of a network of representatives in Coastal Kenya. *Developing World Bioethics*, 13(1), 10-20.

- Karim, Q., Ahrens, H., Arroyo, L., Bakshi, P., Bukusi, E., Cates, W., . . . Duerr, A. (2006). Creating effective partnerships for HIV prevention trials: report of a UNAIDS Consultation, Geneva 20-21 June 2005. *Aids*, 20(6), W1-W11.
- Karim, Q. A. (2013). The global HIV epidemic: current status and challenges. *Current HIV/AIDS Reports*, 10(2), 111-112.
- Karim, Q. A., Karim, S. S. A., Frohlich, J. A., Grobler, A. C., Baxter, C., Mansoor, L. E., . . . Omar, Z. (2010). Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. *Science*, 329(5996), 1168-1174.
- Kerr, D. J., Knox, K., Robertson, D., Stewart, D., & Watson, R. (2008). *Clinical trials explained: A guide to clinical trials in the NHS for healthcare professionals*. London: John Wiley & Sons.
- Kolopack, P. A., & Lavery, J. V. (2017). Informed consent in field trials of gene-drive mosquitoes. *Gates open research*, 1.
- Kothari, C. R. (2004). *Research methodology: Methods and techniques*. New Delhi: New Age International.
- Lada, F. (2016). *On guarding the welfare of clinical trial subjects while promoting novel drug innovation*. Maastricht: Boekenplan.
- LaFrance. (2007). Animal experimentation: Lessons from human experimentation. *Animal Law*, 14(29), 30-52.
- Lakes, K. D., Vaughan, E., Pham, J., Tran, T., Jones, M., Baker, D., . . . Olshansky, E. (2014). Community member and faith leader perspectives on the process of building trusting relationships between communities and researchers. *Clinical and Translational Science.*, 7(1), 20-28.
- Leach, M., & Fairhead, J. (2011). *Being 'with the Medical Research Council': Infant care and the social meanings of cohort membership in Gambia's plural therapeutic landscapes*. Evidence, Ethos and Experiment: The Anthropology and History of Medical Research in Africa. New York, NY: Berghahn Books.
- Lefebvre, C., Eisinga, A., McDonald, S., & Paul, N. (2008). Enhancing access to reports of randomized trials published world-wide—the contribution of EMBASE records to the Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library. *Emerging Themes in Epidemiology*, 5(1), 13.
- Lemke, A. A., Halverson, C., & Ross, L. F. (2012). Biobank participation and returning research results: Perspectives from a deliberative engagement in South Side Chicago. *American Journal of Medical Genetics Part A.*, 158(5), 1029-1037.
- Lilienfeld, A. M. (1982). Ceteris paribus: The evolution of the clinical trial. *Bulletin of the History of Medicine*, 56(1), 1-18.
- Lo, B., & Bayer, R. (2003). Establishing ethical trials for treatment and prevention of AIDS in developing countries. *BMJ*, 327(7410), 337-339.
- Louie, M., Hogan, C., Hurley, A., Simon, V., Chung, C., Padte, N., . . . Di Mascio, M. (2003). Determining the antiviral activity of tenofovir disoproxil fumarate in treatment-naïve chronically HIV-1-infected individuals. *Aids*, 17(8), 1151-1156.
- Lurie, P., & Wolfe, S. M. (1997). Unethical trials of interventions to reduce perinatal transmission of the human immunodeficiency virus in developing countries. *New England Journal of Medicine*, 337(12), 853-856.
- Lwin, K. M., Cheah, P. Y., Cheah, P. K., White, N. J., Day, N. P., Nosten, F., & Parker, M. (2014). Motivations and perceptions of community advisory boards in the ethics of medical research: The case of the Thai-Myanmar border. *BMC Medical Ethics*, 15(1), 12.

