

Cultural Determinants Affect Implementation of Good Clinical Practice (GCP)

in Human Research Studies in Malawi, Africa

by

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## Dedication

I would like to dedicate this thesis to the people of Malawi. You have moved me to change the way that I look at the world, at life, and at myself. You have truly lived up to your reputation for being the “warm heart of Africa.” You have extended your hand of friendship and acceptance and you have greeted me with a smile, no matter what the occasion. Thank you for helping me to take myself less seriously. Thank you for teaching me patience and acceptance. From you, I have learned that “being” is as important as “doing.” Thank you for teaching me that my community and my relationships provide the truly lasting joys. Most of all, thank you for allowing me to build a bridge between your world and mine. It is my wish that we may continue to meet on that bridge.

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## Abstract

Clinical research conduct and Good Clinical Practice (GCP) implementation are influenced by local culture. This study examines the experiences of 26 clinical research personnel in Malawi, Africa, in order to define relevant issues, identify solutions, and give voice to local investigators. Qualitative, semi-structured interviews were conducted, audio-recorded, transcribed, and analyzed. Six themes, related to cultural determinants, emerged: 1) community-based decision-making, 2) illiteracy, 3) patient identifiers, 4) local myths and misconceptions, 5) poverty and disease, and 6) barriers to teamwork. Findings revealed that: 1) Malawians are best at identifying local solutions, 2) operations research is needed 3) greater networking and communication is essential, 4) regulatory requirements should be harmonized, 5) Malawi has made significant progress toward GCP implementation, 6) a “one-size-fits-all” approach to GCP does not work, and 7) Malawians who are engaged in clinical research should be consulted and empowered.

## Table of Acronyms

AIDS	Acquired Immunodeficiency Syndrome
ARV	Anti-Retroviral
CAB	Community Advisory Board
CHHS-HSRC	College of Health and Human Services-Human Subjects Review Committee
CIA	Central Intelligence Agency
CIOMS	Council for International Organizations of Medical Sciences
COM	College of Medicine
COMREC	College of Medicine Research Ethics Committee
EDC	Electronic Data Capture
EMU	Eastern Michigan University
EU	European Union
FDA	Food and Drug Administration
GIS	Geographical Information System
GCP	Good Clinical Practice
GDP	Gross Domestic Product
HIV	Human Immunodeficiency Virus
IC	Informed Consent
ICH	International Conference on Harmonisation
IEC	Institutional Ethics Committee
IRB	Institutional Review Board
MBTS	Malawi Blood Transfusion Service
NGO	Non-Governmental Organization
NHSRC	National Health Sciences Research Committee
NIH	National Institutes of Health
NRCM	National Research Council of Malawi
PI	Principal Investigator
PMPB	Pharmacy, Medicines and Poisons Board
RSC	Research Support Centre
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
TMR	Triple Media Recording
WHO	World Health Organization

Note: The acronym IRB is typically used for ethical review boards in the U.S. In Europe and elsewhere in the world, the term Institutional Ethics Committee and the acronym IEC is more common. In this thesis however, the acronym IRB will be used throughout to reference any ethical review board regardless of location.

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## Terminology Notes

- 1) Since this thesis involves the study of research itself, it is difficult but important to distinguish between the author and others working in the field of research. A concerted effort is made to use the term “researcher” to refer to the author and the term “investigator” to refer to all others who are conducting research. The only exception is a direct quotation of a speaker who uses the word “researcher” to refer to someone other than this author.
- 2) The terms “participant” and “subject” are used interchangeably to denote someone who is enrolled in or considering enrollment in clinical research other than this thesis study. The term “patient” is occasionally used, particularly in quoted references, to refer to a potential research participant.
- 3) The term “interviewee” is used to specify an individual participating in this thesis research study.



## Chapter 1: Background and Literature Review

Implementation of GCP guidelines for clinical trials in developing countries has been the subject of considerable controversy in recent years (Dent, 2000; Editor, 2003; Grimes et al. 2005; Jorgensen, Bach & Friis, 2004; Sweatman, 2003; White, 2006). In 1996, the International Conference on Harmonisation (ICH) finalized and implemented guidelines for GCP in the conduct of clinical research trials (ICH, 1996). The purpose of GCP was explained in the introduction: “Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible” (ICH, 1996). Subsequently, these guidelines were incorporated into regulatory legislation in the U.S., Japan, and the European Union (EU). In 2001, an EU directive, which harmonized principles of clinical trial conduct and participant protection, made the ICH standards of GCP law in the EU, allowing member states until May 2004 to pass legislation and comply with GCP (European Parliament, 2001). The World Health Organization (WHO), in cooperation with Council for International Organizations of Medical Sciences (CIOMS), has also developed clinical research guidelines, as have many other organizations and regulatory bodies (World Health Organization, 2006). McMillan and Conlon (2004) state, “There is no shortage of general research guidelines but there is frustratingly little help for thinking through the complexities of developing world research” (p. 204). Three years later, Acosta et al. (2007) still agree that “The practicalities when applying the ICH-GCPs in less developed countries are seldom discussed and we found no guidelines as how to ‘adapt’ them” (p. 2852).

While the debate continues about if or when clinical trials in developing countries should be fully compliant, the question of how to implement ICH-GCP guidelines becomes the primary

concern. Specific advice for GCP implementation and case histories of GCP introduction are rare but fortunately increasing, as seen in the report of Krosin, Klitzman, Levin, Cheng and Ranney (2006) set in rural and peri-urban Mali, West Africa. Benatar (2002) describes a “relative lack of attention ... to how research is actually conducted” and he notes the “inadequate attention paid to monitoring studies, trying to improve the actual conduct of research” (p. 1135). His views are echoed in a corroborative discussion by Pang (2002). Investigators with clinical trial experience in only developed countries are often unprepared or unaware of the unique issues that arise in a less developed setting. If GCP compliance is to be achieved worldwide, it is important that the nature and the prioritization of issues specific to each developing country are understood. Knowledge of the prevailing local research climate and the culture is a prerequisite for successful GCP implementation.

Issues that are unique to the conduct of clinical trials in developing countries involve an understanding of the prevailing culture and its parameters. The existing literature suggests that important cultural parameters include the concepts of individual autonomy versus community-based consensus, the perception of health and disease, the magnitude of the disease burden considering the Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome (HIV/AIDS) crisis, the accessibility of health care, and the prevailing standards of care (Acosta et al., 2007; Corneli et al., 2007). All these factors influence the informed consent (IC) process and a subject’s willingness and/or ability to participate in clinical research. Other cultural parameters explored by Acosta et al. (2007) and Corneli et al. (2007) include the economic climate, the burden of extreme poverty, and the prevailing legal, political, and social complexities, such as those of confidentiality, corruption, or immigration status.

Corneli et al. (2007) also raise some very specific topics which play a role in GCP implementation in sub-Saharan Africa. One issue is that of the profound deference accorded to health professionals in the local culture. They quote a Malawian mother speaking about a clinical study, “If the medicine is given by doctors, that means they know that the medicine is helpful and can prevent the baby [from getting HIV]” (Corneli et al., 2007, p. 64). Such beliefs blur the distinction between clinical care and research and affect multiple aspects of clinical trial conduct from recruitment to placebo effect to compliance. Another issue is that subjects have concerns about the acceptability of medical procedures, such as the amount of blood drawn. Last, the practice of sharing food and medicines is examined and Corneli et al. (2007) report a focus group participant’s comment, “[In our culture], food has to be shared, no matter how small it is” (p. 65) as an explanation for the fact that 30% of HIV-positive mothers share their medicines with their husbands.

Kohls (2001) contrasts traditional and Western cultures with regard to their concepts of time and their differing legacies of oral versus written tradition. He describes traditional cultures as being past-oriented and using time for the purpose of “being,” while Western cultures are future-oriented and use time for the purpose of “doing.” The success of a clinical trial requires acknowledgment that clinical investigators and trial participants have different concepts of time and that both must be accommodated. Similarly, the oral history legacy of traditional cultures is the diametric opposite of Western written history, and the differences must be reconciled. GCP is an extreme case of written tradition which emphasizes the importance, accuracy, and completeness of documentation to the point that an event is not considered to have taken place unless it is documented. Hence, extensive training must be provided for teaching methods of document retention, case report form completion, and source document verification to study personnel. Another issue related to the oral vs. written tradition is that of illiteracy in the study

participant pool. Studies by Corneli et al. (2007) and van der Horst et al. (2009) examine the effect of literacy levels on adequate understanding of the concepts of research and randomization. They also address the effect that language barriers have on communication between staff and subjects and the requirement for translation of trial documentation into multiple languages. Additional references cite the importance of winning the support and trust of the local community by meeting with local authorities/chiefs and publicizing trials through drama and radio spots (Cutts, Enwere, Zaman & Yallop, 2006; Van den Broeck et al., 2007; Yusuf, 2002).

The shortage of health personnel is another barrier to the conduct of clinical trials in sub-Saharan Africa and is often cited in the literature. The severe shortage of doctors and nurses is compounded by the toll that HIV/AIDS and emigration (“brain drain”) take on the size of the pool of qualified health professionals. The overwhelming patient burden per health care professional adds to the likelihood of burnout among the few who remain. Of these, few are trained for clinical trial activities, so it is unlikely to be able to find previously trained staff at study initiation (Acosta et al., 2007; Muula, 2005; Muula, Panulo & Maseko, 2006; van der Horst et al., 2009; WHO, 2006).

Infrastructure deficiencies also are major problems which impact clinical research conduct in countries like Malawi. Hospital infrastructure issues can involve an absence of standard operating procedures (SOPs) and routine patient records such as medical charts. Civil infrastructure considerations such as lapses in electrical, telephone, fax, and internet service and the need for compensatory provisions such as power supplies or generators are often challenging to address. Other civil considerations such as the absence of birth certificates and the lack of a unique personal identification numbers make subject identification difficult, while

lack of postal service would limit options for the distribution of study-related survey tools (Acosta et al., 2007; Cutts et al., 2006; Yusuf, 2002). Transportation infrastructure can be problematic due to unplanned urbanization, resulting in poor or non-existent roads which lack names and house addresses (Aviles, Ortega, Kuan, Coloma & Harris, 2008; Deen & Clemens, 2006). This may necessitate the use of costly geographical information systems (GIS) for staff travel and reimbursement for subject travel costs. Ensuring the safety of study personnel may involve providing adequate protection from bribery, corruption, guerrilla attacks, petty theft, indigenous disease, and road traffic accidents.

Finally, governmental bureaucracies can slow or halt clinical trial progress with customs regulation of study material shipments, passport and visa regulations affecting clearances for study personnel, currency devaluation, and policy changes in standards of health practice or preferred drug treatment and initiatives such as vaccine campaigns which can affect study-site access. Finally, climactic conditions and natural disasters such as monsoons, fires, and floods can affect the execution of a clinical study by affecting the comfort of subjects, the integrity of biological specimens, the cold chain, and humidity control needed for trial medication (Cutts et al., 2006; van der Horst et al., 2009; Yusuf, 2002).

## Chapter 2: Methodology

### *Rationale and Objective*

The challenges associated with identifying cultural and feasibility issues related to GCP implementation are as unique to each setting as are the solutions needed to overcome them. The extant literature provides important information about such barriers, but few reports consider this topic from the perspective of the clinical trial professional or with a qualitative research approach. Investigators with experience conducting clinical trials in less developed countries have not typically been tapped for their input. Kermani and Lovell-Hoare (2005) state that “developing countries were not involved in the development of ICH-GCPs” (p. 50), and Grimes et al. (2005, p. 172) add that academic investigators did not participate either. Today, more than ever, the voices of investigators in resource-poor settings need to be heard, and this study aims to provide a forum for that voice. Also, regulatory and governmental agencies, policy makers and clinical trial sponsors who advocate, legislate, and enforce GCP compliance are often unfamiliar with the developing country environment, culture, and infrastructure. An important benefit of this study is that it can provide regulators with a description of the current GCP implementation process from the frame of reference and in the words of investigators themselves. Finally, it is hoped that this study will stimulate ongoing discussion of issues among investigators in Malawi and generate ideas for improving, facilitating, and expanding clinical research and executing GCP in Malawi.

The goal of this study is to examine cases of GCP implementation in Malawi, with specific focus on research based in the cities of Blantyre and Lilongwe. This study probes the underlying attitudes toward GCP from the perspective of local clinical research personnel who have been involved in the conduct of clinical research. Additionally, this study allows study

participants to identify the issues which arise during the process of GCP implementation and propose solutions they believe would improve compliance. Reporting of the opinions and views of study participants will accomplish the additional goal of this research, which is to give voice to local investigators and to their ideas.

### *Study Design*

This study uses qualitative research techniques to investigate the topic of GCP implementation. Qualitative research is a multi-faceted, inductive, and iterative type of investigation which aims to represent and describe value-laden phenomena, processes, and personas. Qualitative data analysis can result in ongoing re-formation of the research problem, giving rise to the iterative nature of the process. The rationale for using qualitative research techniques in this study is that implementation of GCP is a venture associated with values that are most easily communicated and conducted in an unstructured open-ended forum.

Phenomenology is a specific approach to qualitative research which creates meaning about a topic, situation, or concept from the perspective of the most directly involved individuals by documenting their lived experience. The importance of such an approach is stated by Colaizzi (1973)

Without thereby first disclosing the foundations of a phenomenon, no progress whatsoever can be made concerning it, not even a first faltering step can be taken towards it, by science or by any other kind of cognition. (p. 28)

It is desirable to study GCP implementation in Malawi from a phenomenological perspective so as to analyze the process from the perspective of the clinical personnel who have actually implemented GCP. The technique of thick, rich description is used to relate the study findings. This terminology denotes the reporting of an extensive and coherent set of details which go beyond the simple rendering of fact. These details include expressions of intent, emotion, and

relationship in order to allow the reader to sense or re-create the environment. The researcher uses both intuition and thick, rich, description to paint a picture of the experiences related by the participants (Creswell, 1998). In qualitative research, it is acknowledged that the researcher is making observations through an admittedly subjective lens. For this reason, it is important that the researcher disclose to the reader the nature of the personal experiences and prejudgments which form the basis for the topic-specific subjectivity. In this study, the researcher describes this observational lens under the heading of Subjectivity in Chapter 2.

This research study is composed of a series of semi-structured interviews and focus group meetings conducted in Malawi with participants who have knowledge and experience with GCP implementation in the context of conducting clinical research. The study is designed to use the aforementioned principles of phenomenological qualitative research and the technique of thick, rich description. Interviews were conducted in Malawi, in person, and in English, solely by this researcher, and they occurred between May 13<sup>th</sup> and June 10<sup>th</sup> of 2009. They were conducted in a manner designed to probe perceptions, opinions, positive and negative feedback, and suggestions for GCP facilitation. Questions that guided this investigation included, but were not limited to, the following (see Appendix B: Interview Guide):

- Can you tell me about your clinical research experiences involving GCP implementation?
- What does GCP mean to you and what are prevailing perceptions about it?
- Are efforts to implement GCP typically met with receptivity or resistance?
- Are investigators prepared to implement GCP and if so, how?
- What resources were needed or are still needed?
- Are there any barriers and if so what are they?



- Are there situational or cultural constraints unique to Malawi and how are these addressed?
- Which aspects of GCP are of highest/lowest priority for implementation?
- Examples include, but may not be limited to: IC, protocol adherence, safety monitoring, ethical review board interactions, document management, records retention, drug accountability, site operations, financial/budgetary considerations
- What would investigators like international regulators to understand?
- What initiatives would improve human subject protection and data integrity?
- Are there other issues which need to be explained?

An interview guide listing these questions was provided to each participant prior to obtaining IC. Prior to the interview, each participant was also given a copy of the thirteen principles of good clinical research practice from the E6(R1) section of the ICH Harmonised Tripartite Guideline as background information (ICH, 1996; Appendix C). The exact location where each interview was held was determined on a case-by-case basis after agreement between the researcher and the participant. As themes emerged from data analysis, participants were asked to corroborate the trustworthiness of such themes, and selected individuals were asked to review this thesis report for the purpose of validation (see Chapter 2, Trustworthiness).

#### *Data Collection.*

The primary method of data collection was the audio-recording of interviews with participants. These interviews, of approximately 60 minutes duration, were audio-recorded using a Sony ICD-PX720 digital recorder and a RCA RPS120 digital recorder as back-up. One selected participant was not available for an in-person interview; therefore an email communication was substituted. Secondary interviews, to be conducted for the sake of clarification as described in the research protocol, were not needed. Demographic information, such as the extent of prior clinical trial experience, was also gathered during the participant

interviews. Field notes were collected by the researcher during the course of the study, for the purpose of recording observations about the interviews and making journal notes about the local clinical research and health care environments. Also, demographic information about Malawi was procured from public-access documents available from governmental and regulatory agencies in order to assist in the description of the local environment and to corroborate and verify themes identified from interviewees.

### *Study Population.*

The study population consists of individuals who were involved in conducting human clinical research studies in Malawi and who had some experience with GCP implementation. Single-stage purposeful sampling (Creswell, 2003, p. 156) was used to select for information-rich cases (Glesne, 2006, p. 34). The researcher had prior access to names, job titles, and contact information for individuals working in the clinical research field. Additional snowball sampling was used when interviewees suggested names of individuals who might offer important insights. The researcher's prior experience in Malawi (see Chapter 2, Subjectivity) led her to believe that there would be significant interest in study participation based on a strong local interest in improving clinical trial conduct and an eagerness to have the experiences in Malawi documented. In order to provide in-depth analysis of all perspectives about GCP implementation, the sample was stratified to include participants of both genders and with varying clinical research experience, job description, rank, and medical specialty. Participants were further stratified to represent native Malawians as well as non-Africans (expatriates) in order to identify culturally specific concerns. A sampling which would result in 16 to 24 interviews was planned, as this would allow for detailed examination of the issues presented by each participant as well as the capture of experiences about GCP implementation from a variety of perspectives. The actual

sample size was to be determined when theoretical saturation was reached, a typical endpoint in phenomenological qualitative research.

