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Mobile Phone Short Message Service (SMS) to Improve Malaria Pharmacoadherence in Zambia

Elinda Steury
University of Central Florida

MOBILE PHONE SHORT MESSAGE SERVICE (SMS) TO IMPROVE MALARIA PHARMACOADHERENCE IN ZAMBIA

by

ELINDA ENRIGHT STEURY
B.S.N. University of Central Florida, 1988
M.S.N. University of Central Florida, 2008

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Major Professor: Mary Lou Sole

ABSTRACT

Malaria significantly contributes to morbidity and mortality rates in Zambia. The currently accepted malaria treatment is artemisinin-based combination therapy (ACT); it is more than 97% effective when the regimen is strictly adhered to. However, the mean ACT adherence rate in sub-Saharan Africa is only approximately 38-48%. Poor pharmacoadherence remains a significant barrier to malaria control and elimination.

The purpose of this study was to determine if adherence rates to a six-dose ACT antimalarial treatment differ between patients in Zambia who received short message service (SMS) reminders and those who did not.

An experimental, randomized, controlled trial was conducted to collect data from a sample of 96 adult patients with malaria who presented to Fisenge Clinic in the Copperbelt Province of Zambia. Participants were randomly assigned to a control or intervention group. The intervention group received SMS messages to remind them to take their medication according to the regimen. An electronic pillbox was used to measure pharmacoadherence for both groups, and patients were classified as *probably adherent* or *probably non-adherent*.

Data were analyzed using Chi-square for association between the SMS intervention and pharmacoadherence, and logistic regression used for predictors of adherence. No significant association was found between SMS reminders and pharmacoadherence among malaria patients being treated with ACT when evaluated with respect to those who received the SMS reminders and those who did not (χ^2=0.19, *df*=1, *p*=0.67). Binary logistic regression indicated that there were no variables associated with adherence (*p*>0.05).

Findings from this study contribute to the research regarding the use of mobile phones to promote adherence. This is the first study of its kind using SMS directly to the patient for ACT adherence in sub-Saharan Africa known to the author. It is possible that the use of the electronic pillbox and/or the novelty of participating in a research study contributed to higher levels of adherence than previously found in this geographical area. While data suggested that there was no association between SMS and adherence, further research is needed to explore the value of this intervention.

To my mom and dad

for raising me to believe that anything is possible,

to my husband

for making everything possible,

and in loving memory of Colonel Dick Gordon.

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LIST OF ABBREVIATIONS

ACT	artemisinin-based combination therapy
AIDS	acquired immunodeficiency syndrome
AL	artemether-lumefantrine
AOR	adjusted odds ratio
ART	anti-retroviral therapy
CDC	Centers for Disease Control
CHW	community health worker
CI	confidence interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CITI	Collaborative Institutional Training Initiative
DOT	direct observation treatment
HIV	human immunodeficiency virus
IRB	institutional review board
IVR	interactive voice response
Kr	Kwacha rebased
MEMS	Medication Event Monitoring System
OR	odds ratio
PA	pharmacoadherence
P. falciparum	Plasmodium falciparum
PI	primary investigator
RBM	Roll Back Malaria
RDT	rapid diagnostic test

RR	relative risk
SD	standard deviation
SIM	subscriber identification module
SMS	short message service
SPSS	Statistical Package For The Social Sciences
SSA	sub-Saharan Africa
TB	tuberculosis
TDRC	Tropical Diseases Research Centre
TPB	Theory of Planned Behavior
tx	treatment
WHO	World Health Organization

CHAPTER ONE: THE PROBLEM

Introduction

The estimated global toll of malaria in 2012 was 207 million cases associated with 627,000 deaths (World Health Organization [WHO], 2013). Eighty-six percent of presumed and confirmed malaria cases in the world occurred in Africa with the majority of these in sub-Saharan Africa. Zambia, located in the heart of sub-Saharan Africa, is plagued by malaria, particularly the **Plasmodium falciparum** (*P. falciparum)* species. The annual number of diagnosed and confirmed cases in Zambia, in 2012, was 4.7 million, 2.3% of the total global cases, with an estimated 11,000 deaths (WHO, 2013). Of individuals diagnosed with *P. falciparum* malaria, 90.5% will die if left untreated (Roll Back Malaria [RBM], 2008). In addition to the significant impact on morbidity and mortality, this parasitic infection is estimated to cost African countries a total of more than $12 billion annually through diagnosis, treatment, and lost productivity, equaling 2-3% of the adjusted Gross National Product of the continent (Gallup & Sachs, 2000; RBM, 2003).

Background

Detection

Accurate malaria detection is critical for combatting the disease. While microscopy is the gold standard for diagnosis of malaria, the cost and lack of availability of trained laboratory technicians prevent widespread use in resource-limited settings (Murray, Gasser, Magill, & Murray, 2008). Currently, Zambian clinics utilize the rapid diagnostic test (RDT) as the accepted diagnostic test.

Treatment

The current pharmacological treatment for uncomplicated *P. falciparum* malaria, recommended by the WHO, is an artemisinin-based combination therapy. Artemesinin-based combination therapy (ACT) utilizes two schizontocidal medications given concurrently with independent modes of action to improve therapeutic efficacy and to interrupt the development of resistance to the separate components of the blend (WHO, 2006a). ACT also helps prevent the emergence of parasite drug resistance through the interference of asexual replication (White et al., 2009; WHO, 2013). The ACT medication regimen, which has not been modified since 2006, consists of six doses to be taken twice daily over three days, with the 2nd dose 8 hours after the initial dose which is administered at the clinic and subsequent days' doses 12 hours apart (President's Malaria Initiative, 2011; WHO, 2006a). The extent to which one follows the prescribed regimen is referred to as adherence or pharmacoadherence. This regimen is critical and has been found to be more than 97% effective when strictly adhered to, resolving clinical symptoms even before the regimen is complete (Abdulla et al., 2008; Makanga et al., 2011). Artemether-Lumefantrine is the accepted first-line ACT being prescribed in Zambia (WHO, 2013). Research shows that giving the second dose of artemether-lumefantrine (AL) 8 hours subsequent to the first ensures that the concentration of artemether is sustained above the minimum effective concentration level. This level is necessary in order to maintain the high level of exposure of malaria parasites to the medication during the portion of their life cycle in which they are most susceptible to anti-malarial agents (Kokwaro, Mwai, & Nzila, 2007; White, 1992).

Though researchers have been able to successfully decrease the duration of treatment from the 14-day chloroquine treatment to the current 3-day ACT treatment, pharmacoadherence

remains a stumbling block in the fight against malaria (RBM, 2010; WHO, 2006a; Yeung & White (2005).

Pharmacoadherence

Current statistics for malaria treatment pharmacoadherence rates in sub-Saharan Africa vary widely in their methods and definitions resulting in a range between 36.5% and 91% (M = 61.2; SD = 20.0). Over 50% of studies use self-report as the primary measurement tool and few take the timing of the medication into consideration (Ansah, Gyapong, Agyepong, & Evans, 2001; Cohen, Yavuz, Morris, Arkedis, & Sabot, 2012; Depoortere et al., 2004; Fogg et al., 2004, Lawford et al., 2011; Lemma, Löfgren, & San Sebastian, 2011; Okonkwo, Akpala, Okafor, Mbah, & Nwaiwu, 2001; Onyango et al., 2012; Yeboah-Antwi et al., 2001).

Non-adherence not only impacts the patient through suboptimal blood concentrations resulting in increased morbidity and mortality, but also impacts the community, through the development of parasitic resistance, disease relapse, and increased disease occurrence (Mace et al., 2011; White & Olliaro 1996; White et al., 2009). This problem requires the development of a multifaceted approach and enhancement of current strategies to improve pharmacoadherence; however, the causes for failure to adhere must first be determined in order to shape effective strategies.

Pharmacoadherence has been associated in part with socio-economic, environmental, and demographic differences (e.g. age, education level, ability to read, and household income), as well as personal characteristics such as forgetfulness, carelessness, symptom reduction, and the side effects associated with the treatment (Morisky, Green, & Levine, 1986; Onyango et al., 2012; WHO, 2003). While there has been significant research conducted in order to explore the

factors related to pharmacoadherence, this study focuses on variables associated with adherence in sub-Saharan Africa.

Specific attempts to improve pharmacoadherence have included observation, the blister pack, and electronic pillboxes such as the Medication Event Monitoring System (MEMS) (Kahook, 2007) and SIMpill (2008). *Observation* encourages adherence through accountability and offers the surest confirmation of pharmacoadherence, but the practicality of observation with medication sequences such as the ACT regimen is prohibitive. Virtual direct observation treatment (DOT) is one method using technology for observation that is currently being researched (Hoffman et al., 2009).

When observation proves impractical, *blister packs* improve pharmacoadherence by addressing the forgetfulness aspect through visual cues that indicate whether a patient has taken his or her dose. These pill containers include individually packaged pills in a "blister" or "bubble" that is pierced to obtain the pill. The vacant blister or bubble indicates that the pill has been removed, and in pharmacoadherence studies, if the pill is removed the patient is assumed to have taken it. The patient and caregiver can use the blister pack container to verify pill counts or to stay on regimen. While at least two studies using blister packs have resulted in greater than 95% adherence using blood tests to confirm presence of the drugs, the timing aspect as a critical component of ACT treatment is not addressed with this method (Qingjun et al., 1998; Shwe, Lwin, & Aung, 1998). Despite the current use of blister packs, poor pharmacoadherence due to forgetfulness, carelessness, symptom reduction or negative side effects continues to thwart malaria eradication.

One *electronic pillbox,* the MEMS cap, monitors and records the number of bottle openings and the date and time of each opening, which can then be downloaded to a computer

for analysis. One prospective descriptive laboratory study verified the reliability of the model of MEMS used in this study resulting in 100% perfect functioning with a total absence of missing registrations and/or over-registrations (DeBleser, DeGeest, Vandenbroeck, Vanhaecke, & Dobbels, 2010).