- Lyseng-Williamson, K., Reynolds, N., & Plosker, G. (2005). Tenofovir disoproxil fumarate: A review of its use in the management of HIV infection. *Drugs*, 65(3), 413.
- Mack, N., Robinson, E. T., MacQueen, K. M., Moffett, J., & Johnson, L. M. (2010). The exploitation of “exploitation” in the Tenofovir PrEP trial in Cameroon: Lessons learned from media coverage of an HIV prevention trial. *Journal of Empirical Research on Human Research Ethics*, 5(2), 3-19.
- MacQueen, Bhan, A., Frohlich, J., Holzer, J., & Sugarman, J. (2015). Evaluating community engagement in global health research: The need for metrics. *BMC Medical Ethics*, 16(1), 44.
- MacQueen, Eley, N. T., Frick, M., & Hamilton, C. (2018). Using theory of change frameworks to develop evaluation strategies for research engagement: Results of a pre-pilot study. *Journal of the International AIDS Society*, 21, e25181.
- MacQueen, Karim, Q. A., & Sugarman, J. (2003). Ethics guidance for HIV prevention trials. *BMJ*, 327(7410), 340.
- MacQueen, Namey, E., Chilongozi, D., Mtweve, S., Mlingo, M., Morar, N., . . . HPTN 035 Standard of Care Assessment Team. (2007). Community perspectives on care options for HIV prevention trial participants. *AIDS Care.*, 19(4), 554-560.
- MacQueen, K., Shapiro, K., Karim, Q., & Sugarman, J. (2004). Ethical challenges in international HIV prevention research. *Accountability in Research: Policies and Quality Assurance*, 11(1), 49-61.
- Major, C. H., & Savin-Baden, M. (2010). *An introduction to qualitative research synthesis: Managing the information explosion in social science research*. London: Routledge.
- Mamotte, N., Wassenaar, D., Koen, J., & Essack, Z. (2010). Convergent ethical issues in HIV/AIDS, tuberculosis and malaria vaccine trials in Africa: Report from the WHO/UNAIDS African AIDS Vaccine Programme's Ethics, Law and Human Rights Collaborating Centre consultation, 10-11 February 2009, Durban, South Africa. *BMC Medical Ethics*, 11(1), 3.
- Manda-Taylor, L. (2013). Establishing community advisory boards for clinical trial research in Malawi: Engendering ethical conduct in research. *Malawi Medical Journal*, 25(4), 96-100.
- Marshall, P. A., & Rotimi, C. (2001). Ethical challenges in community-based research. *American Journal of the Medical Sciences*, 322(5), 241-245.
- McGrory, E., Irvin, A., & Heise, L. (2009). Research Rashomon: Lessons from the Cameroon pre-exposure prophylaxis trial site. *Washington, DC: Global Campaign for Microbicides at PATH*.
- McMillan, J. H., & Schumacher, S. (2010). *Research in education: Evidence-based inquiry* (7th ed.). Boston, MA: Pearson.
- Medical Research Council. (1948). Streptomycin treatment of pulmonary tuberculosis :Streptomycin trial. *BMJ*, 2(4582), 769-782. doi:10.1002/0470011815.b2a17102
- Meesters, R. J., van Kampen, J. J., Scheuer, R. D., van der Ende, M. E., Gruters, R. A., & Luidert, T. M. (2011). Determination of the antiretroviral drug tenofovir in plasma from HIV-infected adults by ultrafast isotope dilution MALDI-triple quadrupole tandem mass spectrometry. *Journal of Mass Spectrometry.*, 46(3), 282-289.
- Meinert, C. L. (2012). *Clinical trials dictionary: Terminology and usage recommendations*. Hoboken, NJ: John Wiley & Sons.
- Merriam, S. B. (2009). *Qualitative research: A guide to design and implementation*. San Francisco, CA: Jossey-Bass.
- Miller, L., Folayan, M., Allman, D., Nkala, B., Kasirye, L., Mingote, L., . . . Ditmore, M. (2010). How ethical is your clinical trial? *International journal of clinical practice*, 64(9), 1179-1182.