Participants are all adults, greater than 18 years of age, and include 17 males and 9 females. The nationality of participants is distributed as follows: 21 African nationals and 5 non-Africans expatriates, with the majority of the African participants being Malawian. No participants could be considered vulnerable subjects. Participants include principal investigators (PIs), clinical officers, clinical monitors, research nurses, clinical trial coordinators, statisticians, data managers, regulatory officials, ethics committee members, and auditors.

In the field, the interview process was terminated after 26 individuals had been interviewed, 22 of whom were interviewed on a one-to-one basis and 4 of whom were members of a focus group forum. At that point, theoretical saturation was reached as indicated by the observation that interviewees were identifying themes that were highly consistent with those of previous interviewees, and no new categories, concepts, or dimensions were emerging.

Participant anonymity was assured at the time of the interview. Participant identity is kept confidential in the thesis report through the use of pseudonyms and by removing any details that could compromise anonymity from quotations. Pseudonyms are used in every instance when data are reported from participant interviewees. While it is customary in the field of qualitative research to use only first names as pseudonyms, full names accompanied by the titles of either Mr. or Ms. were used in this thesis. This is done in order to accommodate the Malawian cultural tradition which deems the sole use of first names and the omission of titles of address to be disrespectful. Any additional titles such as Mrs., Dr., PhD., or MD are deleted. This format also serves to differentiate quotations of interviewees from those deriving from extant literature, as the latter do not include titles or first names. Since the study population of

individuals involved in clinical research in Malawi is not large, two additional accommodations have been made to disguise interviewee identity and maintain confidentiality. First, the nationality and/or gender of a specific interviewee's pseudonym has been allowed to change but the overall profile for the number of African vs. expatriate and male vs. female names is kept consistent with the original composition of interviewees. Second, the job titles of interviewees have been made less specific for the sake of confidentiality. Job classifications in this thesis have been limited to the following five choices: principal investigator (PI), clinical officer, research nurse, clinical monitor, and clinical trial coordinator. The role which most closely approximates the job title of the actual interviewee has been assigned. The identification of a job title/role, albeit approximate, allows the reader to better understand the perspective of the quoted interviewee and yet preserve confidentiality. Of the 26 participants interviewed, this thesis uses direct quotations from 23 selected individuals. Table 1 lists the pseudonyms of quoted individuals alphabetically by surname along with their modified job classification. In the first instance where an interviewee is quoted, a reference is made to the individual's job classification. Subsequent references may or may not include a job classification or a first name as appropriate for the sake of brevity and readability.

Table 1.

Pseudonyms and Job Titles of Study Participants  
(Alphabetical, by surname of pseudonym)

Pseudonym	Job Title
Ms. Chifundo Banda	Research nurse
Mr. Rodwell Chanje	Clinical monitor
Mr. Wilson Chimanga	PI
Mr. Samuel Chiwala	Clinical officer
Ms. Tiyamike Chule	PI
Mr. Gordon Clark	PI
Mr. Amos Gamadzi	PI
Mr. Peter Graves	PI
Mr. Thomas Jones	Clinical trial coordinator
Mr. Simon Joni	Clinical officer
Ms. Gabriella Kaputa	Research nurse
Mr. Nelson Marunda	PI
Mr. Bright Mbalame	Clinical monitor
Ms. Ellen Mbewe	PI
Mr. Faith Mpaka	Research nurse
Mr. Joseph Mwamkwamba	Clinical trial coordinator
Mr. Maxwell Ndege	PI
Ms. Memory Ngoma	PI
Mr. George Ntimu	Clinical monitor
Ms. Patricia Nyalungwe	Clinical trial coordinator
Ms. Esther Pembeleka	PI
Ms. Teresa Swila	PI
Mr. Blessing Thokozani	Clinical monitor

Principal Investigator (PI)

*Study Location.*

Demographically, Malawi is a sub-tropical, landlocked country south of the equator in sub-Saharan Africa. It is bordered by Tanzania, Mozambique, and Zambia. This long, narrow country, stretching from North to South, consists of an elongated plateau with rolling plains and some mountains. A predominant physical feature is Lake Malawi (also called Lake Nyasa), which comprises about 20 percent of the eastern side of the country. Malawi's total area is approximately 118,000 sq. km. (46,000 sq. mi.), making it roughly the size of the state of Pennsylvania (Central Intelligence Agency [CIA], 2009). The population of Malawi, according to the final results of the 2008 census conducted by the Malawi government, is 13.1 million individuals, with 6.4 million males and 6.7 million females (National Statistics Office of Malawi Government, 2009). The median age of the population is about 17 years of age, with 46% age 14 and under, 52% between 15-64 years of age, and only 3% age 65 and over. Annual population growth is 2.4% (2009 est.; CIA, 2009). Life expectancy at birth is 50 years and has dropped in the recent decade, in large part due to the HIV/AIDS crisis (CIA, 2009). The adult prevalence of HIV/AIDS is about 12% (2007 est.; CIA, 2009).

Malawi is a county composed of nine native ethnic groups in addition to the Asian and European populations which have settled in more recent years. Present day Malawi became part of the British protectorate of Nyasaland in 1891 and was renamed the British Central Africa Protectorate in the 1893 and renamed again to Nyasaland in 1907. It gained independence in 1964 and became a multi-party democracy in 1993. The two official languages are Chichewa and English. Of the seven major native languages, Chichewa is the most common, being spoken by 57% of Malawians. The two predominant religions are Christian (80%) and Muslim (13%). Literacy of the total population is 63%, and nine years of schooling is the national average (CIA, 2009). Malawi is one of the poorest countries in the world with a Gross Domestic Product

(GDP) using purchasing power parity of \$12.8 billion USD or \$900 USD per capita. It is ranked between 5<sup>th</sup> and 11<sup>th</sup> from the bottom of all countries in the world, depending on the GDP ranking parameters used. Agriculture accounts for more than a third of the GDP and >90% of the exports and rural inhabitants compose more than 80% of the population (CIA, 2009). On a brighter note, economic growth rose 9.7% in 2008, after three years of surplus harvests (Mchulu, 2009).

Malawian demographics are important to consider when interpreting the data from this study. Factors such as population density, poverty level, disease burden, literacy rate, rural/urban ratios, and geographical distances are important parameters which affect multiple aspects of clinical trial conduct.

This study was conducted in the two major cities of Blantyre and Lilongwe in Malawi, the cities wherein clinical research is predominantly based. Most research was affiliated with the University of Malawi, College of Medicine (COM) in Blantyre. The COM houses a Research Support Centre (RSC) established in 2006 and an independent Institutional Review Board (IRB), the College of Medicine Research Ethics Committee (COMREC). The COM is affiliated with multiple international research units which generate significant collaborative research. Some research involved participants based in the capital city of Lilongwe which is the home of the Malawi Pharmacy, Medicines and Poisons Board (PMPB), the National Research Council of Malawi (NRCM), and an IRB entitled the National Health Sciences Research Committee (NHSRC). Lilongwe is also the base of operations for numerous international academic research units.

*Subjectivity.*

The study location is chosen because of the researcher's prior employment in Malawi as Interim Director of the RSC at the COM for a nine-month period in 2006-2007. This exposure provided the researcher with a sincere desire to give voice to local clinical investigators in their attempt to adapt to international GCP regulation. This study could serve as a prelude to future participatory action research in which suggestions for improvement are implemented and evaluated by local investigators. While description of the meaning of participant's GCP-related experience is not transformational in and of itself, it is the strong belief of the researcher that a full understanding of the issues is necessary to identify appropriate avenues for change. The researcher's presence and the research itself were not expected to be disruptive and it was not. This study was welcomed by the current Director of the RSC. The researcher's familiarity with the Malawian setting proved to be valuable in understanding local issues, in purposeful sampling to identify multiple perspectives, and in obtaining IC for participation. Qualitative research involves reciprocity between researcher and participant that is based on intense sharing, trust, and mutuality. This study benefits from the researcher's previously established trust with many members of the potential participant pool. While qualitative interviewing involves minimization of the distance or objective separateness between interviewer and interviewee, the interviewer must nevertheless bracket her prior experience so as not to influence the content of the participant responses. The researcher forthrightly described and admitted her biases, values, and judgments. The lens through which the researcher observed the study site, the participants, and the data is made clear to the reader of this report.



*Ethical Considerations.*

This study involved only minimal risk to the participants, none of whom could be considered vulnerable subjects. Confidential discussion of GCP implementation was not expected to cause inordinate stress. Participants did not and will not accrue any direct benefit from the study; however, there may be both perceived and real benefit to the research community from the discussion and dissemination of these findings. Ethical approval was sought from the College of Health and Human Services-Human Subjects Review Committee (CHHS-HSRC), the IRB at EMU and from COMREC, the IRB in Malawi. The study did not commence until approval was received from both IRBs. Written IC was obtained from each participant prior to the initiation of an interview. During the study, all study materials including IC documents, audio recordings, notes, and transcriptions were kept under lock and key in the possession of the researcher. At the end of the study, audio recordings and materials, identifying the participants will be destroyed.

*Limitations.*

This researcher did not foresee or encounter any constraints or limitations associated with the conduct of interviews as they were not deemed to pose any more than minimal risk to study participants. If a participant had problems, questions, or comments, a contact number was provided on the IC form to put the participant in touch with Dr. Elizabeth Francis, the faculty adviser for the study; Dr. Gretchen Reeves, chairperson of the CHHS-HSRC at EMU; and Dr. Cameron Bowie, the representative of the University of Malawi, COM. General limitations of the study include the inability to generalize the findings about GCP-related issues and compliance across continents or regions. The Malawian experience may or may not be typical of

the research climate in other African countries and is even less likely to be an adequate predictor for non-African developing countries.

### *Data Analysis*

Digital audio files were downloaded to a computer and transcribed into Microsoft Word documents using an Infinity IN-USB-1 transcription foot pedal and Pedable software.

Transcription took place in the US in June and July of 2009. Systematic methods for data analysis of interview transcripts and field notes were used to identify clusters of themes according to the strategies described by Charmaz (2006). Analysis of focus group and interview transcripts were carried out manually by the researcher. Transcripts of interviews were analyzed by organizing meaningful verbatim quotes into initial codes which were further subdivided until all non-repetitive, non-overlapping codes were identified. Each interview transcript was analyzed individually, after which data was combined with that from other interviews for composite analysis. Codes were examined for correlation with demographic characteristics of participants and then organized into similar groupings as categories. Categories were collapsed into themes and used to describe “what happened,” “how” the phenomenon was experienced, and what comprised the overall “essence” or “meaning” of the experience. Such content analysis follows the methods of Creswell (1998) and Glesne (2006). A schematic depiction of the major meaningful thematic units and their subordinate topics was constructed. Suggestions for new initiatives and interventions proposed by participants were tabulated and reported. Finally, thick, rich description, encompassing the complexity of both divergence and commonality, was combined with verbatim quotes to allow the reader to experience the phenomenon of clinical trial conduct in a developing country through the lived experiences of individual participants. Data analysis took place from June to October 2009, and written documentation of study results was carried out between October 2009 and March 2010.

*Trustworthiness.*

In qualitative research, the validation of finding occurs throughout the study. The accuracy of the findings from the perspective of the researcher, the participant, and the reader, and the credibility of the emergent themes is established in the following ways in this study.

- Lengthy engagement and persistent observation in the field, building trust with participants, learning cultural constructs and verifying records.
- Corroboration of evidence from different sources: public-access documents, observation, field notes, focus groups, and interviews
- Thick, rich description and verbatim quotes
- Corroboration of evidence from different participants: comparing the views of participants selected purposefully from divergent perspectives.
- Thesis committee oversight of data analysis and research conclusion
- Vetting of emergent themes by a subset of study participants, who were asked to provide individual feedback and comments on preliminary drafts of this report
- Adequate clarification of the researcher's subjectivity

Emergent themes were reviewed by study participants who found them to be “realistic” and who found “nothing that would be considered an exaggeration or an understatement.” One participant believes that the report is “articulated in a respectful, non-condescending manner.”

### Chapter 3: Results

Coded data from participant interviews were refined into six major themes. These six themes can be classified under a larger umbrella or theoretical framework of cultural beliefs, realities and adaptations. This framework, which comprises the determinants important for implementing GCP in clinical research in Malawi, is the topic of this thesis. Figure 1 shows a schematic diagram of this framework and its underlying themes. The six themes that are presented and interpreted are 1) community-based decision-making, 2) illiteracy, 3) participant identifiers, 4) local myths and misconceptions, 5) poverty and disease, and 6) barriers to teamwork. As Mr. Peter Graves [pseudonym], an interviewee who is a PI states, “GCP has to adapt itself. If you are doing research in Malawi, which has a different context, you need to adapt the GCP if you want to achieve the intention of GCP.” Hence, the understanding and accommodation of cultural issues in Malawi is a prerequisite for the success of both GCP implementation and clinical research.

In addition to the aforementioned theoretical framework and underlying themes, two other theoretical frameworks were identified which are noteworthy, although beyond the scope of this thesis. These two frameworks are 1) health care infrastructure and operation and 2) GCP-specific training, documentation, and monitoring. Future examination of these frameworks and report of additional findings is planned.

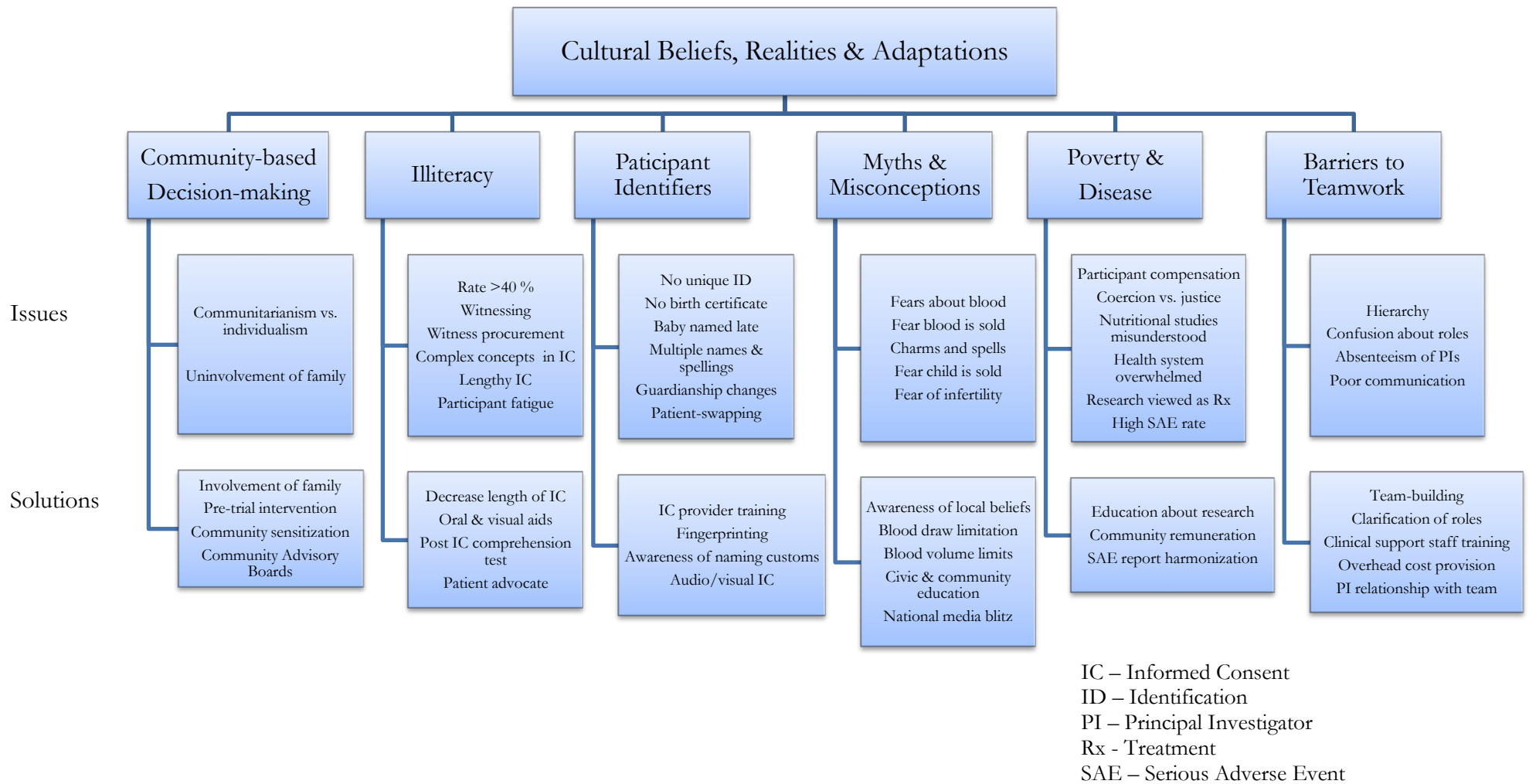


Figure 1. Six Major Themes of the Theoretical Framework

*Theme 1: Community-based Decision-making*

*Issues.*

One of the most important factors to consider during GCP implementation is the manner in which decisions are made in specific cultural settings. Decision-making commences during the IC process when a potential participant considers whether to enroll in a clinical research study. It also continues throughout a study via the IC process whereby an individual may regularly reaffirm participation. The prevailing culture in Malawi with regard to decision-making is described by Mr. Blessing Thokozani, a clinical monitor. He corroborates the comments of ten other interviewees in this insightful quotation,

We [Malawians] believe in what I would call “communitarianism”, whereby consent is just collective. We believe in the community—that *I am* [italics added] because *we are* and since *we are*, therefore *I am*. So, *I am* because of my relative, my husband-- all these people that are around me. . . . Therefore *I am*. This is as opposed to the Western logical dictum: *I am* because *I think*—the so-called Cartesian philosophy. So, if you are recruiting a wife into your study, she would always say, “Well, I have to consult my husband. My husband has to know that I am taking part in this.” She would want the husband to be involved in consenting. . . . We [Malawians] give a sort of collective consent.

Similarly, Ms. Chifundo Banda, a research nurse, relates that a mother who was enrolling her child in a study said, “I have to talk to the uncle. The uncle is the sole one responsible for this child. So, I cannot make my own decision.” In a matrilineal society such as Malawi, the maternal uncle is an important part of the mother’s lineage (Muula, 2007). Furthermore, Mr. Joseph Mwamkwamba, a clinical trial coordinator, comments on the influence of family when he states that in Malawi,

It is all about looking and respecting how the culture is here. You do not live as one entity. You need to consult. . . . It is not just a decision that you can make without . . . thinking, “what will my mother say when she hears this?”