The MEMS has been found to motivate pharmacoadherence through accountability, and has been determined to be suitable and achievable in a resource-limited setting such as sub-Saharan Africa (Fallab-Stubi, Zellweger, Sauty, Uldry, Iorillo, & Burnier, 1998; Kahook, 2007; Lyimo et al., 2011). Some of this research, though conducted with anti-retroviral therapy (ART), resulted in a 97% (n=23, SD = 4.7) adherence rate in the first month of use, the time period relevant to short-term regimens such as ACT (Lyimo et al., 2011). While MEMS is considered to be the imperfect gold standard and more valid than self-report, research indicates that pharmacoadherence studies should not rely on MEMS alone, but use multiple adherence measures (Cook, Schmiege, McClean, Aagaard & Kahook, 2012; Claxton, Cramer, & Pierce, 2001).

An alternative electronic pillbox recently on the market is SIMpill, which electronically monitors pillbox openings and sends the data to a remote server. If the patient does not take his/her medication on schedule, SIMpill sends an SMS to the patient and/or healthcare provider as a reminder (SIMpill, 2008). Though little research has been conducted using SIMpill, one pilot study implemented in South Africa for tuberculosis (TB) medication adherence resulted in increased adherence levels from 83% to 92% (Madyo, 2010). As a new product, SIMpill data and research are limited. The device has currently been removed from the market in Africa halting further research in the current area of focus (Brendan Rens, Director of SIMpill, personal communication, August 30, 2013).

The American Psychological Association's recommendations to improve pharmacoadherence are summarized in Table 1 (Chisholm-Burns & Spivey, 2008). These recommendations are broad and provide opportunity for further study to determine implications to patient outcomes. The intervention addressed in the current research using mobile phones seeks to address forgetfulness as a barrier to adherence.

Table 1: Summary of American Psychological Association Recommendations to Promote Adherence to a Medication Regimen

Recommendations
Explain the medication regimen
Tailor the medication regimen to the patient's lifestyle and daily routine
Establish collaborative relationship with patient, and facilitate patient interaction with other pharmacy staff
Identify and address individual *barriers* (emphasis added) to adherence
Refer special-needs patients to appropriate services
Promote self-efficacy
Create and maintain an environment conducive to pharmacoadherence

Mobile Phones

Recent advancements in mobile phone technology and availability hold promise for health research application in sub-Saharan Africa. Researchers estimate that 65% of all mobile phone users can be found in the developing world, with mobile subscriptions in Africa growing twice as fast from 2003-2008 as any other part of the world (Gardner, Acharya, & Yach, 2007; Hampton, 2012; United Nations Foundation [UNF], 2012). Over two-thirds of the population in Africa is covered by a mobile network, which has resulted in individuals who previously had no access to landlines now having access to low-cost handheld devices with SMS capabilities (Zurovac, Talisuna, & Snow, 2012). Eighty-seven percent of urban Zambian households and 52% of rural households had access to at least one mobile phone in 2008, with expectations for a continued rapid rise as the wave of technology floods the continent (Chirwa, 2010). The three

primary mobile phone providers in Zambia are MTN, Zamtel and Airtel with all mobile phones in Zambia having SMS capability and the majority operating on pre-paid plans. All incoming phone calls and incoming SMS messages are free to the receiver, which presents an economic advantage to the end-user in impoverished areas.

Statement of the Problem

Although effective treatment for *P. falciparum* malaria is available, the problem of poor pharmacoadherence remains a significant barrier to malaria control and elimination (Mace et al., 2011; White & Olliaro, 1996; White et al., 2009).

Purpose of the Study

The primary aim of this study was to assess the efficacy of a program to increase the pharmacoadherence rate of the six-dose ACT treatment of *P. falciparum* malaria in the Copperbelt Province of Zambia using SMS reminders through the mobile phone. The secondary aim was to gather information through a brief end-of-study questionnaire regarding factors affecting pharmacoadherence for further research.

Question

For purposes of this study the original hypothesis was converted to a research question at the request of the Tropical Diseases Research Centre. Are SMS reminders sent to patients associated with adherence rates to a six-dose ACT antimalarial treatment in the Copperbelt Province, Zambia?

Original Hypothesis

The use of SMS reminders through mobile phones will increase the adherence rate to a 6-dose ACT antimalarial treatment in Luanshya District, Zambia.

Assumptions

The primary assumptions made in this research are that people desire to be well, that they intend to take medication according to regimen in order to become well, and that they do not give or sell their medication to others.

Study Significance

Non-adherence to malaria treatment medication continues to impede efforts to eradicate malaria in sub-Saharan Africa. This randomized controlled trial sought to determine if there was an association between SMS reminders and pharmacoadherence, as well as exploring the possible relationship between demographic factors and adherence. This research also sought an understanding of variables that may be targeted to improve adherence rates, thus addressing morbidity and mortality related to malaria. As such, it offers opportunity for repetition and extension to similar studies in this geographical context.

Definition of Terms

Some concepts and definitions used in this research necessitate clarification. Key terms used throughout this study are defined in Table 2, including the expansion of their conceptual and operational definitions.

Table 2: Definition of Terms

Term	Conceptual Definition	Operational Definition
artemether-lumefantrine	A fixed-ratio artemisinin-based combination of two blood schizontocides - artemether with lumefantrine - used for the treatment of malaria (Bell et al., 2009; White et al., 2009).	The currently accepted and effective version of ACT for *P. falciparum* malaria in Zambia as recommended by the World Health Organization (WHO, 2012) and used by Fisenge clinic.
artemisinin-based combination therapy	A combination of artemisinin or one if its derivatives with one or more anti-malarials of a different class (WHO, 2006a).	The general name used herein for artemisinin-based combination anti-malarials.
complicated malaria	A confirmed diagnosis of a malarial infection in an individual presenting with symptoms of malaria, with evidence of vital organ dysfunction or resistance to ACT treatment. (WHO, 2006a).	Complicated malaria was assessed by unresolved symptoms and evidence of vital organ dysfunction as determined by clinic nurse.
mHealth	The use of mobile communication devices to provide health-related services is referred to as mobile health or, in short, mHealth (UNF, 2012)	The use of the mobile phone and SMS messaging.
Medication Event Monitoring System	An electronic pill bottle cap that digitally records the time and date of each opening for later download to a computer for review and analysis.	The MEMS pill bottle cap (MWV Healthcare/Aardex Solution, 501 South 5th St., Richmond, VA 23219) used in this study.
pharmacoadherence	The extent to which an individual follows a medication regimen that has been prescribed by the health care professional in all aspects of the regimen: timing, dosage, method of ingestion, etc.	The measurement of adherence to the ACT regimen schedule of +/- 1 hour for 2nd dose and +/- 2 hours for 3rd-6th doses as measured by MEMS.

Term	Conceptual Definition	Operational Definition
Plasmodium falciparum	The genus and species, respectively of one of the protozoan parasites in the blood that causes malaria in humans. Other *Plasmodium (P.)* species that cause malaria in humans are *P. malariae*, *P. ovale* and *P. vivax* (WHO, 2006a).	Considered the cause of greater than 99% of malaria in Zambia as detected by RDTs (Centers for Disease Control [CDC], 2014).
rapid diagnostic test	A test to determine the presence of malaria parasites. An antigen-based, finger-prick blood stick for malaria in which a colored line indicates the presence of plasmodial antigens (WHO, 2006a). The health care worker can generally obtain results in under 30 minutes.	Test used to detect malaria at Fisenge Clinic: ParaHIT *f* RDT by Span Diagnostics, Ltd. (173-B, New Industrial Estate, Road No. 6-G, Udhna, Surat – 394 210, India).
short message service	Another name often used in Africa to refer to text messaging with mobile phones.	The intervention used in this study to send a reminder to the participant that it was time to take their medication.
Statistical Package for the Social Sciences	A computer program that analyzes and summarizes statistical information.	SPSS Version 22.0 for Mac was used for the statistical analysis.
Theory of Planned Behavior	A model for understanding and seeking to change human behavior as developed by Ajzen (2006).	The theoretical framework used to guide the current research intervention.
uncomplicated malaria	A confirmed diagnosis of a malarial infection in an individual presenting with symptoms of malaria, without evidence of vital organ dysfunction (WHO, 2006).	Positive RDT without additional symptoms of complicated malaria.

Preview

This research sought to address the problem of poor pharmacoadherence in malaria treatment in sub-Saharan Africa. Chapter 2 contains a summary of a review of the literature pertinent to the problem, identifying gaps in the literature to be addressed by the current study,

and introduces the guiding theoretical framework. Chapter 3 details the methods used in the research, and chapter 4 presents the findings in terms of the sample demographics, group results and other statistical data from the research. Chapter 5 follows with a discussion of the research findings, limitations of the study and recommendations for further research.

CHAPTER TWO: REVIEW OF RELEVANT LITERATURE AND INTRODUCTION OF THEORETICAL FRAMEWORK

Review of Literature

Introduction

There are numerous studies related to adherence interventions from developed countries, many of which are associated with chronic illnesses. In addition to having limited relevance to acute illnesses, these studies are also limited by their cultural context, minimizing generalizability. An exploration of the state of the science using technology for pharmacoadherence to a malaria treatment regimen in sub-Saharan Africa was conducted through a review of the literature. An examination of previous research, including definitions of *adherence, factors influencing adherence* and *methods of measurement utilized* was completed with focused attention on sub-Saharan Africa.