- Mills, E., Rachlis, B., Wu, P., Wong, E., Wilson, K., & Singh, S. (2005). Media reporting of tenofovir trials in Cambodia and Cameroon. *BMC International Health and Human Rights*, 5(1), 6.
- Mills, E. J., Singh, S., Singh, J. A., Orbinski, J. J., Warren, M., & Upshur, R. E. (2005). Designing research in vulnerable populations: Lessons from HIV prevention trials that stopped early. *British Medical Journal*, 331(7529), 1403.
- Milstien, J., & Kaddar, M. (2006). Managing the effect of TRIPS on availability of priority vaccines. *Bulletin of the World Health Organization*, 84(5), 360-365.
- Mitchell, Nakamanya, S., Kamali, A., & Whitworth, J. A. (2002). Balancing rigour and acceptability: The use of HIV incidence to evaluate a community-based randomised trial in rural Uganda. *Social Science & medicine*, 54(7), 1081-1091.
- Mitchell, J. C. (1983). Case and situation analysis. *Sociological Review*, 31(2), 187-211.
- Mitsuya, Matsushita, S., Yarchoan, R., & Broder, S. (1984). *Protection of T cells against infectivity and cytopathic effect of HTLV-III in vitro*. Paper presented at the Princess Takamatsu symposia.
- Mitsuya, Weinhold, K. J., Furman, P. A., St Clair, M. H., Lehrman, S. N., Gallo, R. C., . . . Broder, S. (1985). 3'-Azido-3'-deoxythymidine (BW A509U): an antiviral agent that inhibits the infectivity and cytopathic effect of human T-lymphotropic virus type III/lymphadenopathy-associated virus in vitro. *Proceedings of the National Academy of Sciences*, 82(20), 7096-7100.
- Mofenson, L. M. (2010). Protecting the next generation—eliminating perinatal Hiv-1 infection. *New England Journal of Medicine*, 362(24), 2316-2318.
- Molyneux, C., Peshu, N., & Marsh, K. (2004). Understanding of informed consent in a low-income setting: Three case studies from the Kenyan Coast. *Social Science & Medicine*, 59(12), 2547-2559.
- Molyneux, C., Wassenaar, D., Peshu, N., & Marsh, K. (2005). 'Even if they ask you to stand by a tree all day, you will have to do it (laughter)...!': Community voices on the notion and practice of informed consent for biomedical research in developing countries. *Social Science & Medicine*, 61(2), 443-454.
- Moodley, K. (2002). HIV vaccine trial participation in South Africa—an ethical assessment. *Journal of Medicine and Philosophy*, 27(2), 197-215.
- Morin, S. F., Maiorana, A., Koester, K. A., Sheon, N. M., & Richards, T. A. (2003a). Community consultation in HIV prevention research: a study of community advisory boards at 6 research sites. *JAIDS-HAGERSTOWN MD*, 33(4), 513-520.
- Morin, S. F., Maiorana, A., Koester, K. A., Sheon, N. M., & Richards, T. A. (2003b). Community consultation in HIV prevention research: A study of community advisory boards at 6 research sites. *Journal of Acquired Immune Deficiency Syndromes*, 33(4), 513-520.
- Mott, L., Crawford, E., & Group, N. M. H. S. P. T. f. A. A. C. (2008). The role of community advisory boards in project Eban. *Journal of acquired immune deficiency syndromes (1999)*, 49(Suppl 1), S68.
- National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. (1978). *The Belmont report: Ethical principles and guidelines for the protection of human subjects of research*. Washington, DC: DHEW Publication No. (OS) 78-0014.
- Newman, P. A. (2006). Towards a science of community engagement. *Lancet*, 367(9507), 302.
- Nuffield Council on Bioethics. (2002). *The ethics of research related to healthcare in developing countries*. London: Nuffield Foundation.