He describes examples arising in the course of a clinical trial where “even mothers-in-law, cousins come, if they hear that one is participating in a study and . . . want to have an impact on saying ‘No, my child should be taken out from the study.’”

Despite apparent interest by family members in the matter of study participation, nine interviewees speak of the lack of involvement of family in the IC process, particularly the lack of involvement of husbands and fathers where spouses and children are concerned. Mr. George Ntumu, a clinical monitor relates,

There isn’t much male involvement. . . . In rare cases . . . we have males, like the father, being involved in the consenting or taking part in a study. . . . In most cases, they are left out. . . . It is the mother who goes to the hospital with the child; . . . the mother who has consented as a legally acceptable representative and fathers, they just hear that a child has joined the study so there isn’t a distinct mechanism put in place to involve the fathers as well.

In a study which recruited 150 children, clinical investigator Mr. Amos Gamadzi explains that only two men accompanied the children to the hospital; hence a predominantly female population typically provides consent. This common research modality defies the traditional authority held by males in Malawi, who are typically described by interviewees as dominant and as “having the upper hand.” In the prevailing village hierarchy, women do not have much say while the father has the last say about a child. A certain autonomy, bordering on arrogance, is captured in phrases such as “I am the father, what I say goes” quoted by PI, Ms. Teresa Swila,

and by the comment of Mr. Joseph Mwamkwamba that, in one of the instances where the father said no, “*He* [italics added] wanted to be the one that made the decision.”

A related issue is that of general community awareness about the details of an upcoming clinical research study. Few extant literature references document the advantages of community interaction prior to, during, and after a clinical study in a developing country (Mfutso-Bengo, Masiye, Molyneux, Ndebele & Chilungo, 2008; Morin et al., 2008; Van den Broeck et al., 2007; Yusuf 2002). These studies describe community advisory boards (CABs), which are community organizations typically composed of village leaders including headmen, religious leaders, teachers, and other influential lay persons. One of the duties of the CAB is to explain, in layman’s language, the “hows” and “whys” of a particular research protocol and the details of each study visit. Another role for the CAB is to intervene, as needed, to dispel longstanding or emerging myths and manage misconceptions (see Theme 4). The necessity for such a community awareness campaign is not yet widely enough appreciated by investigators, according to interviewees. While a few Malawian investigators make use of CABs, sometimes referred to as village health committees, Mr. Blessing Thokozani states that, “Most of the investigators that are involved in these clinical trials are from the West and so they don’t really understand the need for engaging the community.”

The withdrawal of participants from a study is one of the negative consequences associated with either dismissal or ignorance of the communal nature of decision-making in Malawi. Family members of study subjects who persist in their disapproval of study participation exert societal pressure which can result in the eventual withdrawal of the participant. More serious social consequences, which raise ethical concerns, include the



beatings of the participant or the parent who has enrolled a child. Mr. Joseph Mwamkwamba relates,

There was one time when one of the men came. [He] agreed that the child can participate in the study, as was reported by the mother. But, later on in the program, the mother came to the study site and the mother was beaten [by] the same father. ...The husband ... beat the wife for allowing the child to participate in the study although initially the husband agreed. ...It is not the only example. There were several other mothers ... beaten because the father was having the upper hand.

Such incidents further reinforce potentially negative attitudes toward research in the local community. Beyond the social strife created by discordant decisions about study participation, detrimental consequences affect the study itself. Poor retention rates compromise the quality of the data, and participant withdrawals make poor use of study resources.

### *Solutions.*

What then are some of the solutions proposed by the interviewees for accommodation of the cultural aspects of community decision-making in Malawi? These solutions fall into two categories: 1) those involving accommodation of community members at the time of the IC process and 2) those involving more general community interactions. On the first topic involving the IC process, Mr. Blessing Thokozani argues:

What I'm lobbying for is the involvement of other important people in the decision-making—their involvement, but the decision has to come from the person who is being asked to take part in the clinical trial. . . . We should give them [participants] the time to consult their family members . . . and they should give their consent later, not on the same day.

Many interviewees suggest modification of the IC process to include mechanisms for conferring with relevant family members prior to enrollment. One option is to ask the participant to return at a later time for the IC presentation, thus providing an opportunity to discuss enrollment with family members. A variation on this theme is to ask the spouse/father to attend the IC presentation. Such postponements of IC would likely result in decreased recruitment rates but would accommodate the need for a more communal decision-making process. Decreased enrollment, while not ideal, is less expensive and less detrimental to a study than participant withdrawal post-enrollment, however. The suggestion that the potential participant take home a copy of the IC form to discuss with family members is confounded in Malawi by the high illiteracy rate, making true understanding of a document as complex as an IC form highly unlikely, even in more literate families and despite translation into the local language. Innovative presentation of IC materials via drama, posters, or videos is discussed under Theme 2 of illiteracy and may provide additional means to create adequate understanding among relatives of participants and allow for informed input on a decision.

What types of problems could still exist, despite well-meaning efforts to adapt research practices? Ms. Teresa Swila states,

Fathers are one of the biggest problems. . . I don't know how well the chiefs disseminated the information that they gathered in the meeting that we had with them. We actually did organize a meeting with fathers of study participants, several months into the current study. . . . Part of the problem with that, although there were certainly good reasons to do it, is that you are "preaching to the choir." The fathers who did come for the meeting were those who embraced the ideas of the study.

This argues for pre-trial intervention and consultation, but also cautions that all parties may not be equally informed, interested, able to comprehend, or able to attend the informational

meetings. Another point of ethical concern is raised by Mr. Blessing Thokozani. While he is a strong proponent of garnering community support for study participation, he weighs the validity of a decision made with undue community influence,

For example, when a wife says, “I can’t give this consent. I think I have to talk to my husband and at the end of the day he will probably say yes, that I have to participate. If he says yes, then I will do it because my husband says so.” Would you really consider that IC? Would you say that it is coming from this particular person?

There are however some examples of success, even in the relatively short, 5-8 year long history of GCP guideline implementation in Malawi. Clinical officer, Mr. Simon Joni states,

Towards the end of the study, you will see even fathers writing letters of appreciation to the study staff. . . . Even those who had negative attitudes at first . . . would . . . come again and say, “I wish I didn’t have the negative attitude. I think that my child is doing quite well.”

The second group of proposed solutions involves more general community interactions, including the topic of CAB formation. Clinical trial coordinator Ms. Patricia Nyalungwe explains, “Before we establish a site, we go for community sensitizations and when we notice that there are people who are not willing to participate from a given area . . . we also organize ad hoc sensitization meetings.” The question arises about whose responsibility it is to ensure that CABs are established. Is it that of the sponsor, the PI, the IRB, the governmental funder, the non-governmental organization (NGO) funder, or the regulatory agency? Are all of the above responsible? How do non-Malawian sponsors and PIs who might be unaware of the importance of CABs become aware? Mr. Blessing Thokozani states his opinion that it is the “duty of local PIs to make sure that they inform these [non-Malawian] PIs and make sure that they think about

this community engagement aspect. I mean, it has to be budgeted.” Reference to proper budgeting raises the point that planning for cultural adaptations must occur in the earliest stages of proposal submission and study design, otherwise even the best strategies cannot be carried out without adequate funding. Once financial support is secured, thoughts turn to the specifics of community engagement. Suggestions about the types of approaches to use are made by PI Mr. Nelson Marunda, as he speaks about the manner in which villagers learn. He states, “They [Malawians] remember visually [and orally], not in writing. . . . Anything . . . information-wise . . . is better on a poster, or on the radio or drama performances or megaphones.” Research nurse Ms. Faith Mpaka describes success with such an approach,

We have also used dramas. We have gone to the community, performed these dramas, and while involving people right there in the community, talking to them about this study, involving the chiefs or political people—various groups. We found out that it was acceptable.

Clinical trial coordinator Mr. Thomas Jones adds that it is the continuous interaction and constant feedback between the study site and the community which make CABs so vital.

The importance of adapting GCP to reflect the cultural aspects of decision-making is now appreciated in Malawi. Distinct progress is being made, although the issues are far from resolved. The ethical dilemma involves getting the appropriate balance between community input and individual autonomy. Future attempts to incorporate some of the suggestions made by the interviewees would certainly advance this cause.

## *Theme 2: Illiteracy*

### *Issues.*

While this theme is titled illiteracy, it is actually a compilation of closely related themes linked to illiteracy which involve witnessing, comprehension, and the length of IC documents. When a clinical trial participant is illiterate or cannot sign his/her name, GCP guidelines indicate that the IC document must be witnessed by a person who can attest that the participant fully understands the commitment and agrees voluntarily (ICH, 1996). In Malawi, the participant typically provides a thumbprint and the literate witness provides a signature. This procedure also applies when the guardian of a child who is a potential subject is illiterate. Hence, the procurement of a witness is necessary in each instance of illiteracy. Comprehension issues are involved in achieving true understanding of the IC document, and these are influenced by the language and length of the documentation. Even though IC is considered to be a process by which a participant continually affirms his/her participation in clinical research, the focus here will be on the interactions that take place during the initial meetings when the bulk of the study details are explained.

Illiteracy is a critical challenge for consideration when implementing GCP. According to the final report of the 2008 Population and Housing Census in Malawi, the National Statistics Office calculates the illiteracy rate to be 36% for persons 5 years of age and older. Illiteracy for males is 31% but 41% for females, a difference of 10% (National Statistics Office, 2009, p. 14). This gender differential greatly affects the clinical trial population. Most trial participants or guardians of children who participate are female; hence the target population is strongly skewed toward lower literacy. Interviewees who interact with participants were asked to estimate the illiteracy level of the subjects who undergo screening. These interviewees estimate the illiteracy

of their study populations to be between 40% and 60%. This range is somewhat higher than the national average, but this may be due in part to the fact that illiteracy in rural areas exceeds that in urban areas, a distinction not made by the national census. Catchment areas, which are geographical boundaries within which study participants can be recruited, vary in their ratios of rural to urban sites and could account for the higher illiteracy percentages reported by interviewees. In addition to the influences that gender and rural/urban illiteracy ratios have on the balance of less literate individuals, poverty and disease, which differ in their rural/urban distribution, may also affect this balance (see Theme 5). For example, the inability to afford better-quality non-governmental health care, the higher prevalence of a certain diseases, or the absence of local health care facilities in more rural areas may motivate the participation of less literate individuals in a trial. The magnitude of the illiteracy rate in Malawi confounds clinical research by adding a large burden of work for study staff and increasing the expenditure of both time and money. The extra human and physical resources that are needed must be factored into project management schemes. Besides illiterate study participants, Mr. Thomas Jones reports that semi-literate individuals who claim to be literate are an additional concern. It takes even more time to determine that these individuals are not fully literate and then determine whether a witness is needed, further prolonging the IC process. Mr. Nelson Marunda gives a firsthand account of the challenges involved in conducting an IC session as he describe a real life interaction with a semi-literate subject,

The mom has to go through the whole reading of it [IC form]. . . . the whole x# of pages [actual number removed for sake of confidentiality] but she still has to go through the process of signing, which, in a mum that has difficulty signing, already takes 20 minutes-- to get her to sign *on* the line and not *below* the line and *in* that tick box. And “Ah no, you’ve written your name, but it is not the 13<sup>th</sup> of February, today is the 15<sup>th</sup> of

February”, so then “Sign and date!”, and by the time she has signed and dated her correction, that date is also wrong. . . . “I know you made a mistake and you have to correct it to the date that you did it, but you have to *sign it for today*”. By the time you are on your sixth correction, you think, “Am I doing something really ethical here?” although it is all according to GCP [italics added].

Inability to read a specific language can sometimes be managed by providing IC forms in different local languages, an option which is often exercised. This too requires extra time and effort and adds complexity, because each document must be translated and then back-translated to check for fidelity and accuracy. The staff person who is conducting the IC session must be fluent in the language of the participant, and this adds an additional constraint as there are more than seven local languages in use in Malawi and it is unlikely that the staff person would be fluent in all of these. Translation of a document as complex as an IC form becomes even more difficult when the language of the subject does not have the vocabulary needed to translate the terminology or explain the procedures adequately.

Furthermore, some clinical research concepts are difficult to grasp. In the words of Mr. Marunda, “a placebo-controlled trial is not easy to explain to anyone, let alone an illiterate mom.” It is a challenge, particularly when local perceptions of doctors presuppose that they would only provide something good, not an inactive ingredient. Mr. Marunda remembers a subject who asked, “How can you give me no *mankhwala* [Chichewa word for medicine]? The whole concept of me participating is that I get this drug you are trying!” The rationale for randomization of participants to various study treatment groups is also difficult to convey because the belief that “more drug is better” may cause participants to want to be in the high-dose drug-treatment group only. The advantages of blinding and double-blinding for clinical

studies are also hard to explicate. Mr. Marunda addresses the complexity of these concepts saying,

GCP explains that [the IC form] has to be at the level of a Standard [Grade] 4. Well, it is not. It is not on a Standard 8. It is the level of--sometimes, if you've gone to the University, you have to read it five times and you are still not clear about it. . . . I appreciate that it has to be very clear, but you still have that mom there with a crying baby that sits there for three hours listening to your talk and thinking "When can I get away here?"

Interviewees report frequent boredom, fatigue, and loss of attention during the IC process. Illiteracy certainly can contribute to this phenomenon but the length of the typical IC form can affect attention as well. Copious feedback from interviewees is directed at the undue length of the forms and how this deters participation and lowers recruitment rates. The shortest IC form was reported to be 7 single-spaced pages after translation to Chichewa and the longest reported form was 25 pages, which took an average of 1.5 hours to explain. Such volumes of detail overwhelm participants, whether they are illiterate or not. While it is unethical to rush through the IC process, Mr. Peter Graves asks whether it is truly ethical to provide so much information that it becomes confusing and he uses the term "dis-information" to describe this phenomenon. Ms. Ellen Mbewe, a PI, corroborates this view, stating, "My fear is that sometimes, by dragging out this whole process, we are really not getting IC." Appeals for shorter forms are widely voiced as Ms. Gabriella Kaputa, a research nurse, illustrates by providing the following account,

I would cite the IC form that we used which was x# pages [actual number removed for sake of confidentiality] and you read the whole thing to the mother. She sits there listening to you. She has got a baby on her lap and she has got a small one at the nursery



school, which she would need to go pick up at 11:00. She will have to prepare the meal at lunch. In this case, after reading the IC form to the mother, that is not the only stage. She has to go to another stage, meet the clinical officer who is going to ask her about 18 questions. From there she has to come for the [treatment] if she is eligible and then she has to go to see the research assistant, so this is a whole process. . . . It took us about one and a half hours. . . . I have a feeling that if the IC form would only be short, like four pages, brief, very brief but clear, the message could be straight to the point.

Is it possible to make a complicated study clear in four pages? More than one interviewee seems to think so. What else contributes to the length of IC forms? Mr. Peter Graves offers the following critique,

The weakness of GCP at the moment is the legalistic understanding of the IC. . . . People do not think about protections [for the subjects]. They think about protecting themselves from legal litigation more than protecting human [subjects]. . . . I would like the document [IC] to be precise and concise and not coming to 10-15 pages.

Mr. Maxwell Ndege, a PI, agrees and makes a suggestion about who might benefit from long IC forms, “Investigators are keen to protect themselves against a bad reputation or against some sort of scandal that might arise.”

After a potential subject is determined to be illiterate, the process of finding an appropriate witness begins. It is complex. One choice for a witness might be a relative or friend who is accompanying the potential subject or guardian to the clinic. Mr. George Ntimu states, “I would rather have somebody I know . . . whom at least I can trust, not somebody who is a total stranger.” The drawbacks can exceed the advantages for this option, however. If the subject is illiterate, there is a higher likelihood that the family member or friend might also be illiterate. Beyond this, lies the sensitive matter of confidentiality. Many studies in Africa involve

some aspect of HIV/AIDS testing, even if HIV/AIDS is not the focus of the clinical trial. The stigma and confidentiality concerns associated with disclosure of one's status generally preclude the use of a witness who is familiar to the participant. The option of returning to the clinic at another time with a family member or spouse exists, but the stigma and confidentiality concerns still apply, except in the case where a spouse may know the mate's HIV status. Nevertheless, any procedure which involves a return to the clinic on a subsequent day or at a later time results in lower enrollment due to the number of individuals who simply do not come back.

Study staff must spend extra time and effort to find witnesses. They often search out a nurse or doctor down the hall who works with the general public or on another project. It is not considered ethical to pay someone to be a witness, so there is little incentive to donate one's time for witnessing. Doctors and nurses in developing countries shoulder inordinately large caseloads, in part because of the scarcity of trained health personnel, so study personnel are not always successful as they make their pleas for witnesses. Ms. Tiyamike Chule, a PI, states, "When you want to look for a legally acceptable representative--that will lengthen the whole IC process and reduce your enrollment rate." Ms. Teresa Swila adds that the length of the IC "is part of the constraint in terms of finding a witness." In some cases, study personnel from one clinical trial can offer to act as witnesses for another trial being conducted in a nearby setting. Mr. Thomas Jones describes situations where "the witness is actually not a person completely independent or separate from the study. It is often a peripheral staff member. We've actually got it in the protocol, as an option, if a totally independent witness is not available."

This account of the issues related to illiteracy, witness procurement, and the comprehension of IC documents is remarkable in its extensiveness. The challenges presented

involve many different and diverse facets of clinical research, and the scope of proposed solutions will need to reflect the breadth of these issues.

*Solutions.*

Interviewees suggest a stringent paring down of the length of IC forms. A limit of four pages is proposed; however, the feasibility of such a number in complex or lengthy trials is undetermined. Interviewees also advocate rigorous adherence to the GCP requirement that the reading level be that of Standard 4 (ICH, 1996). As a solution to the issue of boredom or lack of attention, Mr. Thomas Jones emphasizes that “it is very important to tell the participant in advance how long they are going to stay in the clinic.” He believes that fatigue can be avoided with a proper “approach.” He claims,

We have done a lot of training for our clinical staff who do IC, to create an environment where the participant feels welcome and at the same time important. The person should feel respected. The staff should be able to take the participant through [the IC], not just by reading, but by reading a paragraph, pausing, asking a question and trying to assess whether the participant understands. . . . Because of that, there is less boredom and less signs that they want to go.