Methods of Search

A systematic literature review was conducted exploring the use of mobile phones to improve pharmacoadherence in the context of sub-Saharan Africa. Databases searched included Cumulative Index to Nursing and Allied Health Literature (CINAHL), MedLine, and Cochrane Database of Systematic Reviews from 2005-2013. Key terms included *cell phone* or *mobile phone* or *mHealth* AND *adherence* or *compliance* AND *health* or *medication* AND *Africa* or *sub-Sahara* or *Zambia* or *community health workers* or *malaria.*

While the upstream (the patient to clinician or clinician to government agency) use of mobile phones has proven useful in public health programs to monitor disease and communicate supply needs to suppliers, the focus of this literature review is on downstream (government

agency to clinician or clinician to patient) and peer-to-peer (clinician to clinician or patient to patient) use (Asiimwe et al., 2011; Barrington, Wereko-Brobby, Ward, Mwafongo, & Kungulwe, 2010; Davis et al., 2011; Dean et al., 2012; Kabanywanyi et al., 2010; Kamanga, Moono, Stresman, Mharakurwa, & Shiff, 2010; Randrianasolo et al., 2010).

Criteria for inclusion were that the article's context was sub-Saharan Africa and that it was either associated with pharmacoadherence or that technology was used in a downstream or peer-to-peer manner for health-related purposes. Studies were limited to those published in the English language and to current literature due to the recent development of mobile phone technology.

The search resulted in 30 articles. Of these, two were not health-related adherence; seven were not in the sub-Saharan African context; four did not involve the use of technology for adherence and eight were either duplicates or clearly irrelevant. The remaining nine studies were included in the literature review. In addition, 17 other studies were identified through secondary searches from the reference lists of selected articles and systematic reviews, resulting in a total of 25 articles. Of these, six were systematic reviews, ten experimental studies, seven observational analytic studies, one observational descriptive study and one non-research article (see Figure 1 and Table 3).

The remainder of this chapter critically reviews contemporary literature regarding mobile phone use and adherence in sub-Saharan Africa. There are a growing number of studies in this context with varying degrees of significance. Following the summary table, a review of articles regarding ACT adherence is discussed followed by mobile phones used in health in sub-Saharan Africa. Finally, the two are combined and mobile phone use for adherence is reviewed – first for

non-malaria diseases and finally for malaria. This section concludes with a summary and a review of the gaps in the literature.

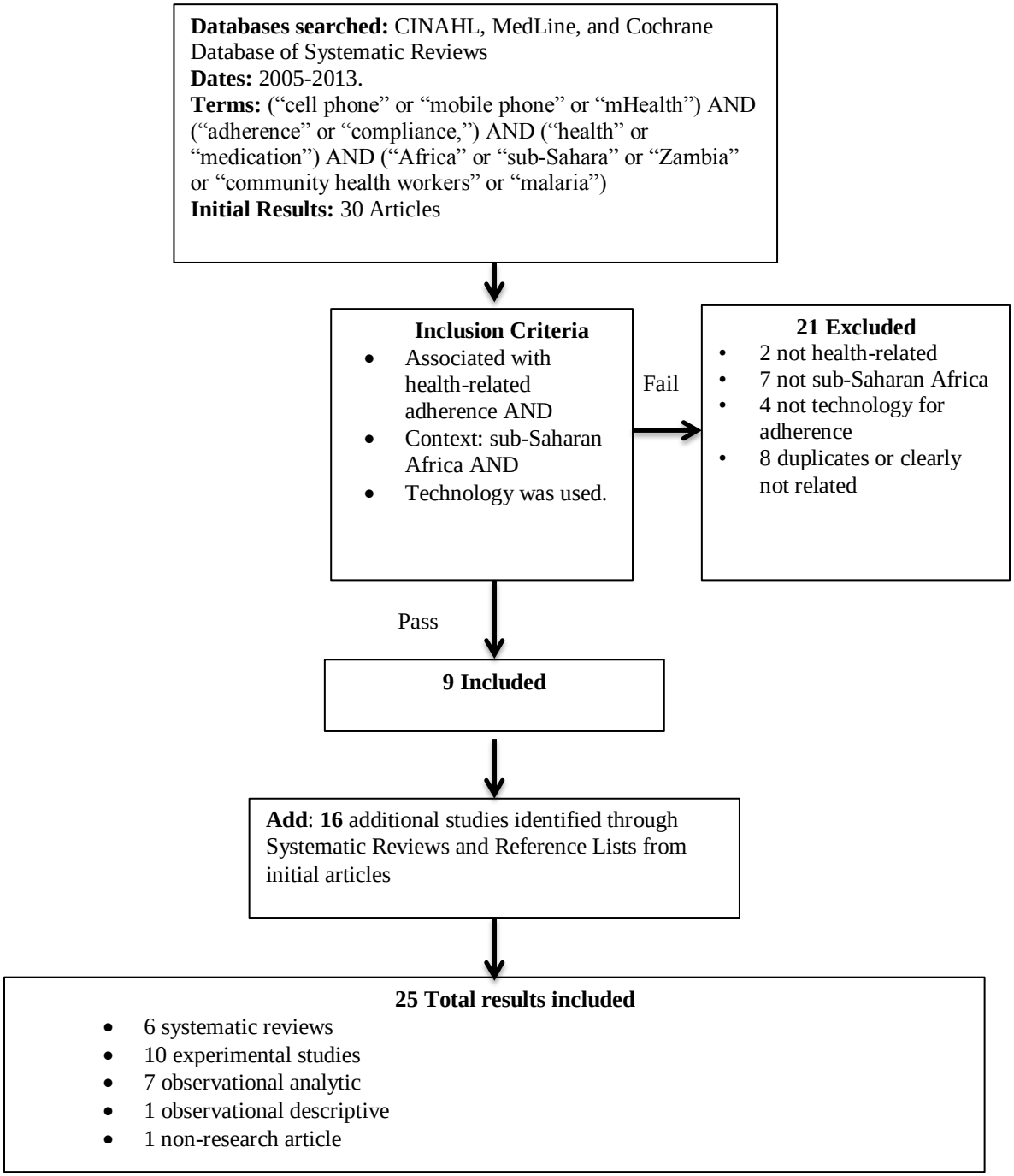


Figure 1: Algorithm for Literature Review

Table 3: Literature Review Summary

Author: (Year)	Purpose	Sample size: Geogra-phic context	Type of study	Methodology	Outcome measures	Analysis	Findings	Limitations
Bahadur & Murray (2010)	Explore use of cell phone SMS in HIV/AIDS care in South Africa	N/A: Sub-Saharan Africa (SSA) - South Africa	Systematic Review (28 articles in SSA)				All 6 RCTs in study found significant results ($p<0.005$) indicating that SMS improve service delivery through reminders (7 studies) and improve communication between community health workers (CHW)	
Barnighausen, et al. (2011)	Explore evidence of effectiveness of interventions to increase ART adherence	N/A: SSA	Systematic Review (27 articles in SSA)				More detailed examination of evidence needed, but initial results indicate SMS can be effective to increase ART adherence in sub-Saharan Africa; Further research on theories of adherence based on behavior change theories is needed in SSA	

Author: (Year)	Purpose	Sample size: Geographic context	Type of study	Methodology	Outcome measures	Analysis	Findings	Limitations
Chi & Stringer (2010)	To critique research of Lester et al.	Kenya	Non-research	Study of mHealth, Adherence			Little outcome data available for mHealth; Comprehensive multi-pronged approach tailored to local settings is necessary for adherence to ART; Estimate < $8/yr/patient for SMS ART adherence reminders in Kenya	
Cohen et al. (2012)	Measure adherence to ACT (AL) (over the counter)	*N*=106 (2 day); 152 (3 day): SSA-Uganda	Experimental: RCT	Patients who purchased ACT randomly assigned to 1 of 3 grps: 1. No follow-up; 2. Follow-up after 2 days; 3. Follow-up after 3 days. Measure: # pills in blister pack or self-report if unavailable	**3 day:** 32.2% (*SD*=47) non-adherent; 2% (*SD*=14) probably non-adherent; 65.8% (*SD*=48) probably adherent.	Analysis of variables associated with adherence: Probit regressions & ordinary least squares regressions	Pharmacoadherence (PA) to ACT in this setting = moderate. Associated variables at $p<0.05$: Some secondary education 22% more likely to complete tx (95% CI [0.063, 0.38]); Able to read English had .47 fewer doses left [-0.93, -0.003]	Generalizability; small sample size; some self-report

Author: (Year)	Purpose	Sample size: Geographic context	Type of study	Methodology	Outcome measures	Analysis	Findings	Limitations
Crankshaw et al. (2010)	Explore dynamics and patterns of mobile phone use to determine feasibility for appointment reminder and adherence messages in ART	*N*=300: SSA - South Africa; cross-sectional	Observational analytic	Questionnaires administered to sample and results analyzed	99% willing to have verbal mobile contact; 96% SMS contact; # owning mobile phone: (*n*=242; 81% of sample)	Logistic regression: *OR*, CI (95%)	Use of cellphone intervention is feasible	Possible overstatement of patient willingness to receive mobile phone reminders due to courtesy bias; possible inaccuracies due to recall bias; generalizability
Dean et al. (2012)	To determine feasibility of SMS for adherence to ART	*N*=7: SSA – South Africa	Experimental pilot study	Cell phones were provided and patients invited to SMS each other and clinician re: HIV, health and pregnancy. Four post-intervention interviews were conducted	Collected info from interviews. Overall satisfaction.	Quantitative analysis for usage patterns; Qualitative for themes	Group was satisfied with the intervention and participants recommended that group be offered in the future.	Pilot study