- Nuremberg Code. (1949). Trials of war criminals before the Nuremberg military tribunals under control council law (Vol. 10(2), pp. 181-182). Washington: U.S. Government Printing Office.
- Nyiyama, T., Mack, N., MacQueen, K., Guest, G., & Namey, E. (2006). *Addressing HIV prevention trial challenges through socio-behavioural research: Cameroon's tenofovir trial*. Paper presented at the XVI International AIDS Conference in Toronto, Ontario.
- Nyika, A., Chilengi, R., Ishengoma, D., Mtenga, S., Thera, M. A., Sissoko, M. S., . . . Sirima, S. B. (2010). Engaging diverse communities participating in clinical trials: case examples from across Africa. *Malaria journal*, 9(1), 86.
- O'Fallon, L. R., & Dearth, A. (2002). Community-based participatory research as a tool to advance environmental health sciences. *Environmental Health Perspectives*, 110(Suppl 2), 155.
- Office for Human Research Protections. (2014). *Federal policy for the protection of human subjects: 45 C.F.R. § 46*. Retrieved from <http://ohrp.osophs.dhhs.gov/humansubjects/guidance/>
- Ong, S. F. (2012). Constructing a survey questionnaire to collect data on service quality of business academics. *European Journal of Social Sciences*, 29(2), 209-221.
- Pantelic, M., Stegling, C., Shackleton, S., & Restoy, E. (2018). Power to participants: A call for person-centred HIV prevention services and research. *Journal of the International AIDS Society*, 21, e25167.
- Petticrew, M., & Roberts, H. (2006). *Systematic reviews in the social sciences: A practical guide*. Malden, MA: Blackwell Publishing.
- Piantadosi, S. (2005). *Clinical trials: A methodologic perspective* (2nd ed.). New York, NY: Wiley.
- Pratt, B., Lwin, K. M., Zion, D., Nosten, F., Loff, B., & Cheah, P. Y. (2015). Exploitation and community engagement: Can community advisory boards successfully assume a role minimising exploitation in international research? *Developing World Bioethics*, 15(1), 18-26.
- Quinn, S. C. (2004a). Ethics in public health research: Protecting human subjects: The role of community advisory boards. *American Journal of Public Health*, 94(6), 918-922.
- Quinn, S. C. (2004b). Ethics in public health research: protecting human subjects: the role of community advisory boards. *American journal of public health*, 94(6), 918-922.
- Ramjee, G., Coumi, N., Dladla-Qwabe, N., Ganesh, S., Gappoo, S., Govinden, R., . . . Morar, N. (2010). Experiences in conducting multiple community-based HIV prevention trials among women in KwaZulu-Natal, South Africa. *AIDS Research and Therapy*, 7(1), 10.
- Rennie, S., Muula, A. S., & Westreich, D. (2007). Male circumcision and HIV prevention: Ethical, medical and public health tradeoffs in low-income countries. *Journal of Medical Ethics*, 33(6), 357-361.
- Rennie, S., Sugarman, J., & HPTN Ethics Working Group. (2009). *HIV Prevention Trials Network ethics guidance for research*. Retrieved from <https://www.hptn.org> > default > files > HPTNEthicsGuidanceV10Jun2009_0
- Rickham, P. (1964). Human experimentation. Code of ethics of the World Medical Association. Declaration of Helsinki. *British Medical Journal*, 2(5402), 177-177.
- Sarafianos, S. G., Marchand, B., Das, K., Himmel, D. M., Parniak, M. A., Hughes, S. H., & Arnold, E. (2009). Structure and function of HIV-1 reverse transcriptase: Molecular mechanisms of polymerization and inhibition. *Journal of Molecular Biology*, 385(3), 693-713.
- Sateesh, M. K. (2008). *Bioethics and biosafety*. New Delhi: IK International Pvt Ltd.