With regard to the procurement of acceptable witnesses in cases of illiteracy, the use of participant advocates is promoted. These advocates may be members of the clinical research staff not directly connected to the specific trial. Mr. Thomas Jones describes such a scenario,

We have trained some cadres [of staff] who do not [typically] interact with participants at any level. We train them as participant advocates. They do not work for a particular study. They could be people in administration, people who are cleaners . . . who are quite literate. . . . They help the participant to make an informed decision. . . . After discussion with monitors and sponsors, this was the best option.

Interviewees endorse greater coordination among investigators, sponsors, and IRBs in order to strategize about acceptable witness profiles. A consensus decision by these groups would clarify whether the aforementioned patient advocates, who are technically still employed by the trial sponsor or the investigator, are truly acceptable witnesses and under which circumstances. This researcher wonders whether there is the potential to establish a more impartial team of patient advocates, independent of any sponsor. Questions arise, however, about whether an academic institution or regulatory agency could fund and manage such a team and how the advocates could logistically be available in the various locations as they are needed. A more unconventional approach to the provision of IC for illiterate subjects, one which could eliminate the need for witnesses, is discussed at the end of Theme 3 since it is also a solution for patient identification issues.

Recommendations are made for the enhanced use of innovative, non-written communication in the IC process. Visual aids such as posters, photos, and videos are proposed, and the use of audio recordings, scripts, dramas, and demonstrations is suggested. Despite finding little or no prior literature which documented the use of such tools, some investigators developed novel communications platforms and report their success. Mr. Simon Joni states that “posters, which involved study procedures, were put in the clinic where the mothers would be taught.” He recounts,

We placed the posters in the room we used to meet our clients, so that it could aid questioning. If, maybe, I am just reading to them like this [*looks down at paper*], a mother taking care of a baby at the same time could miss something from what the nurse is trying to explain. But after reading to them, you go also by the posters, going around showing them what will actually happen. The posters were so good that they could show . . . the site where we were going to take the blood, either on the palm or on the

heel. They were explaining it all—like IV drips if there is dehydration, things like that, so the mother was able to grasp.

These posters, claims Mr. Nelson Marunda, were taken by clinical trial auditors “to meetings in India to show that [they are] a not bad idea . . . if you do research in places where people are not so educated.” Ms. Ellen Mbewe concurs with the value placed on the use of innovative media and advises that,

Using pictures or using drama—all those are ways that you can convey information to simple people. . . . They [Malawians] have understood some democratic principles which are not easy—if you look at how Parliament works, how the general election works . . . all complicated procedures that people understand. That is how you do it—civic education—trying to educate people and repeating information because many of the people who are illiterate are very intelligent people.

The clarity and suitability of an IC form for the general public was tested prior to study initiation in one of the trials discussed by an interviewee. They assessed the level of understanding of the IC form in a pilot test using 50 random individuals. The effort demonstrated that major points of the study were poorly understood or completely misunderstood. Improvements and changes in the IC language and the explanation process were made until the desired comprehension was achieved before the study was initiated. Such pilot testing could become a routine part of start-up operations for clinical trials, especially in developing countries.

Another cluster of suggestions for improved understanding of IC centers on the introduction of post-IC testing mechanisms by which a participant undergoes a written or oral evaluation to determine his/her actual level of understanding. The following example, which

may be one of the first of its kind in Malawi, describes such an intervention and the positive outcome. It is noteworthy that the testing was conducted by an individual different from the one who conducted the IC session. Mr. Nelson Marunda recalls,

We generated feedback questions on the most important things. . . . We had twenty [questions] in the end. Lo and behold, we got very good results. If there were more than three out of twenty wrong, then the clinical officer would go through the whole thing [IC] again, usually on another day. . . . If it was less than three wrong, he would explain those three topics again, then ask the participant again what the answers were. I think that out of \_\_\_ participants, we only had \_\_\_ that had to come back because they had more than three wrong. [actual numbers were deleted for the sake of confidentiality; the percentage of participants with more than three wrong is calculated to be 0.2%.]

A re-consent rate of 0.2% is highly remarkable in a population with 40-60% illiteracy. Such a success story is very heartening and attests to the feasibility and value of initiatives which are locally proposed and designed to resolve issues of GCP implementation, specifically those related to illiteracy.

### *Theme 3: Participant Identifiers*

#### *Issues.*

Establishing unique identifiers for individuals in Malawi is a challenge. There is no governmentally-issued standardized number, equivalent to a Social Security Number or National Insurance Number, to help distinguish two individuals with the same name. Therefore, people with common surnames such as Phiri and Banda, the equivalent of Smith and Jones in the West, may be misidentified. Patient identifiers in clinical research in Malawi consist of names, ages, and dates of birth. Naming conventions in Malawi are an important consideration when conducting clinical trials to GCP specifications. GCP assumes a unique and relatively constant identity for the study participant. In Malawi, naming traditions differ from the Western norm. First, a baby that is born in Malawi is not typically given a name immediately after birth. It is a Malawian tradition that parents should spend a few weeks getting to know the personality of their new baby. Only then can they decide whether a name like “Comfort” or “Alile,” which is translated as “she weeps,” is most appropriate. The following is an example of the multiple IC documents that can be required when attempting to enroll children in a study in which both the mother’s and the baby’s HIV status needed to be determined. PI Mr. Nelson Marunda describes,

Before we can enroll the subject, we have to know if the mother of that subject is HIV negative and Hepatitis B negative, so the first IC form will be with the mom, antenatally. . . . The second one is upon enrolling the child. If that is done properly, she has to enroll her child at the last stage of her pregnancy, because you cannot ask her--ask somebody who is in labor--to sign. . . . So there is no subject then. . . . When it is born, you have a sex, but you haven’t got a name yet, because the name is only given after about two weeks. . . . So we ended up with three IC number twos, 2A, 2B and 2C,--2A where the

mother signs but we have no baby, 2B where we have the mom sign and there is a baby and a sex and a date of birth but no name and then 2C that has a date of birth, a sex and a name. . . . Four times the mom has to go through the whole reading of it . . . through the processing of signing.

Second, it is very common for a Malawian to go by various names including surname, baptismal name, village name, or nickname. Alternative naming paradigms can cause confusion as noted by Mr. Simon Joni, “If [a mother] is married, she may choose to have a surname from her home where she comes from. Others do have the names of their husbands.” A village surname is used interchangeably with a husband’s surname; maiden names are interchanged with married names; nicknames are substituted for given names. Thirdly, spelling variations of names can pose problems as noted by Mr. Thomas Jones,

Some of [the participants] are semi-literate or they will tell you that they are literate but if you tell them to write their name, they will write a name differently. For example, they’ll say, “My name is Mary.” Mary in English is M A R Y, but the same name can be written in Chichewa as M A R E. . . . She would come and write . . . MARY on the screening. If you are not careful, in enrollment, she is going to write MARE, but for somebody looking at this [a monitor/auditor], these are two different names.

Finally, while name changes such as those after marriage, re-marriage, or divorce must be managed in all cultures, in Malawi, the official governmental documentation to support such status changes is typically absent.

The absence of official government documentation is also problematic in determining the personal identifiers of age and date of birth. There is no compulsory government-issued birth certificate. “Some of them [participants] will not know their age,” says Mr. Jones, “It is quite a challenge because we just have to believe them and make your own assessment.” In



determining the year of birth, Ms. Faith Mpaka explains that “We use historical events that happen in the country, just to say, ‘When was the first day that we had the independence celebrations? Were you born at that time?’” Clinical officer Mr. Samuel Chiwala elaborates about identifying the month of birth, saying, “We estimate that this child was born during planting, or when we were harvesting. . . . Then we estimate what month do we plant?” Despite the lack of government-issued unique identifiers, there is, however, in Malawi and also in neighboring Zambia, the systematic use of one type of government-issued record called a “health passport” (van der Hoek, Ngoma, & Soeters, 1994). These health passports contain the records of an individual’s health history, of physician’s assessments and diagnoses, and of test results, vaccinations, and treatments (Chaulagai et al., 2005; Neville & Neville, 2009; Malawi Ministry of Health and Population, 2003). The passport-sized booklets, which are differentially color-coded for males and females, are kept in the possession of the patient and greatly assist in participant identification (Figures 2 and 3). Despite the many benefits of this simple and effective medical records system, problems can arise when health passports are misplaced, lost, or stolen, in part because they do not contain photographic or other unique identifiers.

An inability to positively identify study participants in clinical research can have serious consequences for both the trial participants and for data validity. An example, corroborated in two other reports, is illustrated by PI, Ms. Tiyamike Chule,

You are conducting a nutritional supplement trial in an environment of poverty; therefore the feeling is that [people] might want to maximally benefit from that supplement. . . . So, it is likely that a mother who has three children, one or two years apart . . . might bring a different child the next time that they come for a review, so that the child can also get the supplement. The challenge there is: how do you ensure that you are seeing the same child each time they come—the issue of identifying your study

participant. Not only in supplementation--it could be any study where there is perceived obvious benefit. . . . You might get adults also swapping.

Another issue is the identification of participants who must be excluded because they are concurrently enrolled in another trial. Mr. Rodwell Chanje, a clinical monitor, discusses this, saying, "It is difficult because there are also trans-border crossings, where often you have patients who come from another country and you can't prove that they are actually from somewhere else and participating in separate studies."

Guardianship of children is an identification concern which arises when determining who can sign an IC form on behalf of a child. Certain situations pose dilemmas, such as those where an underage mother wants to enroll a child in a study or where a mother puts her child in the care of a relative, either temporarily or permanently. The cases involving the provision of IC for the child of an underage mother are addressed by Mr. Nelson Marunda,

If you are a minor here and you have a child, the Malawi government regards you as the guardian, and the one in charge even though you are a minor, because you are old enough to have the baby and you are old enough to take that responsibility, so you are also old enough to understand if you want to have it enrolled in a study.

The cases where there is a change in guardianship pose more complex challenges. It is not unusual to learn that a mother has returned to school, or moved to a different village, perhaps because the husband has lost his job, and the dependent child has been left in the care of a grandmother or aunt. If the child is enrolled in a study, then an individual different from the one that signed the original IC is now responsible for the providing day-to-day care and assuring attendance at study visits. Such a change in guardianship, while a common occurrence, is not documented in any official manner. When study personnel learn of such a change, new identification and contact information must be obtained and the consenting process re-initiated

in order to acquaint the new guardian with the study protocol and the schedule. Without the desired confirmatory documentation of guardian transfer, study personnel must take the new guardian's word and accept that a change has taken place.

HMIS-10

## MALAWI

### HEALTH PASSPORT WOMAN HEALTH PROFILE

**NAME** \_\_\_\_\_

**DZINA** \_\_\_\_\_

**DATE OF BIRTH**      /      /

**TSIKU LOBADWIRA**      day / month / year

**VILLAGE** \_\_\_\_\_

Mudzi

Please bring this book each time you come to see the nurse or doctor  
Chonde bweretsani kabukuka podzaonana ndi dotolo kapena namwino

Signature of issuing person: \_\_\_\_\_

Issued date: \_\_\_\_\_

**MK 15**

#### Malangizo kwa eni Chiphaso

- Chiphasochi muli mbiri yofunikira ya moyo wanu.
- Chiphasochi chimaperekedwa kwa mwana wamkazi akatha msinkhu kapena chiphaso cha mwana chikatha.
- Ngati munali ndi chiphaso cha mwana, musunge pamodzi ndi chaphaso ichi nthawi zonse. Chiphaso cha mwana chimakhala ndi mbiri yofunikira ya moyo wanu, imene imathandiza madotolo ndi anamwino kuti apeze chomwe chikukuvutani molunjika ndikukupatsani chithandizo choyenerera.
- Musaiwale kutenga chiphasochi kulikonse komwe mungapite kukalandira chithandizo cha mankhwala kapena thandizo la mtundu uliwonse.
- M'chiphasochi muli magawo awa:
  - Mbiri ya mtundu uli wonse.
  - Chithandizo cha kulera.
  - Sikelo ya amayi apakati ndi kubeleka kawiri.
  - Malo osalembapo ogwiritsa ntchito mayi akadwala polembapo matenda ndi chithandizo chomwe chingaperekedwe.
- Mukhoza kudziwa za m'mene moyo wanu ulili poona matenda amene azunguzidwa mu gawo la mbiri kumayambiriro kwa chiphasochi. Ngati kwazunguzidwa kwambiri ndiye kuti muyenera kusamalira kwambiri moyo wanu.
- Sungani chiphasochi mu pepala la pulasitiki. Mukhoza kugwiritsa ntchito paketi ya ukhondo ya shuga yopanda kanthu kuti chiphasochi chisaonongeke.

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### Antenatal Consultation Record

**LMP date:** \_\_\_\_\_ **EDD:** \_\_\_\_\_

Visit No.	Date	Gestation	Fundal Height	Position & Presentation	Weight	B.P	F H S	REMARKS / MEDICATIONS	Signature	Date of next Visit
1										
2										
3										
4										
5										
6										
7										
8										
9										
10										

VDRL date: \_\_\_\_\_ Hb<sup>1</sup> date: \_\_\_\_\_ Hb 2 date: \_\_\_\_\_ Pelvic assessment: Interspinal diameter

+ - titre result: \_\_\_\_\_ result: \_\_\_\_\_ result: \_\_\_\_\_ sacral promotory reached?      yes      no

Previous Obstetric History - risk factors				Medical/surgical History - risk factors				NOTES:			
Deliveries	0	1	2	3	4	5+	Tuberculosis	no	<input type="checkbox"/>	yes	<input type="checkbox"/>
Abortions	0	1	2	3			Asthma	no	<input type="checkbox"/>	yes	<input type="checkbox"/>
Stillbirths	no	<input type="checkbox"/>					Hypertension	no	<input type="checkbox"/>	yes	<input type="checkbox"/>
Abnormal deliveries							Diabetes	no	<input type="checkbox"/>	yes	<input type="checkbox"/>
C-sections	no	<input type="checkbox"/>					Epilepsy	no	<input type="checkbox"/>	yes	<input type="checkbox"/>
Vacuum	no	<input type="checkbox"/>					Renal disease	no	<input type="checkbox"/>	yes	<input type="checkbox"/>
Symphiotomy	no	<input type="checkbox"/>					Fistula repair	no	<input type="checkbox"/>	yes	<input type="checkbox"/>
Multiple	no	<input type="checkbox"/>					menstrual cycle	regular	<input type="checkbox"/>	abnormal	<input type="checkbox"/>
APH	no	<input type="checkbox"/>								variable	<input type="checkbox"/>
PPH	no	<input type="checkbox"/>									
(Pre)eclampsia	no	<input type="checkbox"/>									

check TTV status inside passport cover & Iron + SP supplements

Physical Development - risk factors			
NORMAL		HIGH	
Height (cm)	150+	less than 150	
leg or spine deformity	no <input type="checkbox"/>	yes <input type="checkbox"/>	
Age	16 - 39yrs	less than 16 yrs or more than 40 yrs	

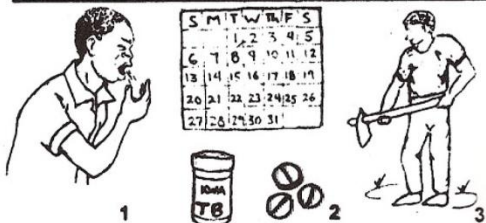
Figure 2. Health Passport, outside cover and centerfold

Tetanus Toxoid Immunisation		
	Date	Signature
TT 1		
TT 2		
TT 3		
TT 4		
TT 5		

Bambo okonda banja lake adzilimbikira pa nkhani yakulera

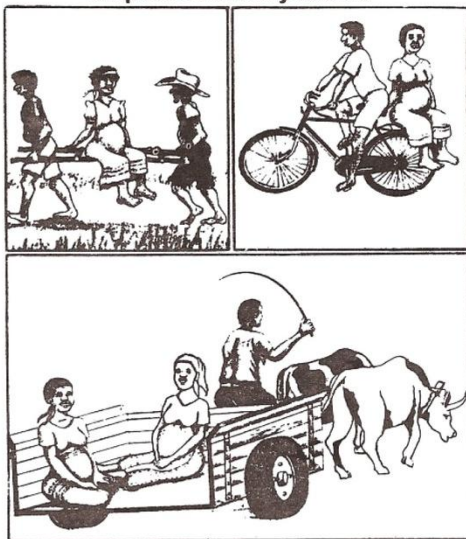


Abambo alimbikitse akazi awo kuyamwitsa mwana wakhandu mkaka wa m'mawere wokha, mpaka akwane miyezi inayi kapena kuposelapo



Wodwala TB amachira ngati amalaza kumwa mankhwala mwa ndondomeko yake

Konzeranitu ulendo wanu wopita ku chipatala nthawi yabwino



Amayi ambiri apakati amamwalira chifukwa chochedwa kupita ku chipatala pamene nthawi yakwana. Chonde abambo tengerani akazi anu msanga ku chipatala panjinga, pa ngolo, kapena pa machira nthawi itakwana kuti akachire mosavutika.

Kusowa magari panthawi yomwe mayi ali ndi pakati ndi vuto laikulu. Dziwani zizindikiro zakusowa magari mthupi  
Musachedwe - Pitani kuchipatala msanga



ANEMIA SYMPTOMS

Tizidya zakudya zosiyanasiyana monga ndiwo za masamba obiriwira, zipatso, nyama, nyemba ndi zina zotere zimawonjezera magari m'thupi

Iron supplementation schedule			
date	number of tabs supplied	signs of anaemia	signature
SP - Malaria prevention for antenatal women			
date	# weeks	signature	Notes:
			1st ANC visit in 2nd trimester between 28 and 34 weeks

Reminder to the passport holder

1. This passport contains valuable information for your life.
2. This passport is issued to a female child at puberty or after finishing the use of child health passport, whichever comes first.
3. If you had a child health passport, always keep that passport together with this one. The child health passport contains valuable information about your life, which helps your doctors and nurses to assess your problems correctly and give you right treatment.
4. Don't forget to carry this passport wherever you go for any consultation or any service.
5. This passport contains sections for:
  - general history,
  - family planning services,
  - antenatal consultations and delivery for two pregnancies, and
  - open space for general consultations, diagnosis and treatment.
6. You may be able to assess your health condition by looking into the circled diseases or conditions in the history section of this passport. Too many circles mean that you need to be more careful about your health.
7. Keep this passport in a plastic pocket. You may use a clean empty packet of a 1-kg sugar bag to keep this passport to prevent it from getting worn-out.