Author: (Year)	Purpose	Sample size: Geographic context	Type of study	Methodology	Outcome measures	Analysis	Findings	Limitations
DeRenzi et al. (2012)	To decrease the number of days that a CHW is past due with routine home visits using a combination of SMS reminders and supervisor informing	*N*=87: SSA-Tanzania	Experimental qualitative	SMS reminders and promise of supervisor notification to CHWs if scheduled home visits were late; CHWs questioned following the studies regarding the SMS intervention	Relevant outcomes related to acceptability on part of CHWs of SMS as a means of reminding	2 RCTs statistical results not applicable to the current study due to multiple interventions; Follow up interviews source of data regarding CHWs feedback	CHWs expressed positive feedback to the use of SMS as reminders	Non-scientific study of responses
Donald et al. (2007)	Evaluate mobile phones in compliance use for HIV patients	*N*=6: SSA – South Africa	Observational analytic qualitative	Individual interviews with councilors using technology 2x 6 mo. apart	Generally positive and strongly supported		Technology was found to be easy to use, eased data collection, and reduced fears around losing notes	Small sample size, restricted setting

Author: (Year)	Purpose	Sample size: Geogra-phic context	Type of study	Methodology	Outcome measures	Analysis	Findings	Limitations
Haberer & Kiwanuda (2010)	To examine the feasibility of using interactive voice response (IVR) and SMS for automated collection of weekly individual level ART adherence data	*N*=19: SSA – Uganda; Cross-sectional	Experimen-tal mixed methods	IVR and SMS used to collect adherence data from caregivers of children; Individual interviews to assess participants' impressions of technologies	Participant interest and participation rates were high; Weekly completion rates low (0-33%) Median adherence rates: IVR = 82% (95% CI [71, 92]) SMS =100% [99, 100]	Logistic regression	Use of IVR and SMS in resource-limited settings is technically feasible. Further research needed Associated variables at $p<0.05$: No potential characteristics associated with successful responses	Low power due to small sample size and low weekly completion rate; Pill counts and MEMS adherence rates lower than self-report suggesting overstatement

Author: (Year)	Purpose	Sample size: Geogra-phic context	Type of study	Methodology	Outcome measures	Analysis	Findings	Limitations
Hoffman et al. (2009)	To assess the feasibility and acceptability among health workers and patients in using video-enabled mobile phones to monitor patient adherence to TB meds and to assess patient response to text and video messages via mobile phone	*N*=13: SSA - Kenya	Experimen-tal quantitative pilot study	Patients provided with video- and text-ready mobile phones. Asked to video capture patient taking dose at home and transmit to central database. Also received health messages in the form of video and text messages on phones	Likert scale from 1 (Awful) to 5 (Great) rating satisfaction with study procedures and technology; Mean overall rating: 4.6		All participants extremely satisfied	Pilot study

Author: (Year)	Purpose	Sample size: Geogra-phic context	Type of study	Methodology	Outcome measures	Analysis	Findings	Limitations
Horvath et al (2012)	To determine whether mobile phone SMS enhances adherence to ART in those with HIV	N/A	Systematic review: Meta-analysis (243 articles; 17 closely reviewed; 2 in SSA)		Any length weekly SMS reminder lowers risk of non-adherence (RR 0.78, 95% CI [0.67, 0.89]; Short weekly SMS better than other lengths (RR 0.77, [0.67, 0.89]		Good evidence that weekly SMS reminders are efficacious for adherence to ART compared to standard care	
Husler (2005)	To determine the effect that Compliance Service had on TB cure rates and treatment completion rates. To identify and describe social and economic impacts. To assess Compliance Service	*N*=221: SSA - South Africa	Observa-tional descriptive; Retrospect-ive quantitative pilot study	Reviewed patient records for cure and completion rates. Framework used to examine social and economic impact.	Compliance service and records could not be used to measure treatment adherence levels due to poor implementa-tion procedures	Insufficient data for analysis	Compliance Service has potential as cost-effective system	Many complications and obstacles in the study severely limiting usability

Author: (Year)	Purpose	Sample size: Geogra-phic context	Type of study	Methodology	Outcome measures	Analysis	Findings	Limitations
Jones et al. (2012)	To investigate perceptions and experiences of health workers involved in an RCT to improve health worker malaria case management	*N*=24: SSA - Kenya	Observa-tional analytic qualitative	Individual interviews regarding perception of message intervention in Zurovac et al. (2011) RCT	Frequency, Length and Timing: *Positive* Duration: *Positive* Messages: *Positive*		SMS messaging is acceptable and effective way of providing front line health workers with active reminders for care of malaria patients	Generalizabi-lity, small sample size
Kaplan (2006)	To look at evidence regarding the idea that fixed or mobile phones could be an effective health care intervention in developing countries	N/A	Systematic review (31 articles; 2 in SSA)				Very little literature on using mobile telephones in mHealth for malaria in low-resource countries; few clinical outcomes	

Author: (Year)	Purpose	Sample size: Geogra-phic context	Type of study	Methodology	Outcome measures	Analysis	Findings	Limitations
Kunutsor et al. (2010)	To assess the use of mobile phones in an ART cohort and ascertain feasibility to improve clinic attendance	*N*=276: SSA - Uganda	Experimen-tal cross-sectional and prospective cohort study	Patients immediately reminded by voice or SMS if they missed appointment; Survey provided analysis on adherence to ART; Adherence support strategies implemented and evaluated	Mean adherence levels assessed before & after mobile phone reminders Before: 96.3% (95% CI [95.2, 97.4]); After: 98.4% [97.8, 98.9]; (p<0.01)	Student's paired *t* test	SMS text messaging and voice calls may be timely intervention for patient clinic attendance, follow-ups and medication adherence in SSA and other low income settings	Generalizabi-lity, design limits ability to exclude confounding factors, design limits ability to reliably conclude reason for those who came back (i.e. if it was due to phone reminder or not)

Author: (Year)	Purpose	Sample size: Geographic context	Type of study	Methodology	Outcome measures	Analysis	Findings	Limitations
Lawford et al. (2011)	To measure adherence to ACT	*N*=918: SSA - Kenya	Observational analytic case study	Patients treated with AL visited at home 4 days after drug prescribed; PA measured by questionnaire and blister packs	64.1% *probably adherent*; 31.7% *definitely non-adherent*; 4.2% *probably non-adherent*	Multivariate logistic regression modeling	Low AL adherence. Associated variables at $p<0.05$: Patient age >15 cf <15 (*AOR* 1.37, 95% CI [1.02, 1.85]); Respondent age 25-50 cf <25 (*AOR* 1.65, [1.10, 2.48]); >1 day delayed (*AOR* 0.73, [0.54-0.99]); Prior drug use (*AOR* 1.46, [1.08, 1.98]); Dislikes to medication (*AOR* 0.62, [0.47, 0.82]); >1 correct statement re: AL (*AOR* 1.76, [1.32-2.35])	Generalizability, self-report

Author: (Year)	Purpose	Sample size: Geographic context	Type of study	Methodology	Outcome measures	Analysis	Findings	Limitations
Lemma et al. (2011)	To measure patient adherence levels to 6-dose AL regimen in treatment of uncomplicated *P. falciparum* malaria and identify factors affecting adherence	*N*=155: SSA-Ethiopia	Observational analytic case study	Structured questionnaire conducted at end of AL regimen and blister packs examined	38.7% *probably adherent*; 34.8% *probably not adherent*; 26.5% *definitely non-adherent*;	Univariate and multivariate logistic regression modeling	Very low adherence to AL raises serious concerns for malaria control in the region. Associated variables at $p<0.05$: Radio ownership (*AOR* 3.8; 95% CI [1.66, 8.75]); Belief in traditional malaria tx (*AOR* 0.09; [0.01, 0.78]); Delay of >1 day in seeking tx after fever onset (*AOR*: 5.39; [1.83, 15.88])	Self-report; dose timing info not able to be accurately collected
Lester et al. (2010)	To determine if SMS improves drug adherence and suppression of plasma HIV-1 RNA load as supported by blood levels	*N*=538 (SMS=273; Control 265): SSA-Kenya	Experimental RCT	Weekly SMS from clinic nurse to inquire about status. Instructed to respond within 48 hrs.	RR for non-adherence was .81, (95% CI [0.69, 0.94], $p<0.01$) SMS=62% PA; Control=50% PA; (*OR* 0.57, 95% CI [.40, .83], $p<0.01$)	Chi square test; RR; *OR*	SMS= Significantly improved adherence	Self-report, generalizability

Author: (Year)	Purpose	Sample size: Geographic context	Type of study	Methodology	Outcome measures	Analysis	Findings	Limitations
Mahmud et al. (2010)	To offer CHWs mobile phones with SMS as a means of communication rather than the need for cost and time in travel	*N*=75: SSA-Malawi	Observational analytic retrospective pilot study	Group was provided cell phones and trained in a variety of usage (including patient adherence reporting, appointment reminders…) FrontlineSMS used to organize data	2,048 worker hours and $2,750 were saved and TB tx capacity was doubled	Calculation, tallying and comparison	mHealth interventions can provide cost-effective solutions to communication barriers in the setting of rural hospitals in the developing world	No bias elimination; costs of initial capital investment not considered; though capacity doubled, no conclusions re: outcome
Odigie et al. (2012)	To determine the usefulness of mobile phones to improve cancer care in low resource settings	*N*=1176: SSA-Nigeria	Experimental qualitative case study	Cancer patients who had access to cell phones were given the contact info of oncologist and encouraged to call anytime	At 24 months, 97.6% who had phone intervention sustained follow-up appointments vs. 19.2% who did not	Qualitative	Confirms the value of the mobile phone to enhance adherence to treatment of cancer as well as infectious diseases in Africa	Selection of comparison group not randomized; generalizability

Author: (Year)	Purpose	Sample size: Geographic context	Type of study	Methodology	Outcome measures	Analysis	Findings	Limitations
Onyango et al. (2012)	To measure adherence to ACT; and to discover factors in non-adherence	*N*=297: SSA-Kenya	Observational analytic cross-sectional case study Qualitative: Individual interviews	Data on adherence collected through interviews; adherence assessed by duration of tx and # of tablets taken in relation to patient age	Adherence rate: Age>13 42.1%; Age ≤ 13 57.9%;	Multivariate logistic regression analyses; Qualitative review	Some demographic factors affect adherence; More than half who get ACT do not take recommended dose and availability is a concern. Need programmatic interventions to encourage patient-centered care. Associated variables: Low age (*OR* 0.57, 95% CI [0.31, 0.91] $p<0.05$); Higher education level (*OR* 0.074, [0.017, 0.32] $p<0.01$); Ability to read (*OR* 0.29, [0.17, 0.49], $p<0.01$); Higher income >9,000 Kenya shillings (*OR* 0.34, [0.17, 0.69], $p<0.01$)	Generalizability; self-report; malaria not confirmed; recall bias