- Schooley, R. T., Ruane, P., Myers, R. A., Beall, G., Lampiris, H., Berger, D., . . . Cheng, A. K. (2002). Tenofovir DF in antiretroviral-experienced patients: results from a 48-week, randomized, double-blind study. *Aids*, *16*(9), 1257-1263.
- Sharp, R. R., & Foster, M. W. (2000). Involving study populations in the review of genetic research. *Journal of Law, Medicine & Ethics*, *28*(1), 41-51.
- Shattock, R. J., & Moore, J. P. (2003). Inhibiting sexual transmission of HIV-1 infection. *Nature Reviews Microbiology*, *1*(1), 25.
- Singh, J. A. (2004). Standards of care in the antiretroviral rollout world. *Lancet*, *364*(9438), 920-922.
- Singh, J. A., & Mills, E. J. (2005). The abandoned trials of pre-exposure prophylaxis for HIV: what went wrong? *Plos medicine*, *2*(9), e234.
- Slevin, K. W., Ukpong, M., & Heise, L. (2008). Community engagement in HIV prevention trials: evolution of the field and opportunities for growth.
- Squires, K., Pozniak, A. L., Pierone, G., Steinhart, C. R., Berger, D., Bellos, N. C., . . . Toole, J. J. (2003). Tenofovir disoproxil fumarate in nucleoside-resistant HIV-1 infection: a randomized trial. *Annals of Internal Medicine*, *139*(5_Part_1), 313-320.
- Staszewski, S., Miller, V., Rehmet, S., Stark, T., De, J. C., De, M. B., . . . De, M. R. (1996). Virological and immunological analysis of a triple combination pilot study with zidovudine, lamivudine and zalcitabine in HIV-1-infected patients. *AIDS (London, England)*, *10*(5), F1-7.
- Staunton, C., & Moodley, K. (2016). Features: Community engagement for biobanking research: Perspectives from Africa. *Asia Pacific Biotech News*, *20*(2), 14-26.
- Steinbrook, R. (2006). Compensation for injured research subjects. *New England Journal of Medicine*, *354*(18), 1871-1873.
- Stoecker, R. (1991). Evaluating and rethinking the case study. *Sociological Review*, *39*(1), 88-112.
- Stone, A., Stones, W., Saxena, B. N., & Chandhiok, N. (2005, December 5-6). *Workshop on socio-behavioural aspects of microbicide trials for HIV prevention, organised jointly by the Indian Council of Medical Research, New Delhi, and the Microbicides Development Programme, UK*. New Delhi, India.
https://assets.publishing.service.gov.uk/media/57a08c27e5274a31e000102c/Long_Report2.pdf
- Strauss, R. P., Sengupta, S., Quinn, S. C., Goepfing, J., Spaulding, C., Kegeles, S. M., & Millett, G. (2001). The role of community advisory boards: Involving communities in the informed consent process. *American Journal of Public Health*, *91*(12), 1938-1943.
- Swainston, K., & Summerbell, C. (2008). The effectiveness of community engagement approaches and methods for health promotion interventions. Rapid Review Phase 3 (including consideration of. *Methodology*, *17*, 31.
- Tangwa, G. B., & Munung, N. S. (2011). Sprinting research and spot jogging regulation: the state of bioethics in Cameroon. *Cambridge Quarterly of Healthcare Ethics*, *20*(3), 356-366.
- Teddle, C., & Tashakkori, A. (2003). Major issues and controversies in the use of mixed methods in the social and behavioral sciences *Handbook of mixed methods in social & behavioral research* (pp. 3-50). Thousand Oaks, CA: Sage.
- Tindana, P. O., Rozmovits, L., Boulanger, R. F., Bandewar, S. V., Aborigo, R. A., Hodgson, A. V., . . . Lavery, J. V. (2011). Aligning community engagement with traditional authority structures in global health research: A case study from northern Ghana. *American Journal of Public Health*, *101*(10), 1857-1867.