Figure 3. Health Passport, inside covers, front and back

*Solutions.*

Mr. Nelson Marunda proposes measures which would streamline GCP documentation in light of the local custom of deferring the naming of a child after a birth,

The name of the child after two weeks is not always the same name it has after a year. . . . We should be allowed, instead of saying “critical finding” . . . to [write] a file note from the investigator . . . to explain the situation.

With regard to alternate surnames, Mr. Simon Joni offers this solution for speaking with participants,

We ask, “Which one would you like to use?” . . . We ask them to make a choice of the name that they want to be written on the card and then stick to that until the end of the study.

This approach is corroborated by Mr. Thomas Jones who suggests telling participants, “You have told us that this is your legal name. Can you please make sure that all the documents that you sign use your legal name, unless there is a change of status that you can explain to us?”

When asked by the researcher how a naming discrepancy is resolved, he continues,

Basically, the first step was to write a memo to file and clarify why there is a discrepancy. The second thing is to . . . have a discussion with the participants, so she can tell us the exact name that she writes. There should be documentation of the discussion with the participant. . . . We would ask the PI, when he is writing a report to the ethics committee, to include that scenario and the steps we have taken as a site. But also, we do not just stop there. When monitors come, we ask them, you know “We had this scenario and this is how we dealt with it. What do you think we could have done?”

Potential institutional solutions, both governmental and private, are cited by interviewees. Ms. Memory Ngoma, a PI, claims that, “When it comes to things like birthdays, I think that there is some movement in terms of introducing birth certificates. I think that will be very valuable and important.” Ms. Chifundo Banda adds that “the government has now implemented that each and every . . . village should have a register book where they can write [when] each and every child is born in the village.” An example of a privately designed solution is the approach of the non-profit Baobab Health Partnership initiative at Kamuzu Central Hospital in the capital city of Lilongwe. Their computerized patient management system is able to bar-code health passports and associated clinical and laboratory data, making unique identification possible for more than 800,000 patients for the first time in Malawian history (Douglas & Deula, 2003; Douglas, Deula, & Conner, 2003; Douglas et al., 2005; Fraser et al., 2007).

Another solution, that of fingerprinting study participants, was raised by interviewees as a potential deterrent to participant “swapping” but it was noted that this approach is fraught with controversy and fear, much as it is in the West. Concerns include fears that fingerprints might be used for purposes unrelated to research such as criminal conviction and unresolved legal and ethical issues around the fingerprinting of children. These concerns about fingerprinting must be balanced with the recognition that fingerprints are used at the present time in clinical trials when the adult study participant is illiterate. The thumbprint of the illiterate participant is routinely captured on the IC form along with the signature of the witness.

The last suggestion made by interviewees emphasizes the importance of making investigators, especially non-Malawian ones, aware of local naming and identity issues for trial participants prior to trial design and initiation. Overall, the proposed solutions fall into two

categories, one involving practicalities such as “notes to file” or awareness of local naming traditions and a second involving theoretical “wishes” for government programs which would issue birth certificates and/or unique identifiers. Clinical research personnel have control over the first of these categories but little or no ability to orchestrate Malawi-wide governmental initiatives.

While the goal of this thesis is to document local solutions to locally identified issues, this researcher is struck by the paucity of realistic short-term solutions for both the problem of participant identifiers and for issues of IC for illiterate subjects. It would appear that, in a world of technological advances, innovative solutions should be possible, such as the audio or video recording of a participant’s IC. Such mechanisms could simultaneously address both problems. Recently, electronic data capture (EDC) is becoming more widely accepted for clinical research data handling. What would prevent a similar acceptance of the EDC of a participant’s identity and IC? A literature search on this topic revealed two recent reports of studies where EDC has been attempted documentation of IC. In a 2002 report, Benitez, Devaux, and Dausset describe a study in Paraguay which was conducted with participants of the Guarani Indian tribe, a population with a high rate of illiteracy. A process called triple media recording (TMR), which consists of simultaneous audio recording, video recording, and photography, was used to document the oral consent process in the local language in a manner consistent with CIOMS guidelines. Of the one hundred individuals involved at the screening stage, Benitez et al. (2007) found that,

More than half of the potential participants did not come forward to give consent. We believe that these people were able to exercise their freedom of refusal by not stepping forward, because explicit refusal is not part of the Guarani social codes and customs, whereas implicit refusal by silence or inaction is perfectly acceptable. . . . Illiterate people



should not be denied the benefits of clinical research . . . [and] audiovisual documentation of oral consent . . . enables valid informed consent to be obtained. (p. 1407)

The second study involved obtaining IC prior to major surgery, but not as part of a clinical trial, and also took place in an illiterate population (Danino, Chahraoui, Lile, Moutel, Herve & Malka, 2006). Participants were randomized into two groups of 30 which were similar in age, sex, education, and baseline anxiety. One group underwent classic IC while the other was documented using TMR during the IC. The TMR group was also shown a CD-ROM which explained the procedures and potential complications using pictures and artwork prior to the final consent step. Both groups underwent a second anxiety test prior to surgery. Results showed that 1) the patients in the TMR group were significantly less anxious before surgery than the control group and 2) ten patients from the TMR group chose not to consent to surgery, while none from the classic IC group abstained. Danino et al. (2006) believe that TMR and the audiovisual CD-ROM presentation allowed illiterate people to decline a highly recommended surgery. This study emphasizes the value of an audiovisual CD-ROM type of IC process, a concept that aligns with the suggestion to use posters and other visual aids enhance IC for illiterate individuals (Theme 2). Despite the focus on the CD-ROM intervention, this study nevertheless provides evidence that TMR alone is an appropriate and effective alternative for documenting the IC process. These two studies raise the question of whether TMR would be an effective means for documenting patient identity and IC in the Malawian clinical research environment. A study to evaluate this technology would certainly be beneficial.

#### *Theme 4: Local Myths and Misconceptions*

##### *Issues.*

Cultural beliefs are important considerations when trying to initiate a clinical trial and recruit and retain participants. Mr. George Ntimu states that sometimes the particulars of a protocol are in direct conflict with the norms of local society. He says that “people in Malawi just receive a consent form that has been formulated elsewhere without necessarily looking at the cultural beliefs of the people.” Mr. Joseph Mwamkwamba concurs that one needs to “look into the whole issue of culture,” and Mr. Peter Graves elaborates about culture as an aspect of GCP,

We are talking about behavior. It is the way you understand and respect rules. People who are different respect rules in different contexts and with different motivation, so if you want to abide by GCP you have to know the culture . . . so that you can . . . adapt. Local myths and misconceptions are one of the primary aspects of culture that need to be understood.

Some of the most commonly circulated myths affecting clinical research in Malawi revolve around blood and blood draws. Twelve of the interviewees in the study mentioned the issue of fears related to blood. While these fears are also found in other parts of Africa and the world, they appear particularly pervasive in Malawi. A generalized, widespread anxiety about blood and blood-related procedures is fueled in part by beliefs about witchcraft and Satanism. Witchcraft, defined as the “human harnessing of supernatural powers for the malevolent purpose of practicing black magic” differs from Satanism which is “devil worship . . . dedicated to the antithesis of the God of the Christian Bible” (Mather, Nichols, & Schmidt, 1999, p. 312,

p. 41). The importance of blood in both is described in the Encyclopedia of Witches and Witchcraft by Guiley (1999),

Blood is called the “river of life.” It is identified with the soul and carries the vital energy of the universe through the body. It is revered and feared for the miraculous power it possesses and confers. Blood that is let is believed to unleash power. . . . Blood is used to bind oaths and brotherhood and . . . Devil’s pacts are always signed in blood. A few drops of blood of a person . . . used in magical charms and spells . . . is said to give a witch or magician power over that person, in the same manner as hair and nail clippings.

(p. 26)

Blood is deemed to be a vital life force; therefore repeated blood draws are feared to be unhealthy as they deplete this force. Mr. George Ntimu explains that “the issue of blood draws is a very delicate thing in Malawi,” and adds that “Notes for a participant withdrawn from one study stated that ‘the father didn’t want any further participation of the son in the study because there were just too many blood draws.’” Doctors, clinical officers, and nurses relate stories of being called vampires or bloodsuckers. Clinical officer Mr. Samuel Chiwala speaks of his experiences, saying,

If you go to primary school and say, “I have come to withdraw blood,” it is a fact that all the children will disperse. We always have a very bad feeling about drawing blood. . . . Many people do not like withdrawing blood from a very young child. They feel that the child might die quickly.

There is also the expected fear of pain associated with blood draws or finger pricks, which are commonly used in the diagnosis and follow-up of malarial and other disease.

The connection of blood to witchcraft and Satanism, occult terms that are used interchangeably in Malawi, is strong. Clinical officer Mr. Simon Joni relates that “Recruitment

was very hard. Why? . . . There was a belief that our study was involved with Satanic activities.”

Mr. Amos Gamadzi concurs, saying, “When it comes to trials which involve the drawing of blood, people think that blood is being used for Satanic activities and . . . is being sold so that investigators can make money.” Interviewee Mr. George Ntimu explains that in some cases, “the consent form does not explain what the blood samples will be used for.” Even in cases where details are provided, the notion that blood is being sold or re-sold, either to outsiders or to local individuals with the sinister purpose of casting a charm or spell, is still common belief. This is supported by the experience of Mr. Thomas Jones;

We’ve had cases where there have been rumors in the community that the blood . . . is sent to the U.S. . . . and is sold, because you have told them that some of the specimens will be sent to a laboratory in the U.S.

Fears are that the blood will be sold by study nurses or doctors to someone who will then be able to put on a hex or spell on the donor. Satanism is also involved in cases such as the one described by Mr. Joseph Mwamkwamba where “people think that you might be selling their children [study subjects] to the devil,” or the instance recalled by Mr. Samuel Chiwala “when mothers who were barren . . . told their friends [who had children in a study] that their children would die.”

Local misconceptions about clinical research include beliefs related to a woman’s fertility. It is a common misunderstanding that drugs or investigational products “will make you become infertile or . . . likely to bear a child who is disabled,” as noted by Mr. Blessing Thokozani. Another misconception arose and was perpetuated about the vaginal swabs collected during a research study. Mr. Thomas Jones explains that the swabs were thought to be “sold . . . and given to women who cannot bear children in the U.S.” Mr. Thokozani

acknowledges that there are “lots of misconceptions” and that they lead people to the “make decisions without having an informed mind.”

Mr. Nelson Marunda addresses the fact that misunderstandings can exist in the opposite direction as well, noting that investigators and auditors have “lots of misconceptions” about local issues. He relates a humorous example in which an auditor underestimates the savvy of a prospective Malawian participant.

The auditor, who thinks he/she is very culturally right, says that it [randomization] is like the flipping of a coin . . . and the mother, who is the patient, says, “We don’t do that here in Malawi. We do it with a computer. . . .We do it for the secondary schools. . . . If you get above a certain percentage [in school], the computer spits out, ‘yes, you get a grant or no, you don’t’ and that comes out in the newspaper.”

In what major ways do myths and misconceptions affect clinical research? Superstitions deter participation, decrease enrollment, and increase withdrawal rates. Rumors feed on one another and get propagated within the community from one generation to the next. All of these work to undermine the general conduct of health care and negatively impact the clinical research climate.

### *Solutions.*

A recurring plea made by interviewees is for increased awareness of prevailing myths and misconceptions on the part of investigators, especially non-Malawians investigators. Local IRBs, governmental regulatory agencies, and entities such as the RSC at the COM could serve as educational forums for the dissemination of information about local myths to investigators. The involvement of local PIs in international studies is also stressed, as this is an important mechanism for expanding cultural understanding. Interviewees advocate for the translation of

such awareness into actions, such as the careful scrutiny of proposals, protocols, and IC forms to ensure that terminology as well as procedures and practices do not conflict with cultural beliefs and customs. Special attention should be paid when blood or blood drawing is involved. Interviewees encourage detailed explanation to each participant of the purpose for each blood sample and the importance of multiple blood draws in a longitudinal study. Whenever possible and appropriate, the test results from a blood draw ought to be provided to the patient so that he/she can associate these with the prior sampling. Attempts should be made to keep the volume of blood that is drawn low and the frequency of sampling to a minimum for Malawian studies. Techniques to facilitate better understanding, such as the use of lay terms like “tablespoon” instead of the more scientific “milliliter” to describe blood volumes, are mentioned and their use is urged in order to avoid misconceptions.

In addition to an awareness of myths and misconceptions on the part of investigators, there is need to provide education to the general public in order to dispel inappropriate local beliefs about clinical trials, including those which may be rooted in witchcraft and Satanism. Attempts to educate can take various forms. First, interviewees identify three important educational opportunities: pre-trial community awareness campaigns, community interactions throughout the course of a study, and post-study feedback meetings. Mr. Thomas Jones aptly advises that one must “continually manage misconceptions” by correcting and deflecting them in a timely manner before they get out of hand. Second, in a Malawian journal citation, Kavinya (2008b) captures a sentiment expressed by interviewees when she encourages investigators to “publish their research articles in the mass media,” not just scientific journals, and “to write their article in the layman’s language as much as possible” (p. 104). Third, a vision for expanded education of the general public is proposed. Educational interventions could explain why blood samples are needed in clinical research and could provide assurance that blood will never be sold

or used for illicit purpose. The potential for a national media blitz about myths surrounding research is raised and discussed. Mr. Amos Gamadzi states, “I think that [radio or drama] would help a lot, especially the use of those media houses which have access to the larger population. That would be quite helpful.” Brainstorming sessions among clinical research professionals are also advocated as a means to identify which mechanisms, such as TV, newspaper and billboard ads, songs, posters, and community teach-ins, would best demystify both clinical research and general health practices. The integration of GCP into the cultural understanding of basic health care was postulated as a more long-range goal.

Is the vision of re-educating the general public possible? Is it realistic to think that beliefs in witchcraft and Satanism can be countered? A brief history of the advent of the Malawi Blood Transfusion Service (MBTS) attests that both are possible. The MBTS was started in 2004 in an environment where fears about blood abounded. Prior to that time, units of blood in Malawi were collected exclusively from “directed donations” sought from family members whose blood was screened and cross-matched, often in the midst of emergency circumstances. The MBTS, headed by Mr. Bridon M’baya, was charged with establishing anonymous voluntary donation systems to replace the old directed donations system (Cheema, 2007). Mr. M’baya describes the challenges and the changes, saying,

The MBTS started operating at a time when there were rumours of blood suckers in Malawi, . . . when blood collection issues were discussed even in parliament and we had journalists being arrested for issues of blood sucking—so to come from that angle to reach this kind of expansion is something that we are proud of. (Cheema, 2007, p. 91)

The expansion to which Mr. M’baya refers is the increase in the number of blood units from 5,000 to 25,000 collected by the MBTS between 2004 and 2006 and the fact that collections have continued to multiply since then. This researcher saw first-hand evidence of the interface of the

MBTS with the public and the acceptance which the MBTS was afforded in 2009. Teams of individuals wearing clothing with MBTS logos regularly stood on street corners in Blantyre with plastic buckets for the purpose of soliciting monetary donations for MBTS. These solicitors raised the general consciousness about MBTS and also served as spokespersons/advocates. They were generally treated with respect and appeared effective in their advertising role. This example affirms the feasibility of progress and details the surprisingly rapid pace at which change can take place. If the vision of the MBTS can materialize, then the vision for improvement of both clinical research and health care delivery can also be realized. It is time to begin and as the new vision catches hold the research climate in Malawi is certain to improve.



*Theme 5: Poverty and Disease**Issues.*

In Malawi, poverty is extremely prevalent. This is attested to by the low average yearly income, the per capita equivalent of \$900 USD (CIA, 2009). The pressure to seek out monetary remuneration of any kind is very strong. Most potential research participants in Malawi would be considered vulnerable subjects in the context of clinical research. According to the ICH definition, vulnerable subjects are “individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate. . . . Vulnerable subjects include impoverished persons (ICH, 1996). Compensation for research participation in Malawi involves careful consideration of whether the “expectation of benefit” would “unduly influence” or coerce someone to enroll in a study. There are two sides to the issue of compensation in Malawi. The first is the view that compensation for poor and vulnerable populations in developing countries is too low and is not on a par with that provided to participants in developed countries, thus inherently unfair and unjust (Ndebele, Mfutso-Bengo & Mduluzza, 2008). The second is that even low compensation levels can provide inducement that could be interpreted by some as coercive. Both perspectives are addressed by interviewees.

The first side of the issue, the unfairness of low remunerations, was noted in the context of side-bar comments made to this researcher. Clinical research personnel in Malawi, who are well aware of the magnitude of the compensation provided for study subjects in the West, complained about this unfairness [field journal notes]. They see it as highly ironic that an impoverished population benefits less from clinical research than a wealthy one. To them, this imbalance raises issues of justice and ethics. A related perspective that was frequently voiced by

interviewees, particularly those responsible for recruitment, is noted in Ms. Patricia Nyalungwe's statement,

I would like international regulators to understand . . . that for people to participate in a clinical trial, in an African setting, there has to be a motivation factor, an incentive, which is not allowed in GCP. They come to a clinical trial, hoping to get something. They do get better care, but they also need extra things on top, apart from the better care. . . . They need something for their time because most of these people are business people so [they are] spending their whole day coming to the hospital.

Study recruitment, which is fraught with a multitude of logistical and cultural issues in Malawi (Theme 2), is made even more difficult because clinical trial coordinators can offer few incentives which would make study participation inviting.