Author: (Year)	Purpose	Sample size: Geogra-phic context	Type of study	Methodology	Outcome measures	Analysis	Findings	Limitations
Pop-Eleches et al. (2011)	To test the efficacy of SMS reminders on ART adherence	*N*=431: SSA - Kenya	Experimen-tal RCT	Participants in intervention groups received SMS reminders either long or short and sent daily or weekly	Treatment gp (SMS) Adherence decreased 12% from weeks 1-12 to weeks 37-48 compared to control gp (No SMS) adherence decreased 14% (χ^2=7.36, p<0.01); 53% patients had >90% PA with weekly SMS reminders vs. 40% patients without SMS (p<0.05); 81% tx interruptions exceeding 48 hours with weekly SMS vs. 90% without SMS (p<0.05)	Chi-square test & logistic regression	SMS reminders may be an important tool to achieve optimal tx response in resource limited settings	Inconclusive results; cannot corroborate adherence with viral suppression; assumption that adherence in 1 tablet = adherence to entire regimen

Author: (Year)	Purpose	Sample size: Geogra-phic context	Type of study	Methodology	Outcome measures	Analysis	Findings	Limitations
Yeung & White (2005)	To summarize current knowledge on antimalarial adherence, the effectiveness of interventions to increase usage, and the effects of drug adherence to therapeutic response	N/A	Systematic Review (24 articles; 13 in SSA)				Overall quality and quantity of data available very inadequate and results from studies so variable that generalizability regarding level of adherence to antimalarials is not possible	
Zurovac et al. (2011)	To assess if SMS reminders to health workers improve and maintain adherence to treatment guidelines for outpatient pediatric malaria	*N*=107: SSA-Kenya	Experimen-tal Cluster RCT	Intervention – all health workers received SMS reminders re: malaria case-management for 6 months vs. Control – no SMS	Correct management of AL improved by 23.7% (95% [7.6, 40]; $p<0.01$) immediately after intervention & by 24.5% [8.1-41.0]; $p<0.01$) 6 months later	Descriptive Difference-of-differences effect sizes, 95% CIs & *p* values, & confound-ing	In resource-limited settings, malaria control programs should consider use of SMS to improve health workers' case-mgmt practices	Generalizabi-lity

Author: (Year)	Purpose	Sample size: Geogra-phic context	Type of study	Methodology	Outcome measures	Analysis	Findings	Limitations
Zurovac et al. (2012)	To review studies using SMS for malaria control in Africa	N/A: SSA-Africa	Systematic Review (6 articles in SSA)				Scarcity of peer-reviewed studies and lack of evidence to determine effectiveness of SMS for malaria control; Suggest 6 areas of malaria control in which SMS may improve delivery of services and health outcomes including pharmaco-vigilance and patient adherence to medication regimens	

Results of Search

ACT Pharmacoadherence

The pharmacoadherence rates to ACT in two independent studies in sub-Saharan Africa demonstrate surprising similarity to each other with a moderate *probable adherence* ranging from 64% to 66% (Cohen et al., 2012; Lawford et al., 2011). In contrast, other studies found that *probable adherence* fell in the 38-48% range (Gerstl, Dunkley, Mukhtar, Baker, & Malkere, 2010; Lemma et al., 2011; Onyango et al., 2012). The variance is likely associated with a stricter definition of *probably adherent* in the latter three studies, which considered not only the consumption of all pills, but the timing of consumption as well. This inconsistency accentuates the failure to achieve comparability in adherence-related investigations.

Health researchers have attempted to identify factors associated with adherence to malarial treatment, in order to better identify interventions to improve adherence, and have had widely varying results. Three studies identified several variables, which are often linked with a more affluent socio-economic status, that were found to be associated with adherence including monthly income, education level achieved, radio ownership and literacy (Cohen et al., 2012; Lemma et al., 2011; Onyango, et al., 2012). Though income, education level and literacy are easily explained factors, radio ownership has raised some questions. One possible explanation for association with radio ownership could be exposure to the national anti-malarial initiatives promoted through the media. Lemma et al. (2011) also identified the belief that malaria can be treated traditionally (without medication) as a factor associated with lower adherence. Another factor found in two independent studies in Kenya to be associated with ACT adherence was age, though the findings appeared to contradict each other. One study found that younger (<13 years) participants adhered better, while the other

found that older (25-50 years) participants had better adherence, though the former results may be related to the attentiveness of the caregiver to ensure that children received medication (Lawford et al., 2011; Onyango, et al., 2012). Seeking treatment more than one day after the onset of fever was also linked to adherence although in one study it increased adherence, while in the other it decreased the adherence rate (Lawford et al., 2011; Lemma et al., 2011). Lawford et al. (2011) also discovered that several factors related to the patient's knowledge and exposure to the drug were significant. The wide range of differences in the identified factors linked with adherence appears to be due to the inclusion of dissimilar aspects in studies and/or the disparate definitions of those items studied. Again, lack of uniformity in definitions and in measurement instruments presents a challenge, limiting comparability among studies.

While some researchers have focused on finding factors associated with adherence, others have identified barriers preventing or impeding better rates. Some reasons given for low rates of pharmacoadherence are forgetfulness and inattentiveness to the regimen schedule. Two researchers found that symptom reduction and negative side effects associated with the treatment may also lead to early cessation of the regimen (Morisky et al., 1986; Jones et al., 2012), while others indicated that early resolution of symptoms resulted in better adherence rates (Depoortere et al., 2004; Fogg et al., 2004; Yeung & White, 2005).

The search for factors associated with adherence can lead to possible interventions to improve it. Many of the demographic factors that are linked to adherence such as education, literacy and income require long-term, socio-economic changes. Recent studies, however, have been conducted to assess the effectiveness of possible interventions that could be implemented to produce immediate improvements in adherence such as the presentation and packaging of the medication. These interventions include a formulation study in which tablets resulted in 91% adherence compared with only 42% using syrup (Ansah et al., 2001).

In a packaging study, the dosages that were pre-packaged improved adherence from 60.5% to 82% for tablets and from 32.5% to 54.3% for syrup (Yeboah-Antwi et al., 2001). Provider instructions in a third study improved adherence significantly from 36.5% when no instruction was given to 51.9% for pictorial insert only, and to 73.3% for pictorial insert plus verbal instruction (Okonkwo et al., 2001). These results utilizing simple, low-cost, short-term interventions offer incentive for further exploration and investigation.

Adherence to malarial treatment continues to present a multi-faceted challenge. The plurality of factors and results from adherence studies indicate a strong need for further study and standardization. The rapid expansion of technology offers great opportunity for innovative research to address some of these areas.

Mobile Health

The recent rise in technology and mobile phone use in Africa offers an unlimited number of resources for multiple healthcare applications to a wide range of diseases. mHealth, the common name given to mobile technology used for healthcare, is expanding as quickly as the technology it utilizes. Studies exploring the patterns of mobile phone use in sub-Saharan Africa have found the response to the use of cellphones in healthcare to be very positive and cost-effective (Crankshaw et al., 2010; Dean et al., 2012; DeRenzi et al., 2012; Donald, Ulrike, Charissa, & Skinner, 2007; Hoffman et al., 2009; Jones et al., 2012; Kamanga et al., 2010; Odigie et al., 2012). Results indicate that as many as 99% of healthcare clients were willing to have verbal mobile clinical contact, and 96% were willing to have SMS contact (Crankshaw et al., 2010). Study participants have cited ease of use and reduced travel time as primary incentives for mobile phone use (Crankshaw et al., 2010; Odigie et al., 2012).

While some mHealth interventions focus on voice communication, SMS offers the lowest cost mobile phone approach and therefore one of the best alternatives in a resource-limited setting. SMS interventions have been used to attempt to improve the delivery of health services by reminding patients of appointments, assisting with communication between health care workers, promoting health, improving pharmacoadherence, and offering accountability (Bahadur & Murray, 2010; Barnighausen, Tanser, Dabis, & Newell, 2011; DeRenzi et al., 2012; Husler, 2005; Zurovac, 2011).

One pilot study in Malawi measured the effects of SMS communication among CHWs for purposes such as adherence reporting and appointment reminders. The focus was on financial and labor hour savings, which were substantial over a 6-month study ($2,750 net; 2,048 hours of worker time), and resulted in an increase in productivity for healthcare providers (Mahmud, Rodriguez, & Nesbit, 2010).

Other preliminary studies that suggest promising results in the use of SMS utilize mobile phones for upstream cancer care adherence and downstream reminders to CHWs to adhere to the prescribed home-visit schedule (DeRenzi et al., 2012; Odigie et al., 2012). One of these studies discovered that at 24 months, 97.6% of cancer patients who had been given the contact information of their doctor and encouraged to call had continued with their follow-up appointments compared with only 19.2% of those who had not been given the physician's phone number (Odigie et al., 2012). While the other study had no quantitative statistical evidence relevant to this study, they received positive feedback to mobile phone use with CHWs (DeRenzi et al., 2012).

One unique interaction using mobile phones in South Africa connected patients not only to caregivers, but also to each other, in order to offer community support in a largely collective society. Pregnant women diagnosed with HIV were invited to use SMS to communicate with the nurse or with each other about health-related questions and to offer

one another support and/or advice. The response of the participants to an open-ended questionnaire was very positive, with patients expressing the experience of interconnectedness and increased disease-related knowledge (Dean et al., 2012).