- Tsai, C.-C., Emau, P., Follis, K. E., Beck, T. W., Benveniste, R. E., Bischofberger, N., . . . Morton, W. R. (1998). Effectiveness of postinoculation (R)-9-(2-phosphonylmethoxypropyl) adenine treatment for prevention of persistent simian immunodeficiency virus SIV_{mac} infection depends critically on timing of initiation and duration of treatment. *Journal of Virology*, 72(5), 4265-4273.
- UN Integrated Regional Information Networks. (2005). *Cameroon: Clinical trial of anti-HIV drug on sex workers in question*. Retrieved from <https://allafrica.com/stories/200501270562.html>
- UNAIDS. (2000). Ethical considerations in HIV preventive vaccine research. Geneva: Joint United Nations Programme on HIV/AIDS.
- UNAIDS. (2006). Creating effective partnerships for HIV prevention trials. *Report of a UNAIDS Consultation, Geneva 20-21 June 2005*. *AIDS*, 20(6), W1-11.
- UNAIDS, A. (2004). epidemic update 2006. *Geneva, Switzerland: Joint United Nations Programme on HIV/AIDS (UNAIDS) and World Health Organization (WHO), 2006*, 1-94.
- UNAIDS/AVAC. (2007). *Good participatory practice: Guidelines for biomedical HIV prevention trials*. Geneva: UNAIDS.
- UNAIDS/AVAC. (2011). *Good participatory practice: Guidelines for biomedical HIV prevention trials*. UNAIDS. Retrieved from <https://www.avac.org/good-participatory-practice>
- UNAIDS/AVAC. (2012). *Ethical considerations in biomedical HIV prevention trials*. Retrieved from https://www.unaids.org/en/resources/documents/2012/20120701_jc1399_ethical_considerations
- UNAIDS/WHO. (2007). *Ethical considerations in biomedical HIV prevention trials*. Retrieved from http://data.unaids.org/pub/Report/2007/jc1399_ethical_considerations_en.pdf.
- Valley, A., Shagi, C., Lees, S., Shapiro, K., Masanja, J., Nikolau, L., . . . Chagalucha, J. (2009). Microbicides development programme: Engaging the community in the standard of care debate in a vaginal microbicide trial in Mwanza, Tanzania. *BMC Medical Ethics*, 10(1), 17.
- Van Rompay, A. R., Johansson, M., & Karlsson, A. (1999). Phosphorylation of deoxycytidine analog monophosphates by UMP-CMP kinase: Molecular characterization of the human enzyme. *Molecular Pharmacology*, 56(3), 562-569.
- Vreeman, R., Kamaara, E., Kamanda, A., Ayuku, D., Nyandiko, W., Atwoli, L., . . . Braitstein, P. (2012). A qualitative study using traditional community assemblies to investigate community perspectives on informed consent and research participation in western Kenya. *BMC Medical Ethics*, 13(1), 23.
- Weijer, C., & Emanuel, E. J. (2000). Protecting communities in biomedical research. *Science*, 289(5482), 1142-1144.
- Weijer, C., & Miller, P. (2004). Protecting communities in pharmacogenetic and pharmacogenomic research. *Pharmacogenomics Journal*, 4(1), 9-16.
- Woodson, C., & Karim, Q. A. (2005). A model designed to enhance informed consent: experiences from the HIV prevention trials network. *American Journal of Public Health*, 95(3), 412-419.
- World Health Organization (WHO). (2016). *Health analytical profile , Cameroon*. Retrieved from <https://www.afro.who.int> > publications > health-analytical-profile-camero...
- World Medical Association (WMA). (1964). Human experimentation: Code of ethics of the World Medical Association (Declaration of Helsinki). *Canadian Medical Association Journal*, 91(11), 619.

- Yin, R. (2003). Case study research: Design and methods. *Thousand Oaks, CA : Sage Publications.*
- Young, F. E. (1988). The role of the FDA in the effort against AIDS. *Public Health Reports.*, 103(3), 242.

Appendix 1: Ethical Approval Final Letter - BREC UKZN



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14 September 2018

Mr AC Ntabe (217075674)
School of Applied Human Sciences
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Dear Mr Ntabe

Protocol: Rethinking the Practice of Community Engagement in Health Research: The case of the early stopped trials in Cambodia and Cameroon in the year 2004/2005.

Degree: MSocSc

BREC Ref No: EXM538/18

I refer to your application to BREC received on 22 August 2018 and wish to advise you that exemption of ethics review has been granted for this study.

This exemption will be noted at the next Biomedical Research Ethics Committee meeting to be held on **09 October 2018**.

Yours sincerely

Professor V Rambiritch
Chair: Biomedical Research Ethics Committee

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