The second side of the compensation issue in Malawi is the view that even low compensation levels can provide inducement to participate in a study for the wrong reasons. In Malawi, because of fear that it is unethical and coercive to pay vulnerable patients for their participation, only the most minimal of remunerations is typically allowed, such as transportation reimbursement or the provision of material incentives. Even a small transportation allowance, however, can prove to be a motivational factor in such an impoverished country. The same is true for the provision of material incentives such as soap, diapers, mosquito nets, iron tablets, napkins, basins, and *zitenje* [cloth wraps/slings] or foodstuffs such as peanut butter, *nsima* [ground maize flour], sugar, and lunches (Masiye, Kass, Hyder, Ndebele, & Mfutso-Bengo, 2008; Muula, 2007). Interviewees report abuses of even such very low cost reimbursement schemes by some participants. An example is described by Mr. Bright Mbalame (B.M.), a clinical monitor, in conversation with the interviewer (Int.),

B.M.: A father comes to the . . . trial which is recruiting patients aged . . . between 12 months and 10 years. . . . The father escorts his child to the study clinic. At the end of the visit, they are given back transport money and the father, seeing that there is transport reimbursement at the end, decides to bring some more children and the father just identifies those children in his neighborhood and he tries to convince the investigator . . . because there is some money given at the end. . . . Each child is going to be given a transport reimbursement of 200 MK in our local currency, which is about \$1.50 USD.

Int: Is he attempting to bring them in to the trial and call them his children?

B.M.: Of course, yes. Actually there have been some reports where, as long as some people hear that there is some benefit associated with participating in a particular trial, they will do everything possible to make sure that either [they] themselves or some other people that they can bring [get] into the study. They should do so, so that they can get as much of the benefit as possible.

Mr. Mbalame describes another, more innocuous, example of a participant's misuse of remuneration to her own advantage.

Let's say you are recruiting your study participants from within the city. . . . Some who attend the first and second visit, on the third visit they will lie to you to say that, "I relocated to another place, very far from the city." Why do they do that? Often in studies when a participant relocates to another place, they still retain the participant in the study but they increase the stipend. . . . We had the case . . . where somebody cheated the study team, to say she had relocated . . . one or two hundred kilometers from here, with an intention of getting more transport reimbursement.

Such evidence of abuse supports the view that "undue influence" or "coercion" can be associated with even the smallest of remuneration. Not everyone agrees with this view,

however. Emmanuel, Currie, and Herman (2005) make a distinction in terminology between coercion, a threat of worse consequence, and undue inducement, the dangling of an unduly positive good. They note that both can result in unethical or illegal action or cause bad judgment but that coercion is remedied by removing the threat and undue inducement is avoided by reducing the value of the “carrot.” In the reports from Malawi however, the value of “carrot” is already exceedingly low and yet demonstrations of bad judgment persist. Emmanuel et al. (2005) elaborate, saying that, “Being forced to make a decision because of a ‘tempting good’ in unfortunate circumstances is insufficient to compromise autonomy and create an undue inducement” (p. 338). While instances of abuse may be the exception rather than the rule, they still underscore the effect that poverty can have on participant motivation and GCP implementation. Hence, the debate about how to strike a balance between international equity and protection against coercion or undue inducement continues.

In addition to concerns about remuneration, poverty can affect clinical trials in other ways. Research studies involving nutritional supplements, which have been discussed under Theme 3 in reference to participant identity, are fraught with additional complications when hunger is present. In Malawi, many NGOs provide nutritional supplements as a form of charitable aid. Because the general public is familiar with this paradigm, it is difficult to convey the concept that nutritional supplements that are provided as part of a clinical trial are unproven and still being tested. The common assumption is that nutritional supplements are, by nature, effective and beneficial. Hence, study staff must counter these assumptions with extra education during the IC process about the nature of nutritional supplement research and testing.

Poverty is closely correlated with the high burden of disease in Malawi, and these factors can affect clinical trial conduct synergistically. In a report which combines WHO statistics and

local measures of diseases in Malawi, Bowie (2006) states that infectious disease is the most common cause of death, accounting for approximately 60% of deaths in 2002. Among the communicable diseases, HIV/AIDS is predominant, being responsible for 34% of deaths, and is related to the leading risk factor of unsafe sex. Malnutrition and poverty-related risk factors such as unsafe water, sanitation, or hygiene, the underweight status of children and mothers, and vitamin or mineral deficiencies account for an additional 34% of total deaths. Hence the sum total of poverty-related risk factors has an impact on survival that is as great as the risk factor of HIV/AIDS. The largest burden of disease is carried by the subpopulation of children under five years of age which has the highest mortality, accounting for almost 50,000 or about 20% of the approximately 250,000 yearly deaths in 2002 in Malawi (Bowie, 2006).

What types of pressure does this high burden of disease create? In a resource-poor country, the health care infrastructure cannot easily cope with the amount of care that is needed. This inability to respond to prevailing need is evidenced by long queues at government health centers, sporadic and limited availability of clinical officers or nurses, and inadequate supplies or medications. The unresponsiveness of the system acts as a motivator for individuals to enroll in a research study, for which the standard of care is distinctly higher. As Mr. George Ntimu states,

People just jump into the study . . . [and] think that it is an alternative route to obtaining treatment. . . . Do people really join the clinical trials out of the feeling that “I want to contribute to the development of Drug A or Drug B”? In most cases, it is not anything along those lines. . . . [They think] “I’ll be able to get the health care free of charge, probably the best care, because we understand that this project is coming from the UK or the US.”

For many people, participation in research is a very realistic route to better care. It is a choice, often made out of desperation, which can mean a difference between life and death for the participant (Mfutso-Bengo, Ndebele & Masiye, 2008; Mfutso-Bengo et al., 2008). Muula (2007) relates an example of a rural subsistence farmer, whose wife has died from HIV/AIDS-related causes prior to the era of widely available anti-retroviral (ARV) therapy in Malawi. The farmer must decide whether to enroll in a study where ARV therapy is provided or choose the usual standard of care which is “essentially not much” (Muula, 2007, p. 262). This example is evidence of the better standard of care that is provided in clinical research. The variability in the standards of care in developing countries is a problem which is confounded by an absence of universally accepted measures of quality. This is recognized by Ms. Ellen Mbewe, a PI, who states,

Quality is a really a very sensitive thing when it comes to the setting where you are.

What you would call quality here--quality service in terms of medicines that you get, or kinds of treatment that you get--may not be the same as elsewhere.

Poverty and disease are factors which fuel one of the commonly mentioned deterrents to study participation, which is the difficulty in attending all study and follow-up visits. These visits can be multiple and frequent and can span several years for some longitudinal studies. The logistics of travel to a study site on a regular basis are more complicated when study catchment areas are large, transportation options are few, and the wellness of participants or family members is compromised.

Finally, the high burden of disease has an important but seldom described consequence for clinical research conduct in developing countries--that of coping with routinely high numbers of serious adverse events (SAEs). ICH-GCP guidelines define an SAE as “any

untoward medical occurrence that at any dose: results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/ incapacity, or is a congenital anomaly/birth defect” (ICH, 1996). In Malawi, as in many developing countries, death rates are high, as are the number of life-threatening events and hospitalizations. Patients are hospitalized for conditions which could be managed on an outpatient basis in developed countries which have a better health care infrastructure. All of these factors contribute to high numbers of reported SAEs. According to PI Ms. Tiyamike Chule,

Most of these SAEs are related to the severity of illness, so they are expected in many instances. . . . They are related to the outcome that you are looking at. Do you really want to stop a study because you have so many people suffering from malaria? Those are the challenges.

Ms. Patricia Nyalungwe emphatically states that SAEs “are not rare!” The percentage of SAEs was estimated by PI, Ms. Esther Pembeleka,

Out of 1000 people enrolled . . . [there are] 200 SAEs (20%). . . . During the malaria season there are a lot more. . . . I would usually see three per week that would need to be sent out. . . . I sort of expect that in our setting we would have these numbers of SAEs, but the process of actually sending them, the expedited ones especially, is quite taxing. . . . When we get an SAE . . . we have to fill in two types of forms. Now, there is going to be another. . . . The PMPB, a regulatory authority, now wants to get adverse events forms. . . . For one SAE, you would have to fill in three forms.

Ms. Teresa Swila, a PI, reports an SAE rate of approximately 8% and comments,

Say you are doing a clinical trial, following each child for as much as a year, children from 6 months to 5 years of age . . . are going to get sick. One of the criteria for an SAE is hospitalization so anytime any of these kids get hospitalized . . . it is an SAE.

The burden of disease dramatically increases the time that is required for the variety and quantity of SAE documentation in developing countries such as Malawi. This, in turn, increases the pressure on already strained human resources and study budgets.

### *Solutions.*

With regard to participant remuneration, Mr. Joseph Mwamkwamba suggests that encouragement is needed along with more education and awareness of clinical research in order to help people understand that one can be motivated simply by an altruistic benefit to society. He would like Malawians to understand that they can give freely without always getting a monetary return. Since remuneration and motivation are linked, it might also be useful to modify some of the commonly held beliefs about health research as expressed by Malawian individuals polled in a survey by Kavinya (2008a). Seven of the ten people believe that ordinary individuals do NOT benefit from research. In addition, one individual comments, “They [investigators] don’t come back and tell us the findings and results,” while another says, “I haven’t had a chance to read their reports or even to hear from them” (Kavinya, 2008a, p. 103). These views suggest that improved communication of study results to participants would enhance the value they place on health research. Another individual comments, “I think research is actually benefitting the researchers only, because there are few who disseminate their results to the public” (Kavinya, 2008a, p. 103). This suggests that investigators should communicate to an even wider audience—the general public—in order to make their voice heard in a setting where the need is great due to poverty and disease.



Suggestions for creative remuneration under developing country circumstances include targeting communities as beneficiaries, in addition to participants. Innovative compensation schemes can consist of extending electrical service to a community, drilling borehole water wells, or improving sanitation facilities. Mfutso-Bengo, Ndebele and Masiye (2008) relate a suggestion to researchers, “They [investigators] can show their gratitude to us by digging boreholes in the areas where water is a problem. By looking at the borehole, people will remember the research always and appreciate what the researchers did” (p. 64). Funds can also be used to support, improve, or construct local health clinics or to initiate community projects to promote public health (Ndebele et al., 2008). Furthermore, these authors suggest “raising resources from international research grants that can be used to support local research as well as research institutions” (Ndebele et al., 2008, p. 44) for purposes such as technology transfer, training, and staff remuneration. If it were possible to set standard compensation levels that would be applicable world-wide, Ndebele et al. suggest that the percentage of standard compensation which is above and beyond locally appropriate reimbursement for time, travel, and inconvenience in a developing country should be diverted to fund community initiatives. They suggest that ethics boards could negotiate on behalf of communities for fair compensation that would benefit all, not just study participants (Ndebele et al., 2008).

Few realistic or short term solutions for alleviating the burden of poverty and disease are envisioned by the interviewees in this study, so coping strategies must suffice. Also, the gap between the common standard of health care and that afforded via clinical research is not likely to narrow rapidly. However, Mr. Gordon Clark, a PI, makes the following observation, “The research projects have created what you would see in a hospital in a developed country and ideally maybe that would spill over into the regular hospital care . . . but it won’t without more resources.” Nevertheless, some evidence that GCP and rigorous documentation does transfer

into the hospital setting by the example of health personnel trained in a research environment was noted by this researcher [field journal note].

With regard to solutions for streamlining SAE documentation, Ms. Esther Pembeleka states, “I would ask them [the sponsor, drug manufacturer, IRB, government regulator, all the powers that be] . . . to have a standard form . . . and harmonize the information.” Ms. Patricia Nyalungwe further describes the conundrum of filling out four different SAE forms,

For [one SAE form], they need the age, the weight and the like, of course the date of onset, the dosing and the ranges of doses. . . . For [another], what we need is just the date of onset, date of last drug administration, brief summary of SAE and the lab results. . . . Another is even more complicated. . . . Another is just a just a letter.

The difficulties involved in completing SAE forms in Malawi are illustrated by Mr. George Ntumu in his description of the typical sequence of events,

You may have to consult the medical personnel who administered the case, like from the hospital, and we don’t have a record tracking system in most of the hospitals where you can look in a log and find out about the problem. You have to go in person to find the guy who administered the treatment and then ask him or her, and ask about what really happened. . . . It would depend how busy . . . that person is that particular day. We have very few health personnel in our hospitals. You go there and find . . . that he has about 100 other patients waiting at the door who need his attention so he might not be able to get the information. Then you have to wait for him or her to be free.

This scenario is the basis for a solution proposed by Mr. Nelson Marunda. He advocates the creation a new part-time position, that of an SAE consultant, so that there is always a study team member present in the local hospital where SAE cases would likely present. He says that “when somebody is admitted, [an SAE consultant] would fish out the person from the ward who

knows [about the SAE] and follow and get the story—the why, the history, the lab results, all on an SAE form.” Creative adaptations such as these may not solve the issues of poverty and disease, but they provide some mechanisms for maintaining GCP compliance in populations where poverty and disease burdens are high.

## *Theme 6: Barriers to Teamwork*

### *Issues.*

Kohls (2001) describes how cultural beliefs and behaviors determine social relationship styles which range from authoritarian in traditional societies, on one hand, to individualistic in more Westernized societies, on the other hand. A group-orientation style straddles the middle of the social relationship spectrum. Both extremes, authoritarian and individualistic, can be at odds with teamwork, which is an essential characteristic of clinical research. The group-orientation style is the one which best facilitates the necessary teamwork. There is no way that a single sponsor or investigator can carry out a clinical trial alone. Clinical research brings together a team of people with different backgrounds, from statisticians to laboratory personnel, to nurses, doctors, or computer programmers, and the list of roles goes on. Most team members have specific skills not found elsewhere in the group. Successful research is usually the result of a team effort characterized by communication, interdependence, and cooperation. In Malawi, cultural factors can work for and against teamwork. The Chichewa proverb, *Mutu umodzi susenza denga*, which means “One head does not carry the roof,” reflects the communal basis of Malawian culture and this mindset encourages teamwork (An Afro-centric Alliance, 2001). On the other hand, interviewees identify four factors which impede teamwork: 1) hierarchy, 2) confusion about roles, 3) absentee leadership, and 4) poor communication.

Mr. Rodwell Chanje describes the first of the factors which prevent teamwork, saying, “What it boils down to--is hierarchy.” Such ranking includes economic, gender-related, educational, political, social, and work-place hierarchy. Mr. Chanje describes the work-place hierarchy present in the clinical research arena, “Investigators have a very high-powered situation. So, who tells them what they are doing wrong and that they should do it a different way? . . . Does it have to come from somebody at the same level?” Whether authority figures

are non-Malawian PIs or Malawians who hold a title and exert influence, there is a pronounced deference accorded to them that seems to go beyond rightful respect. This deference can extrapolate to capitulation and resignation on the part of clinical research team members [field journal note]. Authority and status seem to breed fear, as described by Mr. Chanje,

People are scared to actually take a step because they might just be thumbed down by somebody saying, “You are not the right person. I will not talk to you.” . . . What position you have . . . will determine whether they actually speak to you.

An individual with a less prestigious status may feel that his/her ideas will not be considered.

Mr. Joseph Mwamkwamba said,

Because of the hierarchy here in Malawi, there are instances where, instead of people saying no, when someone says or speaks on something, simply because the person of authority is higher, they will say yes whilst they really mean no because they are afraid to say no.

This is an underlying attitude noted by this researcher during conversations with interviewees.

There is a sense of disempowerment [field journal note]. Is this the resignation that results from repeatedly being disregarded? Mr. Chanje describes the barriers faced when trying to develop assertiveness,

There is a lack of initiative-- taking the initiative to do certain things and to carry on. . . . As soon as you have somebody [a mentor] . . . who is pulling them through, they are going to rely on them [the mentor]. Is the initiative going to be there in the end to follow through once that shadow person [mentor] has left? . . . Will the PI accept what the local person has said? . . . You know what you want to get across, but the PI is blocking you.

Differences in educational or career achievement as well as stratification along economic and political lines can form the basis for some of the work-place hierarchy that is described above. Interviewees mention an additional factor that is encountered--gender-related social hierarchy. Mr. Chanje observes that "In Malawi, they've got the hierarchy of 'women don't have much say'." Kamkwamba and Mealer (2009) describe gender-related cultural practices in Malawi saying, "If I [male] called my younger sister over and held out a hundred-kwacha note, saying, 'Run quickly to the shop and get some bread', she'd bow on one knee before taking it. It's like that." (p. 93). In such a climate, will a female team member be empowered to express her ideas freely and will she be vetted fairly? Whether the origins of these hierarchical elements are grounded in traditional Malawian culture, in the history of colonial influence, and/or in modern-day Western organizational structure is unclear. Regardless of origin however, rigidly-applied hierarchies can confound the teamwork needed for GCP implementation.

The second factor which impedes teamwork in Malawi and in many developing countries is a profound lack of clarity about the roles and responsibilities of each clinical research partner. The roles of sponsors, investigators, coordinators, clinical officers, monitors, other staff, and even IRBs are poorly defined and the resultant confusion compromises clinical trial conduct. Sponsors and funders of international trials are seldom single entities but are often participants in elaborate consortiums composed of many partners, including NGOs, governmental regulatory agencies, educational institutions, pharmaceutical companies, drug manufacturing factories and more. In one recent trial conducted in Malawi, seven institutional partners on three different continents were involved, in addition to multiple investigators and IRBs. This example is not atypical. The role of an organization which provides funding but may or may not act as a true sponsor is particularly tricky. Mr. Rodwell Chanje states,

All around—site vs. sponsor, sponsor vs. site, etc., . . . I sometimes wonder about the amount of communication that comes back from a sponsor. If they get a question in regard to a protocol or a study-related procedure, not responding to that . . . shows me that they don't quite understand what is going on in the research. They fund it and that is it.