Kaplan's (2006) review of the literature provides evidence that can either support or refute the hypothesis that phones can be effectively used in healthcare intervention in low-resource countries. The review indicated a gap in the literature regarding the use of mobile phones to address HIV, tuberculosis, malaria, and chronic conditions in developing countries, as well as a lack of measured clinical outcomes and quality studies. However by 2012, four literature reviews noted in this study indicated that research exploring SMS for healthcare is increasing rapidly. Three of those four reviews (28+ articles) focus on ART adherence with only a single literature review focusing on antimalarial adherence comprised of a mere six articles (Bahadur & Murray, 2010; Barnighausen et al., 2011; Horvath, Azman, Kennedy, & Rutherford, 2012; Zurovac et al., 2012).

These studies represent a broad use of mobile phones and a broad range of results. Overall results indicate that mHealth is emerging as a potential gold-mine of innovations, containing limitless applications and opportunity for further research including interventions to improve pharmacoadherence in general and ACT in particular.

Mobile Phones to Improve Adherence

Non-Malaria

The majority of the research on mobile phone use for adherence in sub-Saharan Africa focuses on ART adherence in South Africa, a country that is arguably the most technologically advanced in this geographic context (Bärnighausen et al., 2011; Chi &

Stringer, 2010; Crankshaw et al., 2010; Dean et al., 2012; Donald et al., 2007; Haberer & Kiwanuda, 2010; Lester et al., 2010; Pop-Eleches et al., 2011).

Mobile phones applied to pharmacoadherence provide a variety of interaction methods for communication ranging from SMS on the simple end to virtual DOT via mobile phone video transmission on the more complex. All of the articles mentioned above include SMS as one potential intervention, indicating the broad awareness of the growing possibilities and affordability of this simple application.

Often SMS is explored in parallel with other interventions. One innovative study used both IVR and SMS to collect adherence information from caregivers of children infected with HIV in Uganda. This qualitative study determined that, while the rates of interest and participation were high, the completion rate for questionnaires was low (0-33%) possibly because of the new nature of IVR in this cultural setting. This was the only study found in sub-Saharan Africa using IVR for medication adherence. The authors suggest that the use of IVR and SMS is technically feasible, however setup costs for more complex uses of technology such as IVR need to be considered and may prove prohibitive in resource-limited settings (Haberer & Kiwanuka, 2010).

Most research regarding mobile phones and adherence utilized the cheapest, simplest and most common means of communication via mobile phone - SMS or simple phone calls – to remind the patient directly to take their medication. Kunutsor et al. (2010) addressed medication adherence indirectly by reminding patients through voice and SMS about missed clinic appointments, which included the patient picking up their medication refills. Adherence levels were assessed to determine the effect of reminders on optimal adherence. Mean adherence was determined to be significant with 96.3% before and 98.4% after mobile phone intervention.

Two systematic reviews were found to specifically explore mobile phone use in sub-Saharan Africa associated with ART adherence (Bärnighausen et al., 2011; Horvath et al., 2012). Within these reviews, two RCTs from Kenya compared the adherence of those with SMS communication to those without SMS. In both studies, the use of a short weekly SMS reminder resulted in improved rates of adherence (53-62%) when compared to the control group without reminders (40-50%). In addition, one study explored the effectiveness of different lengths and frequencies of SMS. Both studies found that SMS reminders were associated with increased adherence, and a short weekly SMS was found to be more effective than other lengths and frequencies (Lester et al., 2010; Pop-Eleches et al., 2011). Findings also included a decrease in treatment interruption in those receiving weekly reminders (81%) compared with the control group (90%) (Pop-Eleches et al., 2011). There is significant evidence validating the use of SMS reminders to increase adherence to ART in sub-Saharan Africa, however Chi and Stringer (2010) suggest that a multi-faceted approach tailored to local settings may prove more effective than any single intervention.

Studies using mobile phones for adherence are not restricted to HIV medications nor are they limited to low-tech applications of mobile phones. Hoffman et al. (2009) conducted a pilot study in Kenya to assess the feasibility and acceptability of mobile phones to monitor TB adherence through upstream video reporting. They offered video-enabled mobile phones to 13 patients, and trained a health care assistant in the home to video the patient taking their TB medication. These data were then immediately transmitted to a central database where healthcare workers observed them as required by DOT protocol. The investigators also sent video and SMS health messages downstream to the patients. The patients completed a brief questionnaire at intake, after 15 days and at one month after intake asking them to rate their experience. The results indicated a mean response of 4.6 on a 5-point Likert scale from 1 ("Awful") to 5 ("Great") suggesting that participants were very satisfied with study

procedures and technology. Mobile phone technology is becoming a viable alternative to direct observation offering a virtual DOT in some areas where mobile phone videos can be sent.

One service in South Africa sends SMS downstream to patients to remind them to take their TB medication according to regimen. One pilot study of the company evaluated the use of the reminder service on TB recovery to identify socio-economic impacts of technology in that context, and to conduct an assessment of the management of the project. While the treatment outcomes involving the SMS intervention were comparable to clinical outcomes, the results were not statistically significant. Nevertheless, the authors conclude that the use of SMS for medication reminders offers a cost-effective potential resource to complement clinical care (Husler, 2005).

Much of the non-malaria research utilizing mobile phones for adherence has implemented similar techniques using SMS direct to patients for reminders and many of them offer hope for achievable wide-spread results. Studies have not produced statistical significance across the board, but many suggest promise for new implementations and continued research.

Malaria

Only six studies were found using SMS for malaria control in Africa with five of these focusing on upstream uses such as disease surveillance or commodity monitoring (Zurovac et al., 2012). The only RCT discovered using downstream SMS reminders for malaria treatment in sub-Saharan Africa is that of Zurovac et al. (2011) in which SMS are sent to CHWs.

In more developed nations, a team of health care professionals including nurses, physicians and pharmacists conducts the role of health care. In sub-Saharan Africa, CHWs

or medical assistants (comparable to a nurse practitioner) function independently, diagnosing, prescribing and monitoring treatment, generally with no involvement from others (Rueda, 2008). Resource-intensive interventions directed towards the individual have been considered difficult to implement in sub-Saharan Africa due to the large numbers of patients and limited number of health providers (Safren et al., 2012). Therefore, research to date has focused primarily on adherence interventions to the provider of the medication.

The Kenyan study conducted by Zurovac et al. (2011) assessed the effectiveness of SMS malaria case-management reminders from primary investigators (PI) to HCWs in promoting adherence to standard malaria treatment. While the standard care protocol for malaria is relatively simple, it is challenging to ensure that practice conforms to the standard, so SMS messages consisting of educational reminders related to the ACT regimen were sent. The study revealed an improved adherence to medication guidelines by 23.7% immediately after intervention, with a 6-month improvement rate of 24.5%. In a follow up article to the RCT, Zurovac et al., (2012) confirmed that non-adherence is a major area of deficiency in the treatment of malaria, and they support the idea that SMS is potentially beneficial in increasing pharmacoadherence. In a qualitative study examining Zurovac's research, the authors found that there was a high acceptance of all the aspects of the intervention using SMS as reminders to bring about behavioral change (Jones et al., 2012).

While the research of Zurovac et al. (2011) and Jones et al. (2012) involved SMS to malaria HCWs rather than the patient, Lester et al. (2010) and Pop-Eleches et al. (2011) have also demonstrated that SMS interventions directly to the patient can be effective, though their research focuses on ART adherence. No studies were discovered that utilized SMS directly to patients for ACT pharmacoadherence in sub-Saharan Africa indicating a significant gap in the literature and research. The current study offers an attempt to address this gap and change adherence behavior.

Theoretical Framework

Introduction

The National Malaria Control Center of Zambia states that the primary goal of the national communication strategy "…is to facilitate *positive behavior change* (emphasis added) and capacity building through the provision of correct and relevant information to empower people for more effective decision-making in health" (National Malaria Control Center, 2012, "Behavior Change" para. 2). Addressing the many factors affecting adherence can be overwhelming, however the singular focus is on changing behavior. If one's behavior in taking medication can be altered, pharmacoadherence rates can be improved. A theory addressing the needed change is essential to underlie continuing attempts to improve health habits.

The theoretical framework underlying the suggested intervention is the Theory of Planned Behavior. The Theory of Planned Behavior (TPB) is a social cognitive model credited to Icek Ajzen as an extension of his and Fishbein's Theory of Reasoned Action, and incorporates aspects of Bandura's Theory of Self-Efficacy (Ajzen, 1988; Fishbein & Ajzen, 2010; Kuhl & Beckman, 1985). This theory (see Figure 2) provides the most relevant framework for implementing the targeted intervention for improving antimalarial pharmacoadherence through planned behavioral change using SMS messages**.**

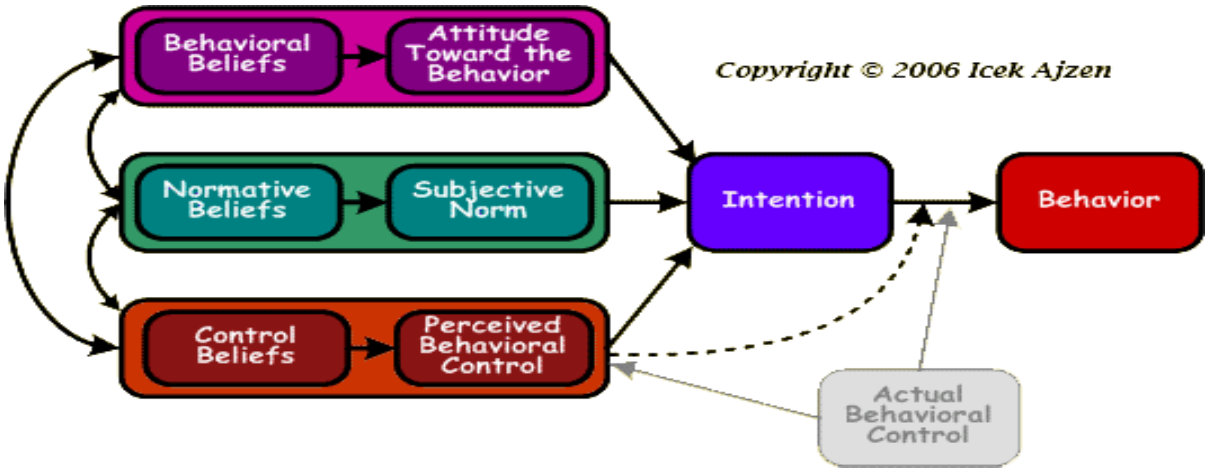


Figure 2: Theory of Planned Behavior

Adapted from "Theory of Planned Behavior," by Icek Ajzen, 2006, retrieved from Icek Ajzen, TPB, http://people.umass.edu/aizen/tpb.diag.html. Used by permission as stated on website.

The TPB postulates that there are three constructs that guide behavior. The first construct is that of behavioral beliefs, involving the individual's beliefs about the expected outcomes of a particular behavior. The collective behavioral beliefs result in a particular favorable or unfavorable attitude towards the behavior. The second, normative beliefs, focuses on the perceived expectations of significant others and one's motivation to meet those expectations. The collective normative beliefs comprise a subjective norm or social pressure to behave or not to behave in a certain manner. The third and final construct, control beliefs, measures the perception of factors that may facilitate or inhibit this behavior, and the perceived power inherent in those factors. Collective beliefs about control result in a perception of the amount of control one has over one's own behavior. The sum of these three outcomes – behavioral attitudes, subjective norms and perceived control - results in a level of intention, which, if sufficiently significant, generally results in the desired behavior. Increasing any one of these constructs increases the level of intention, which in turn increases the likelihood of the individual carrying out the behavior (Ajzen, 2006).

For an intervention using TPB to be successful in the long term, it will likely focus on one or more of the factors that affect the intention and therefore the behavior: Attitude toward the behavior, subjective norms and/or perceived control over behavior. Because each of these is grounded in corresponding beliefs, the most effective and lasting change will address the belief system itself, though this is also the most difficult level to address and involves prolonged commitment to change (Ajzen, 2006). This theory has great potential for long-term future research and exploration of beliefs and attitudes to discover factors affecting pharmacoadherence for malaria treatment in Zambia. The current intervention, however, offers a short-term method for addressing one aspect of the theory through focusing on barriers that limit actual behavioral control.

While perceived control is a critical element in the TPB, there can be barriers to the execution of a behavior, making actual control less than perceived control. These barriers may interrupt one's intention, preventing the individual from carrying out the behavior. This limit on volitional control indicates that the actual control that one has over a behavior, rather than merely the perceived control, is what determines the resultant action (Ajzen, 2006). While the TPB offers a sound framework for interventions to promote pharmacoadherence, some concerns and opposition appear in the literature.

The SMS Intervention within the Theoretical Model

Patients generally believe that they control their ability to adhere (control beliefs). The patient's beliefs lead to the perception that they can *and will* have control to adhere to the prescribed regimen because of their desire to be well, and the perception of the benefits of good health (perceived behavioral control).

When focusing on the right hand side of the TPB model (see Figure 3), it is evident that an individual's likelihood of engaging in adherent behavior correlates with the strength

of the intention to actually adhere, assuming that barriers do not prevent the intention from resulting in actual adherent behavior. Barriers interfere with, and therefore decrease actual control. Some of the barriers to regimen adherence that are identified in the literature review are: Forgetfulness, the medication having a bad taste, the negative side effects (e.g. nausea, vomiting) caused by the medication, and tendency to quit taking the medication when symptoms subside. The intervention of SMS used in this study sought to overcome some of the barriers to adherence by providing both a reminder to address forgetfulness and encouragement to complete the regimen. In addition, the study included a short questionnaire collecting information that may prove helpful in the more difficult task of initiating long-term change in beliefs that can bring about deep-seated, long-term change in behavior.

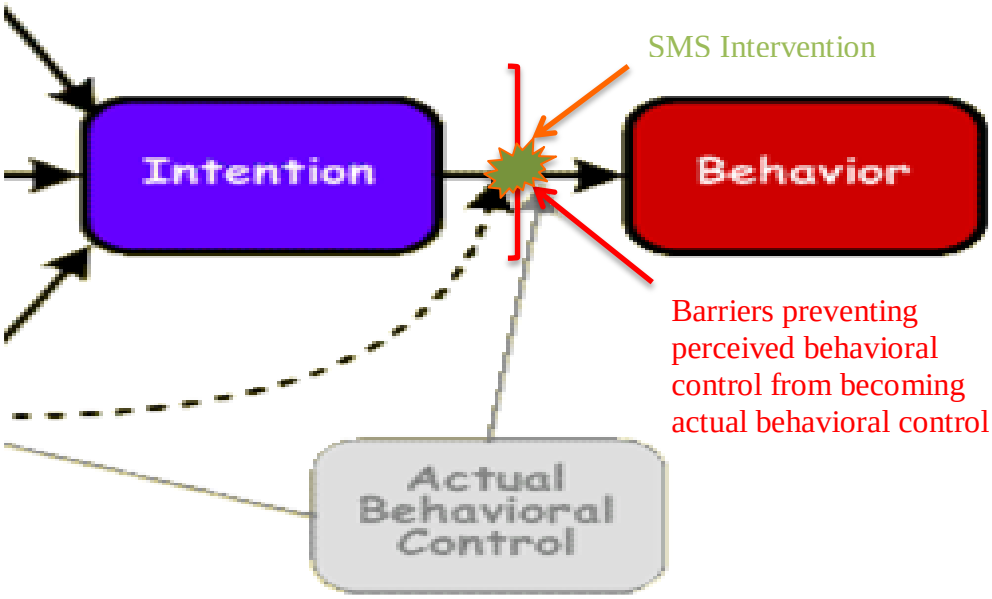


Figure 3: Detail of Figure 2: SMS to Address Barriers

Adapted from "Theory of Planned Behavior," by Icek Ajzen, 2006, retrieved from Icek Ajzen, TPB, http://people.umass.edu/aizen/tpb.diag.html. Used by permission as stated on website.

Critique of the TPB

While no objections specifically to the TPB for pharmacoadherence in sub-Saharan Africa were discovered, some general objections to the efficacy of the model exist. Ogden

(2003) expresses several concerns: He posits that models of social cognition cannot be tested because they cannot be proven false; he insists that the relationships between the model components are true by definition, therefore ensuring a strong correlation; he asserts that the questionnaires to test the constructs might actually cause and influence cognitions that impact behavior rather than merely assessing them.

The TPB would, however, be proven false if all three constructs of the model failed to predict intention, which research has not indicated (Ajzen & Fishbein, 2004). The constructs have been validated in equation analysis and in other investigations that have tested the validity of the construct, and the evidence indicates that assessment methods do not significantly affect the cognitive constructs in the TPB (Ajzen & Fishbein, 2004).

Some critics question the assumptions of all reasoned action theories, a category into which the TPB falls. Wegner (2002) doubts the significance of consciousness as an agent of causation. Greenwald and Banaji (1995) believe behavior to be driven by implicit attitudes while others (Aarts & Kijksterjuis, 2000) suggest that behavior is a result of other mental processes, of which a person is not conscious. These objections do not lend themselves to clear empirical verification.

Critics also claim three other limitations of the model. Some researchers question the sufficiency of the model or suggest that the limits inherent in it are too great. Another of the criticisms of TPB is that it does not account for affect and emotions, that the model is too rational, while yet another argument suggests that the TPB is not sufficient to explain behavior. Critics claim that other components should be added, but rarely agree about which component(s). Ajzen (2011) addresses these concerns.

Regarding the limits of predictive validity in terms of correlations among constructs, the best that can be reasonably expected in this type of model is around 0.6, a measure that approximates the results in the studies he references.

The TPB does not assume that beliefs are formed rationally. The "planned" nature of the behavior does not refer to a rational belief basis, but rather to the nature in which beliefs lead to attitudes that influence intention and, ultimately, impact behavior. Affect and emotions serve as foundational factors to beliefs, and as influencers to direct which beliefs within our memories affect one's attitude or intention (Ajzen, 2011).

Ajzen and Fishbein (2004) expect further developments in the model and provide guidance for the criteria that any additions would need to meet, while rejecting any specific additions proposed to date based on failure to comply with said criteria.

Population of Interest

One of the primary objections is that the TPB is individualistic and therefore not applicable to more communal societies such as those found in sub-Saharan Africa (Campbell, 2003; Kagee & van der Merwe, 2006). Fishbein (2002) indicates that, when properly applied, this model is in fact sensitive to cultural differences, since it incorporates the belief system of the population being observed. For example, communal influence would be addressed in the TPB in the normative beliefs construct.

Since there is room within the model for considering cultural differences, applying the TPB to pharmacoadherence in sub-Saharan Africa has integrity. In one study in South Africa, TPB significantly explained variance in patients' intentions and behavior related to adherence. TPB variables explained 47% of the variance in adherence intentions, resulting in a large effect (Kagee & van der Merwe, 2006; Polit & Beck, 2004). When combined, attitudes and perceived behavioral control explained 23% of the self-reported pharmacoadherence variance. While TPB was found to only explain a portion of adherence intentions in the sample, the strongest predictor of pharmacoadherence intentions was perceived behavioral control (β=0.59), indicating that improving the perception of behavioral

control may be an effective way to increase pharmacoadherence (Armitage & Conner, 2001; Kagee, 2008). Offering the patient a reminder by SMS is likely to increase the perception of behavioral control as well as to overcome the barrier of forgetfulness thus increasing actual behavioral control. The end result would be an increased probability of the desired behavior. The TPB provided a sound theoretical model for the current research.