Such complexity blurs the responsibilities of “sponsor” and “investigator” as defined by ICH-GCPs and results in difficulties in coordination and communication. The physical distances between partners and between the partners and the study sites escalate the costs associated with international travel and create additional barriers to good oversight and proper monitoring. International partners become involved out of necessity for a number of reasons, one of which is the lack of a pharmaceutical company or drug manufacturing factory that is based in Malawi. Funding is another. Sole sponsorship of a research study by the Malawian government, a local academic institution, or a local NGO is unlikely because their financial resources are insufficient at present. In the cases where a clinical trial involves a new drug entity for which regulatory approval is being sought, the roles are more clearly defined than they are in the case of academic or investigator-initiated trials, the types which currently predominate in Malawi. When an international PI is not based in Malawi during a study, he/she typically relies on one or more local investigators for oversight. The local investigators, who are typically medical doctors, then delegate much of the patient care at clinical trial sites to clinical officers because of the shortage of doctors. Unless role-sharing parameters and demarcations of authority are anticipated and defined in advance, any problems which arise must be dealt with on an ad hoc basis, and this is seldom ideal.

The third barrier to teamwork is one which is frequently cited by interviewees. It is the “absentee” nature of the PI’s oversight of day-to-day site operations. Mr. Joseph Mwamkwamba said,

Where the PIs are not involved . . . what is seen is . . . those kinds of segregations. . . . You’ll have the clinical officers; you’ll have the nurses. You’ll start seeing more segregation in teams, where people do not come and share together. Then issues of authority become something that impacts on that as well.

The “segregations” to which Mr. Mwamkwamba refers impede the cohesive pursuit of a common goal by a research team, and the hierarchy issues mentioned previously can play out again. Similar remarks are made by Mr. Rodwell Chanje,

Lots of the PIs are not hands-on people. . . . They don’t really understand what it actually all involves, especially at the working level. . . . Does the investigator really understand the whole process that happens at the site? Does he understand all the work that is involved and how his staff work? If he sits in an office here and he has sites all over the country, does he actually know what is going on at the sites?

While it is obviously not possible for a PI to be present concurrently at all clinical sites in a multi-site trial, the generalized degree of absenteeism is both disconcerting and serious if the following comment of Mr. Blessing Thokozani describes the reality accurately. He states that “In all the sites that I’ve visited, I’ve never met the PI. . . . You just find the trial coordinator and the research study staff.” Reference to this pattern by multiple interviewees supports the premise that this scenario is prevalent. Although the status quo may be widely understood by Malawians, one wonders if sponsors and funders are fully aware. Some of the commentary that PIs are too often absent originates from the investigators themselves. Many PIs understand that it would be preferable to be more involved, but the duties, pressures, and constraints of distance,



time, and budget prevent more active leadership. Mr. Blessing Thokozani, a clinical monitor, defends PIs saying, “The PIs do not have time to spend at the research sites and they tend to delegate almost all their duties to the study staff like the trial coordinator and the research nurses,” although adequate training is often lacking for these support roles. Mr. Thokozani continues, advising that, “They cannot just leave the conduct of the trial with the trial coordinator and the other study staff. They have to be there to check that these people are doing a good job.” But, he concedes, “These PIs are busy. They are busy with teaching.” Mr. Maxwell Ndege, himself a PI, describes the dilemma,

In Malawi, there are few scientists who are PIs. We are so busy writing protocols, attending meetings . . . teaching, doing all sorts of things. It is unlikely that on a weekly basis we would be able to go to the sites where our patients are being recruited and observe whether . . . there are any deviations. . . . One study is being done 200 km from here. . . . You can't do it because of time limitations. . . . We [PIs] perform multiple things—even the budgets. I'm sure you [outside of Malawi] have a grants office. . . . Here, you have to do that all yourself. . . . You have to chase the receipts. . . . You have to keep your eye on a lot of things--some of them are administrative. . . . emails, where in the West you download documents in a second, here . . . [they] take 15 minutes [and] to communicate with your collaborators, you need to be on top of your emails. . . . Also, for the study I'm implementing, I've had to write about 42 SOPs. . . . It is not a great use of my time.

This quotation touches on just a few of the wide-ranging duties that a PI in a developing country must perform because there is a lack of capacity in terms of trained support personnel. Mr. Ndege's description substantiates the argument that PIs in Malawi are overburdened. Are sponsors fully aware of the difficulties inherent in conducting clinical research in developing

countries? Do they appreciate the magnitude of the burden that local PIs face? Do they provide sufficient support for these PIs?

The fourth barrier to teamwork is poor communication. Communication via mail, phone, fax, and internet is often a challenge in Malawi, but infrastructure insufficiencies fall outside the scope of this thesis. However, some aspects of poor communication are related to the cultural determinants under examination. The quantity and quality of communication can suffer when there is a belief that information is power. This interplay with hierarchy can result in diminished transparency across the board. An individual in a high-level position may be unmotivated to relay all pertinent information to subordinates because this could diminish his/her own status. Similarly, a subordinate may withhold or delay the reporting of problems and progress to a supervisor or colleague in a reverse power play. Interviewees claim to have experienced both scenarios. For example, Mr. Chanje states, “I think that lack of communication is a huge problem and it comes from the investigator all the way down. Certain people are omitted, either by mistake or because the other person wants to have more power.” In addition, the cultural practice of nodding and agreeing as a matter of courtesy also confounds good communication. According to Malawi Missions (2010), “In Malawi, it is preferable not to tell someone ‘no’ outright when they ask for something. Delays and elaborate excuses are more customary.” A “no” might be interpreted as an attempt to sever a relationship and this is to be avoided in a culture where relationships are highly important. This cultural practice can cause misunderstandings and hence poor communication in clinical research practice as well as well as everyday life.

To summarize, the interviewees in this study identify hierarchy, confusion about roles, absentee leadership, and poor communication as barriers to teamwork. There is considerable

interplay between these related topics. For example, poor communication can result from absentee leadership while it contributes to entrenched hierarchy and aggravates confusion about roles. In light of this interplay, solutions which address the larger topic of teamwork will be most effective. While interviewees describe a situation lacking in teamwork, they do not view the status quo as static. They believe that change for the better is coming slowly and they propose the following solutions to step up the pace for adopting a mindset of teamwork.

*Solutions.*

Surprisingly, interviewees report that a mechanism which promotes teamwork in clinical research, by reducing hierarchy, is GCP training itself, along with the subsequent execution of GCP principles. These comments were not prompted by the suggestion of the interviewer but were responses to the question, “Which one thing has helped the most to improve the conduct of clinical trials in Malawi?” Mr. Simon Joni reports,

I think GCP helped a lot in teamwork. . . . To the staff, I think [GCP] is a very good experience, because you tend to work as a team. You tend to help one another. You keep time and you are accurate. Mostly what you aim at is good results so, to the staff, it [GCP] improved . . . our working standards. We saw that and we tried to help one another.

Mr. Joseph Mwamkwamba similarly stresses the value of teamwork and relates these practical experiences about how teamwork was implemented in the Malawian setting, saying,

What you start finding is that when there is good teamwork among staff members, it is easier to share some of the experiences. . . . There could be some meetings where people just come in. Sometimes there is no need to have an agenda. . . . You come in and say, “Let’s share our experiences.” . . . That team spirit helps because there will never be this thing where people now start thinking of competition. . . . We are focusing in one

direction. That becomes quite helpful. . . . Why not have one lunch, a meal together. . . . once a week? If it is possible, maybe cook together. . . . Once you . . . share together with everyone, then there will be time when you can be able to speak on some other topics, informally and the impact of the formal part becomes greater.

Mr. Mwamkwamba urges the adoption of this informal teamwork style of organization despite the fact that a more hierarchical approach is typical in Malawi.

Confusion about the roles of partners in clinical research collaborations is an issue addressed by Mr. Rodwell Chanje. He suggests that good sponsor-investigator relationships need

clear guidelines, right from the beginning about who can do what. Up to what authority can the investigator change things or implement things without having to let the sponsor know? [Answers] need to be fed to all individuals involved. . . . Authority . . . needs to be set down clearly in the beginning.

He does not elaborate, however, on how this can be accomplished; therefore, many questions remain. Are sponsors aware of the particulars related to the limited capacity for clinical research in developing countries? Are they aware that their support role may need to be bolstered?

Would greater discussion of these issues in the clinical research literature be useful? Should the local IRBs ensure that all roles and responsibilities are adequately defined and properly carried out? Most of these questions serve as starting points for future discussions. There is some precedent, however, for the involvement of local IRBs in this process of clarifying roles. Both the NHSRC and COMREC, the two IRBs in Malawi, have hired auditors who are commissioned to inspect the human clinical research studies which the IRBs have reviewed [field journal notes]. While it is not known whether the IRBs monitor the definition of roles and responsibilities during proposal review process, the IRB auditors are certainly positioned to

identify any gaps or deficiencies that result from confusion about roles or responsibilities in sponsor-investigator or consortium partnering arrangements.

The third barrier to teamwork, minimal PI involvement at some clinical trial sites, can be remedied with interventions that relieve the PI of some of his/her duties. These would allow the PI to be present more frequently at the clinical site and would enhance teamwork, thereby improving clinical research conduct. Solutions suggested by interviewees cluster around two topics: 1) training and mentorship for local individuals so that they can fill clinical trial support positions and 2) capacity building measures to enhance clinical research infrastructure. Both initiatives would decrease the workload and pressure on local PIs. The need for training for new clinical trial support staff is a topic addressed in such detail by interviewees that it could form the basis for another thesis. While their comments include ideas for how training could be implemented, it suffices here to say that interviewees strongly urge training and mentorship for the roles of coordinator, monitor, and auditor. Mr. Maxwell Ndege comments on the perceived need and the positive impact that support staff would have, saying,

I would say that we are enrolling half of what we could have possibly done if we had the additional . . . human resources. . . . I think what we need is mentorship . . . If we were in an environment where there was good mentorship by some experienced clinical trials coordinators . . . that would be great, but now the responsibility is on me as the PI.

Hence, training would not only improve enrollment but also facilitate better clinical trial conduct by allowing the PI to delegate some of his responsibilities to properly trained individuals. Mr. Gordon Clark, a PI, also describes how clinical trial coordinator training would reduce the workload of a PI who is trying to manage clinical trial data queries alone. He says,

Even, if . . . you [the PI] have set aside one day to work on the queries that have come from the sponsor, you are still not on the ward. Someone else has to be on the ward. I

think it is really a resource issue, a human resource issue. . . . [But] even if we had the money, we haven't trained clinical trial coordinators. That is the gap. . . . Because if we haven't trained them and I took a good clinical officer or a good nurse and trained them, then we would have to replace them so . . . It is a cascade. But that niche, a clinical trial coordinator, . . . doesn't exist and the new recognition is that when you do a study you need a person with those capacities. That is going to be a time and labor-intensive process because what you are really going to have to do is train that person and then have someone mentor them through a study or two until they have gained the confidence to do it.

To reiterate, while Mr. Clark speaks specifically about clinical trial coordinators, other interviewees make similar comments about monitors and other support staff positions.

With regard to the other initiative which would lessen PI workload, that of generalized clinical research capacity building, Mr. Maxwell Ndege speaks about the resources needed to develop that infrastructure,

I was mentioning about the 8% overhead that National Institute of Health (NIH) gives us [referring to academic institutions in Malawi]. Now, an institution like . . . the University of Liverpool, they have . . . a compliance office. . . . They have a dedicated person, paid . . . to look at compliance issues with regard to GCP. . . . That is an institutional position. Well, 8% NIH overhead has to pay for the accountants that are looking at our books. Is there money there to employ . . . a technical person looking at these things [compliance]? There is literally no money. If you look at US universities . . . some of them get 40% overhead. . . . But look at us here. We are already starting from the bottom. Our universities want to comply . . . but they simply do not have the money and the capacity to do it by the book. Now, the task is shifted from the institution to the

investigator who should be doing the science--who should be writing the publications--who should be writing proposals. . . . What I'm asking is for consideration . . . We have to implement things according to GCP and this is what we need.

Mr. Ndege's plea for more liberal and equitable overhead allowances in grant awards is corroborated by two other interviewees. Increased funding for Malawian research institutions is only one means to increase research capacity and support, a necessary goal with which no one would disagree. This researcher, in the context of serving as interim director of the RSC at the COM, has first-hand knowledge of the difficulties involved in building clinical research infrastructure in Malawi. Support resources for activities such as grant and protocol writing, IC and CRF form development, financial administration, and so on would certainly relieve PIs of technical concerns and allow them to concentrate on the care of study participants and quality of clinical research data. In the interim, before this enormous task of training and capacity-building can commence, is there a guideline for the frequency of PI site visits? Mr. Blessing Thokozani suggests that PIs ought to "be there at least once in a fortnight. They should visit the site and find out what is happening." Specific minimal intervals for the periodic presence of a PI at a site are arguable. Would discussion of this topic among the local research community be possible, and could a consensus about minimal frequency be achieved? Can adherence to such a locally-derived, Malawi-specific guideline be monitored by either local IRB auditors or national regulatory authorities? While questions remain, implementation of any initiatives that could limit PI absenteeism would enhance teamwork.

Some solutions for minimizing poor communication, the fourth barrier to teamwork, are suggested by Mr. Joseph Mwamkwamba. He addresses the cultural inclination to respond in the affirmative saying,

In Malawi, when they say yes, they mean no. When they say no, they mean yes. That becomes a challenge. . . . The thing that you need to reiterate . . . here in Malawi would be to be sure that if someone says yes, ensure that they really mean yes, and ensure when they really mean no. There is no “just an in-between”.

More important, Mr. Mwamkwamba describes what he believes to be the underpinning for good communication and increased transparency among team members. In response to the question, “What was most helpful in getting GCP implemented in Malawi?” he states,

One of the most helpful things is the relationship that . . . the investigator builds with the staff. Because when investigators build that relationship with the staff, then because that good relationship is there, it becomes easier to understand the reasoning for any change that comes in. . . . One of the key things is the relationship between investigators and their site staff.

It is interesting that Mr. Mwamkwamba uses the words “building a relationship” in describing investigator-staff interactions. His insight aligns perfectly with the emphasis that Malawian cultural tradition places on the importance of relationships. In his opinion, such relationships, characterized by the informal lunch-time meetings which minimize hierarchy, can facilitate communication about any protocol-related changes or directives. This researcher notes that good investigator-staff relationships are strikingly obvious from the comments of interviewees in groups where positive examples of communication and effective clinical trial conduct are reported [field journal note]. The opposite is also apparent when poor communication and difficulty in GCP implementation are reported by interviewees from clinical teams where investigator-staff relations are described as weak.

The concept of teamwork is an integral component of GCP training and implementation. Even as the specific barriers to teamwork emerged from this series of



interviews, it was evident that subsets of the research community have already begun to overcome them. Their stories document their success. Dissemination of the knowledge gained by these leaders would benefit the wider research community and hasten progress in Malawi.

#### Chapter 4: Recommendations for the Future

The discussions of issues and solutions in Chapter 3 center on specific aspects of clinical research and GCP implementation. This chapter concentrates on the more general recommendations made by interviewees, which would have an overarching impact on clinical trial conduct. These ideas are outlined under the following four headings:

1) Malawians should be key players in adapting GCP to the local clinical research environment.

According to Mr. Maxwell Ndege, “We [Malawians] are the best people to come up with solutions . . . with research proposals or ideas about how to better implement health services and what are the good interventions.” While other interviewees did not state their ideas quite as directly as Mr. Ndege, they nevertheless conveyed the belief that Malawians best understand their own local culture and are well positioned to suggest innovative adaptations for implementing GCP guidelines. A corollary to this idea is that Malawian IRBs are also the “best people” to help adapt protocols, IC forms, CRFs and other clinical research documentation so that they better conform to on-the-ground realities.

2) GCP-related “operations research” is needed to identify and solve culturally specific issues.

Operations research can be defined as research which applies analytical and scientific methods to problem-solving and decision-making. It involves optimization of processes, resources, and support systems within an organization. When Ms. Ellen Mbewe was asked what one thing was most needed to move Malawi forward toward better GCP implementation and a higher standard of clinical research, she replied,

What needs to be done in the future is maybe exactly what you [this researcher] are trying to do here--people just to look at alternative ways of, let's say for example, IC-- people experimenting with alternative ways of getting information out--so some kind of operational research, where people really go back and say, "Is this working the same way that we would want it to?"--and even trying to look at this in different settings. What do people really need in different settings?

Operations research with a focus on clinical trial conduct has been conducted in Malawi on a small scale in the studies of Corneli et al. (2007) and van der Horst et al. (2009), but more targeted research is needed. Specific areas for emphasis, in addition to those identified in this thesis, include data management, indemnification insurance, trial master file archival processes, clinical trial laboratory operations, clinical trial pharmacy operations, source documentation, regulatory affairs, and the interface of clinical research with Malawian hospital infrastructure.

3) Greater networking and communication among investigators and their staffs is essential.

As stated earlier (Theme 6, Solutions), subsets of investigators in Malawi have made valiant efforts, against formidable odds, to execute clinical studies in compliance with GCP guidelines. Some have achieved remarkable success while others have struggled, but there is much to be learned from all attempts. Because clinical trial data must be kept confidential, there is a tendency for investigators to treat even the operational aspects of clinical research confidentially. It would be highly beneficial, however, if investigators could discuss and brainstorm about non-confidential lessons which were learned about operational matters, culturally-specific adaptations or local GCP implementation strategies. Mr. Joseph Mwamkwamba describes the goal and an explicit means to that end saying that there is a need to

have people that you would be able to consult . . . throughout the networks. I would start looking at having teaching sessions. . . . It could be something that is done quarterly or monthly . . . then it becomes a standing kind of program. . . . They can [also] have a place where people can be able to drop in their emails, where they can be asking questions. . . . “We have this kind of knowledge...” “We are finding...” “These questions have come up.” “How do we help you?” . . . “What are the trends?” You discuss the practical things.

When asked how to step up the pace of networking, Mr. Thomas Jones replies similarly,

It needs somebody to start. . . . email, just a blog, talking. . . . Bring them [clinical research personnel] together. Let them talk. From there, how do you communicate? You can come up with email, you know. It doesn’t mean that you should be physically meeting all the time. You can share information.

Mr. Thomas Jones relates the success of one networking meeting, saying,

I gave a talk and people came to listen about what we do, about quality assurance details and what procedures are involved. . . . So many people were brought together. We talked; we discussed. We didn’t know about these things. We spent the whole day. By the end of the day we learned some things from other people, the way they were doing things. . . . We need to network. We can network just through emails asking each other, “We have this scenario. You have been doing this. How do you go about it?” . . . At the end of the day, it is Malawi as a country that benefits. We are going to do trials that respect the rights of the participant. That is what is key—not just a matter of quality data.

Speaking about the possibility for teach-ins or group brainstorming sessions, Mr. Amos

Gamadzi comments, “It would be very welcome by the research community here. It would be

*very* [italics added] helpful. . . . If you heard a number of people having the same problems . . . you would want to attend that.” Hence, it is widely agreed that it would be useful to develop new forums and use available technology to open up communications among investigators and among all cadres of clinical research personnel in Malawi.

4) Harmonization and coordination of capacity building and regulatory initiatives is needed.

Mr. Wilson Chimanga, a PI, comments on the need to align clinical research guidelines between governing bodies within and outside of Malawi. He states that he would like “to bring together the ICH, the Food and Drug Administration (FDA), the NRCM, COMREC and the NHSRC guidelines and see what could come out of that, to come up with some really good GCP training for Malawi. That would help.” Agreement on the specifics of how guidelines should be adapted and implemented in developing countries is long overdue. A meeting, conference, or other mechanism by which international regulatory bodies could receive direct feedback from investigators and regulatory bodies in developing countries would certainly be welcome. Within Malawi itself, however, there is an additional need for harmonization. Mr. Bright Mbalame states,

I would want that these three institutions [PMPB, NHSRC and COMREC] come closer in a kind of collaboration. . . . I would want that the regulatory authorities establish a closer working relationship with the RSC. . . . If all operations were harmonized, it would offer more protections to study participants in the various clinical trials happening around the country.

The RSC, an academic entity independent of the PMPB, the IRBs, and individual sponsors, is strategically situated such that it could serve an important role for communication, training and coordination. Ms. Tiyamike Chule comments on this, saying, “The RSC is not seen as a

regulator but as a support service to help adhere to GCP. . . My feeling is if the RSC could play a facilitatory role, they could become the link between the researcher and the regulators.” If this is so, then all effort must be made to bolster and fund the RSC, building its capacity to carry on this important mission.

In summary, the recommendations of interviewees are logical, reasonable and valuable. It is the hope that by giving voice to ideas of Malawian clinical research personnel that their needs and requests will be heard and acted upon.

## Chapter 5: Conclusions

This study examines six themes which are classified under the theoretical framework of cultural determinants which affect GCP implementation in clinical research in Malawi. The 26 study participants advance both topic-specific issues and solutions (Chapter 3) and more general commentaries (Chapter 4). Because this sampling of participants in Malawi is small, it is clear that this thesis does not address all of the relevant issues which fall under this theoretical framework. Nevertheless, after analyzing the totality of the data, this researcher believes that one can step back and assess the situation in Malawi from a broader perspective and also provide some insight about the way forward. From that vantage point, this researcher would like to make three conclusions related to GCP implementation in the conduct of the clinical research. They are enumerated as follows.

1) Much progress has been made toward GCP compliance in human clinical studies in Malawi.

An encouraging commentary about GCP implementation in Malawi is made by Ms. Teresa Swila.

GCP is an excellent concept and I think that the expectation is that these high standards are applied wherever in the world you are. That is obviously a very good thing. . . . From my experience, it raises people to a higher level—a level where they really need to be. . . . GCP is the ace in my back pocket, in terms of when I have issues with my staff not doing things the way they are supposed to. I always know,- listen, this is the way you have to do it. You can't cut corners. You've got to do this. There are good reasons for doing it, because we want to protect our patients and we want to ensure that the data that we are gathering is of the utmost quality.

While this statement is very positive, the most encouraging aspect of it is that this attitude is now more commonplace. The energy and enthusiasm with which new young investigators have embraced GCP, viewing the guidelines more as a friend than an enemy, is distinctly different from the wariness and caution that this researcher experienced in Malawi in 2006 and 2007. This change bodes well for the future of clinical research in Malawi.

2) A one-size-fits-all approach to world-wide GCP implementation does not work.

Specific examples from this thesis, together with literature reference about clinical research in other developing countries, support the premise that human research guidelines must be flexible and adaptable enough to conform to local realities. Jesani (2008) states, “The concept of cultural relativism is becoming much more real as cross-border science collaborations grow,” and goes on to quote bioethicist Glenn McGee, saying, “You cannot conceive of a world in which there will be one set of global ethic” (p. 59). So how does the continent of Africa and more specifically, Malawi, fit into this scheme of relativism? Miltos Ladikas, international development officer at the Center for Professional Ethics in the UK, states, “We have no choice but to bring Western ethical guidelines into Africa, as they are the only ones we’re familiar with. In time, Africa will develop its own” (Jesani, 2008, p. 58). This is already beginning to happen, as evidenced by responses from participants in this study. Capacity building programs which strengthen research and increase the number of studies, particularly those headed by local PIs, will help Africa and Malawi in particular to develop realistic ethical GCP guidelines.

3) Malawians who are engaged in clinical research should be consulted and empowered.

“Ask, ask, ask” is the first expression in the formula for moving clinical research forward in Malawi in the coming months and years. It is all too easy, if one is familiar with the operational



paradigms used in developed countries, to import that knowledge wholesale into the world of less developed countries whether it is applicable or not. This approach is likely to evoke the type of resistance commonly seen when any externally-originated directive is imposed. Since teamwork is necessary for good clinical conduct, it is obvious that success in Malawi will involve incorporating local personnel into teams as equal members and thereby opening up opportunities for their ideas to be heard and tested.

Above and beyond “asking and listening,” what Malawi needs is empowerment. Empowerment involves both strengthening and advocacy measures. It means state-of-the-art training, along with the incorporation of traditional wisdom, in order to provide the qualifications and capacity needed to allow Malawians to build their own research communities. Empowerment includes commitments to delegate opportunities for management and leadership and to maintain accountability from the grassroots to the top. Is there precedent for such initiatives? The Green Belt movement promoted in Africa by Nobel Peace Prize recipient, Wangari Maathai, is one such model. The principles used by this movement to mobilize, motivate, and empower community groups to plant trees for the re-greening of Africa could well be applied to the field of clinical research (Maathai, 2006). The sense of ownership and pride in achievement which characterizes successful empowerment is a self-reinforcing motivator which could improve the quality of clinical research conduct in Malawi.

It is the belief of this researcher that when someone discovers and knows what he/she truly “wants,” as opposed to allowing the “shoulds” imposed by others to shape future goals, then he/she will “see” how those goals can be accomplished. The way forward will be clear if the vision is clear. This principle applies to groups and countries as well as individuals. It is the

sincere wish of this researcher that Malawians will come together and discover their own vision for clinical research. It will then surely be realized.

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## APPENDICES

## Appendix A: Informed Consent Document

**TITLE: Identification of Issues Relevant to Implementation of Good Clinical Practice (GCP) in Non-Regulatory, Academic Clinical Research at the University of Malawi College of Medicine, Blantyre, Malawi**

**CONSENT TO PARTICIPATE IN A RESEARCH STUDY ABOUT GCP IMPLEMENTATION.**

Version 1.2, March 26, 2009

**INVESTIGATOR'S NAME:**

Joann Schmidt, BS Medical Technology

Candidate for Master in Clinical Research Administration, Eastern Michigan University,

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**FACULTY ADVISER AT EASTERN MICHIGAN UNIVERSITY:**

Dr. Elizabeth Francis-Connolly, PhD, OTR

Director, School of Health Sciences, College of Health and Human Services, Eastern Michigan University

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**COLLEGE OF HEALTH AND HUMAN SERVICES(CHHS) Human Subjects Review Committee:**

Dr. Gretchen Dahl Reeves, Interim Chairperson Tel: 001.734.487.4096

Email: [chhs\\_human\\_subjects@emich.edu](mailto:chhs_human_subjects@emich.edu)

**COLLABORATOR: UNIVERSITY OF MALAWI, COLLEGE OF MEDICINE**

Professor Cameron Bowie, MB BS MRCP DCH FFFPHM

Associate Professor of Community Health, College of Medicine, University of Malawi

Tel: 00265(0)8844248

Email: [cbowie@medcol.mw](mailto:cbowie@medcol.mw)

**INTRODUCTION**

The purpose of this research study is to gain a better understanding of issues relevant to implementation of Good Clinical Practice (GCP) in non-regulatory, academic clinical research at the University of Malawi, College of Medicine, Blantyre, Malawi. Research studies only include subjects who choose to participate. As a study participant you have the right to know about the methods that will be used in this research study so that you can make the decision whether or not to participate. The information presented here is to make you better informed so that you may give or withhold your consent to participate in this research study. Please take your time to make your decision. Participant eligibility is based on experience in various aspects of the conduct of clinical research involving the application of Good Clinical Practices (GCP). You are being asked to participate in this study because you have experience with GCP in the context of clinical research. Participation is voluntary. In order to participate in this study, it will be necessary to give your written consent.

**HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?**

Between 16 and 24 people will take part in this study.

**WHO WILL CONDUCT THIS STUDY?**

Joann Schmidt will conduct this study, interview all participants, analyze study results and report findings.

**PROCEDURES**

An interview guide listing the types of questions which may be asked and a copy of the ICH Principles of GCP will be provided to you. The researcher will explain the study to you, answer any questions you may have, and witness your signature on this consent form. You will meet with the researcher for a 60 minute interview at a location that you have both agreed upon. You will be asked to answer open-ended questions about your experiences with regard to GCP in clinical research. You will also be asked some demographic questions about how long you have been involved in research, whether you are Malawian or other nationality, what your clinical role is or what your medical specialty is. The interviews will be audio-recorded and transcribed. Upon completing the interviews, you will be given a duplicate copy of this informed consent, which includes contact information.

**LENGTH OF THE STUDY**

The study will involve a 60 minute interview. All interviews will take place within a 12 week period in 2009. Selected participants may be asked if they would like to be part of a focus group meeting at the end of the study to obtain feedback from participants on the validity of the themes which have emerged from interviews.

**WITHDRAWAL FROM THE STUDY**

You can decide to stop at any time. Tell the researcher/interviewer if you are would like to stop. The researcher may also decide to terminate your participation in case of unforeseen logistical problems.

**RISKS OF THE STUDY**

There are no foreseeable risks to you from participating in this study.

**BENEFITS OF THE STUDY**

Participants will not accrue any direct benefit, monetary or otherwise, from this study. There may however be both a perceived and real benefit from the discussion and dissemination of suggestions for potential improvements in GCP.

**WHAT OTHER CHOICES DO I HAVE IF I DO NOT TAKE PART IN THIS STUDY?**

Your alternative is not to take part in this study. If you choose not to take part in this study, your future will not be affected.

**CONFIDENTIALITY**

The researcher agrees to keep confidential all information that would in any way identify the participant. Anonymity of participants will be maintained by substituting pseudonyms in the research reports. Subjects will have an opportunity to choose the pseudonym of their choice. If it is necessary to further protect participant confidentiality, the identity of the study site will not be disclosed. Audio recordings and transcripts of interviews will be kept in the possession of the investigator under lock and key.

Audio recordings and transcripts which identify participants will be destroyed upon completion of the research. The results will be stored separately from the consent form, which includes your name and any other identifying information. If information from the study is published or presented at scientific meetings, your name and other personal information will not be used. Participants will be asked whether they would like to be informed of relevant publications and will be so informed if they choose. Requests for information about publications can be made by contacting the researcher by email at: [joannjschmidt@yahoo.com](mailto:joannjschmidt@yahoo.com).

### **QUESTIONS ABOUT THE STUDY?**

If you have any questions about this study, the contact numbers that you may call are 001.734.487.3231 or 001.734.487.4096 or the local Malawi number 00265(0)888844248.

### **COSTS OF THE STUDY**

There is no charge for you to participate in this study. The participant and researcher will agree on a meeting place for the interview which will not involve any cost to the participant.

### **COMPENSATION/ REIMBURSEMENT**

You will not be paid for being involved in the study.

### **RIGHTS OF THE STUDY SUBJECTS**

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you.

### **CONFLICT OF INTEREST**

The researcher has no financial conflict of interest in the conduct of this study. This study does however, form the basis for the researcher's Master's thesis.

### **CONTACT INFORMATION**

This research protocol and informed consent document have been reviewed and approved by the Eastern Michigan University Human Subjects Review Committee and COMREC in Malawi for use through December 31, 2009. If you ever have questions about this study, you should contact Dr. Elizabeth Francis at 001.734.487.3231 / [efrancis@emich.edu](mailto:efrancis@emich.edu) or Dr. Gretchen Dahl Reeves, the chairperson of the CHHS Human Subjects Review Committee, at 001.734.487.4096 / [chhs\\_human\\_subjects@emich.edu](mailto:chhs_human_subjects@emich.edu) or the local contact in Malawi at 00265(0)888844248.

**STATEMENT OF INFORMED CONSENT FOR:****A RESEARCH STUDY OF ISSUES RELEVANT TO  
GOOD CLINICAL PRACTICE IMPLEMENTATION**

Please sign in the space below once you have:

1. Had the informed consent form explained to you and had all your questions answered
2. Been told what will happen during the study
3. Been told the good and bad things that might happen to you for being in the study
4. AND that you choose to take part in the study by your own choice

_____	_____	_____
Participant's name [print]	Participant's signature	Date
_____	_____	_____
Study staff's name [print]	Study staff's Signature	Date

## Appendix B: Interview Guide

**Title: Identification of Issues Relevant to Implementation of Good Clinical Practice (GCP) in Non-Regulatory, Academic Clinical Research at the University of Malawi College of Medicine, Blantyre, Malawi**

**Interview Guide:**

Questions that will guide this investigation include, but may not be limited to:

- Can you tell me about your clinical research experiences involving GCP implementation?
- What does GCP mean to you and what are prevailing perceptions about it?
- Are efforts to implement GCP typically met with receptivity or resistance?
- Are investigators prepared to implement GCP and if so, how?
- What resources were needed or are still needed?
- Are there any barriers and if so what are they?
- Are there situational or cultural constraints unique to Malawi and how are these addressed?
- Which aspects of GCP are of highest/lowest priority for implementation?
  - Examples include, but may not be limited to: informed consent, protocol adherence, safety monitoring, ethical review board interactions, document management, records retention, drug accountability, site operations, financial/budgetary considerations  
(see attached International Conference on Harmonization Principles of GCP)
- What would investigators like international regulators to understand?
- What initiatives would improve human subject protection and data integrity?
- Are there other issues which need to be explained?



## Appendix C: ICH-GCP Guidelines

**PRINCIPLES OF GOOD CLINICAL RESEARCH PRACTICE (GCP)****Part of International Conference on Harmonization (ICH) Tripartite Guideline E6 (R1)**

- 2.1 Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).
- 2.2 Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.
- 2.3 The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.
- 2.4 The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.
- 2.5 Clinical trials should be scientifically sound, and described in a clear, detailed protocol.
- 2.6 A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favourable opinion.
- 2.7 The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.
- 2.8 Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).
- 2.9 Freely given informed consent should be obtained from every subject prior to clinical trial participation.
- 2.10 All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.
- 2.11 The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).
- 2.12 Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.
- 2.13 Systems with procedures that assure the quality of every aspect of the trial should be implemented.

**EASTERN MICHIGAN UNIVERSITY**

February 11, 2009

Joann Schmidt  
c/o Elizabeth Francis-Connolly  
Eastern Michigan University  
School of Health Sciences  
Ypsilanti, Michigan 48197

Dear Joann Schmidt,

The CHHS Human Subjects Review Committee has reviewed the revisions to your proposal entitled: "Identification of Issues Relevant to Implementation of Good Clinical Practice (GCP) in Non-Regulatory, Academic Clinical Research at the University of Malawi College of Medicine, Blantyre, Malawi" (CHHS 09-25).

The committee reviewed your proposal and recommends the following additions to your proposal and informed consent:

- Contact information for the CHHS-HSRC Chair should be included

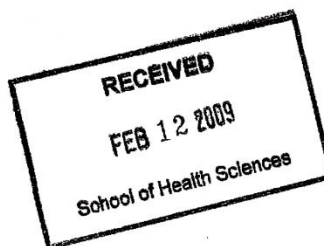
Your study is approved by the committee with the revisions requested above. Please return documents with revisions at your earliest convenience to [chhs\\_human\\_subjects@emich.edu](mailto:chhs_human_subjects@emich.edu).

Good luck in your research endeavors.

Sincerely,

A handwritten signature in cursive script that reads "Gretchen Dahl Reeves".

Gretchen Dahl Reeves, Ph.D.  
Interim Chair, CHHS Human Subjects Review Committee



## Appendix E: IRB Approval, COMREC, Blantyre, Malawi



## UNIVERSITY OF MALAWI

Principal  
 Prof. R.L. Broadhead, MBBS, FRCP, FRCPC, DCH

Our Ref.:  
 Your Ref.: P.02/09/732

College of Medicine  
 Private Bag 360  
 Chichiri  
 Blantyre 3  
 Malawi  
 Telephone: 677 245  
 677 291  
 Fax: 674 700  
 Telex: 43744

23 April 2009

Joan Schmidt  
 C/O Prof. E. Gomo  
 Research Support Centre  
 College of Medicine  
 P/Bag 360  
Blantyre 3

Dear Joan,

RE: P.02/09/732 - Identification of Issues Relevant to Implementation of Good Clinical practice (GCP) in Non-Regulatory, Academic Clinical Research at the university of Malawi College of Medicine, Blantyre, Malawi

I would like to inform you that COMREC reviewed your proposal which you resubmitted for an expedited review. I am pleased to inform you that your proposal was approved after considering that you addressed all the issues which were raised during the previous review.

As you proceed with the implementation of your study I would like you to take note that all requirements by the college are followed as indicated on the attached page.

Yours Sincerely,

Prof J. M. Mfutso Bengo  
CHAIRMAN - COMREC

JMB/ck

**REQUIREMENTS FOR ALL COMREC APPROVED RESEARCH PROTOCOLS**

1. Pay the research fees as required by College of Medicine for all approved studies.
2. You should note that the follow-up committee will monitor the conduct of the approved protocol and any deviation from the approved protocol may result in your study being stopped.
3. You will provide an interim report in the course of the study and an end of study report.
4. You are required to obtain a continuation approval after 12 months from the date of approval.
5. All investigators must be fully registered with the Medical Council of Malawi.