Summary of the Literature Review and Theoretical Framework

Overall, the literature review indicates that SMS is efficacious in enhancing pharmacoadherence, offering the potential to be effective in malarial treatment in sub-Saharan Africa and hence result in a greater recovery rate and decreased drug-resistance. This innovation is a powerful method to disperse information, offering an effectual, simple and low-cost application of technology to reach a population in a timely and efficient manner (Gardner et al., 2007; Zurovac, et al., 2011). Nevertheless, the use of SMS to initiate behavioral change in health is in the early stages of exploration, and there is very little evidence-based research of the use of this technology directly to patients to address pharmacoadherence behavior in sub-Saharan Africa (Hampton, 2012; Zurovac et al., 2011). No studies were found using this specific application for malaria. This inspires continued attention to this area of research.

CHAPTER THREE: METHODS

Introduction and Design

This chapter presents the methods used in this study beginning with the design, sample and setting, population and inclusion/exclusion criteria. In addition, the precautions for working with human subjects are identified and the intervention and instruments used are explicated. Finally, the procedures and the statistical analysis for the study are described.

This prospective, quantitative, randomized controlled trial was an experimental, between-groups design. Pharmacoadherence was the dependent variable and the SMS intervention was the independent variable.

Sample and Setting

The convenience sample was comprised of individuals who presented to the public clinic in Fisenge, Zambia, tested positive for uncomplicated *P. falciparum* malaria, and met inclusion criteria. The setting for this study was the rural village of Fisenge, Zambia located just off the Luanshya Road close to the Ndola/Kitwe road in the Copperbelt Province. Fisenge has a population of 13,000 with a household income below the national average of USD $1,200/year (Zambia Census of Population and Housing, 2000). Fisenge is representative of rural villages in the Copperbelt Province, with the majority of citizens educated in the public schools where, up until 2014, all education was delivered in English. This site was chosen based on the large number of patients diagnosed with malaria according to clinic records during a site visit in 2012.

Population

The target population of this study was rural Zambians over 18 years of age who were at least minimally literate in English, and who were diagnosed with uncomplicated *P.*

falciparum malaria. Literacy is defined by the United Nations as being able to read and write a short and simple statement about every day life, a definition that 70% of Zambians meet (United Nations Development Programme, 2011). The term "minimally literate" used in this study indicates an ability to read sample phrases, which are similar to those that were sent by SMS.

Inclusion/Exclusion Criteria

To be included in the proposed study, participants must have been at least 18 years of age; had continuous access to a mobile phone for the three days following their clinic visit; were able to communicate via SMS; and were able to read three health-related phrases chosen from a selection of those that were sent by SMS. Participants were excluded if another member of the household was already a part of the study. In addition, if potential subjects had been treated for malaria in the two weeks immediately prior to their presentation, they were excluded. While the original exclusion criteria also included a recorded fever more than 24 hours before clinic visit in order to avoid complicated malaria cases, none of the participants had records of fever measurement.

Sample Size

For the purpose of this study, a medium effect size for a Chi-square analysis and bivariate linear regression was assumed for the intervention. An apriori power analysis was conducted using G*Power (ver. 3.1.6) to determine sample size to provide a medium effect size (.30), with a level of significance of $\alpha = .05$, and power of .80 (Cohen, 2003; Faul, Erdfelder, Lang, & Bucher, 2009). The computation resulted in a required sample size of 88. A targeted sample size of 126 was determined to allow for attrition and incomplete data.

Ethical Considerations

Protection of Human Subjects

Provisions to insure safety of participants were maintained through the adherence to legal and ethical institutional review board (IRB) policies of the University of Central Florida (see Appendix F), as well as those of the Tropical Diseases Research Centre (TDRC) in Ndola, Zambia (see Appendix G) as directed through the Zambia Ministry of Health (see Appendix H). The TDRC prospectively agreed to serve as an external collaborator to support the research (See Appendix I).

Minimal risk was present for participants. The only risks from participation in the study were those involved with travel back to the clinic to return the electronic pillbox. A return trip to the clinic for a post-treatment reevaluation is already one aspect of the current standard of care, though compliance is rare. All other risks - physical, psychological, social, legal and economic - were minimal in probability, magnitude and duration.

Confidentiality can also be a concern in studies involving human subjects. The SMS interventions in this study did not jeopardize confidentiality since the SMS intervention did not address the individual by name, nor did it include any information about the patient. In addition, malaria carries no stigma in Zambia. Within the Zambian culture, illness and medicine are treated very differently than in western world. There is some stigma associated with leprosy and sexually transmitted diseases, but with the clinic being a communal place, where gathering neighbors discuss their illnesses, and with malaria being extremely common, this diagnosis does not necessitate confidentiality (J. J. Enright, personal communication, June 23, 2014).

The collection of data was communicated from the assistant directly to the PI, who entered the information by patient number rather than name on a secure, password-protected

computer accessible only to the PI. Numbers were generally assigned in the order in which they presented to the clinic. Paper documents that link the name and the patient's number were stored in a locked file cabinet in the PI's secure house. The paper documents were destroyed at the conclusion of the presentation of the study findings. Data will be stored indefinitely but without patient identifiers. The PI will not use names or other patient identifiers when communicating data or results. The SMS intervention did not address the individual by name nor did it include any information about the patient.

There were no study-related costs to participants, and all costs for the electronic pillbox product were borne by the investigator. No transportation costs were required from the patients since the primary method of access to the clinic is by foot. There was a small risk that participants involved in the study could have been bothered by the SMS reminders.

Benefits to Human Subjects

Potential benefits to the individual participants included a higher likelihood of adherence and therefore more successful treatment for malaria. The possible benefits to the community from a decrease in resistance are substantial and public policy could potentially be impacted. In addition, the phone card offered in appreciation for participation benefitted those in the study.

Intervention

The intervention used was a series of SMS messages in English (see Appendix A) sent directly to the participant by the PI at the times that the regimen prescribed the malaria medication was to be taken. These SMS messages were to remind and encourage them to take their medication at that time. The content of the messages varied slightly, but each

addressed the taking of the medication and, when the last dose was due, the SMS stated that it was the last dose.

Instruments

The ParaHIT *f* RDT used in this research was manufactured by Span Diagnostics Ltd. WHO recommends a minimum standard of 95% sensitivity and 95% specificity for *P. falciparum* densities of 100/µl (WHO, 2006b). Independent research evaluating this RDT resulted in a 97.6% (95% CI [95.6, 98.8]) sensitivity and 87.7% [83.0, 90.6] specificity, and concluded that it performed well, was appropriate for field use and can contribute to effective diagnosis of malaria (Guthmann et al., 2002). The manufacturer's literature indicates a sensitivity of 99.42% [98.3, 100] and a specificity of 99.59% [99.2, 100] (Span Diagnostics Ltd., 2013). Differences in results may be attributed to improvements in the RDT in recent years. A study of the average 2012 weighted cost for RDTs in Zambia was $0.31 (USAID Deliver Project, 2012). Since RDTs are provided free of charge to government clinics in Zambia, there was no cost in the current study for the diagnostic tools.

Although the PI's and the participants' phones were used to communicate via SMS, the only new instrument that was introduced into the study that was not standard care was the MEMS. As discussed in the literature review and despite the limitations, the MEMS is considered the imperfect gold standard in pharmacoadherence measurement where direct observation is not feasible.

Procedures

Research Assistant

The PI selected and hired a female research assistant after significant screening of potential applicants. Qualifications included the completion of high school and fluency in

Bemba, the local language, and English, the national language. The assistant was trained to interview potential participants, collect demographic data and educate the patient regarding the medication regimen. She also completed Collaborative Institutional Training Initiative (CITI) Training as required by the University of Central Florida under the supervision of the PI.

Recruitment

The clinic nurse identified a potential participant through observational use of inclusion criteria, and referred him or her to the assistant. The assistant then established the eligibility of the individual as a participant using inclusion/exclusion criteria, described details of participation, including the voluntary nature of the study and the incentive offered, and inquired regarding their willingness to participate. If the individual was willing to take part in the study, the assistant obtained permission to record the conversation, educated the participant regarding the regimen, and obtained consent through signature on an Invitation to Participate which was printed in English (see Appendix B). Information sessions were conducted in English, the national language of Zambia. Participants received a copy of the study information form for their records. The assistant's interaction with patients was audio-recorded, transcribed and randomly assessed for fidelity. These recordings were destroyed upon completion of transcription and aggregation.

Demographics and End-of-Study Questionnaire

After consent was obtained, the assistant collected baseline demographic data and illness characteristics using a questionnaire (see Appendix C) designed for this study, which included demographic variables that were found in the literature review to be associated with adherence. The demographic questionnaires had the patients' names removed when they

returned the electronic pillbox for human subject protection. All participants were asked a question as part of the end-of-study questionnaire when they returned the electronic pillbox that addressed the awareness of the existence of the other group in order to analyze for the possible effect of contamination.

Pilot Study

The first ten patients recruited comprised a pilot study to determine whether adjustments to the study were needed and to refine procedures before completing the study. The pilot included analysis of the use of the electronic pillbox and a determination of which SMS messages were most appreciated through an end-of-study questionnaire. Adjustments were made as necessary, and those in the pilot study who needed no adjustments are included in the full and final sample.

Random Assignment

Each participant was randomly assigned to either the intervention group or the control group by block randomization through an envelope system.

Participant Instructions

The research assistant verbally instructed all participants on the treatment regimen. Patients were educated regarding the need to take medication with food, and, if vomiting occurs within one hour of the ingestion, to take the next dose and obtain a replacement dose from the clinic. The healthcare provider administered the first dose of the medication in the clinic with the research assistant observing. The assistant reviewed pictorial instructions and provided the remaining nurse-prepared medications per clinic protocol in perforated foil blister packs containing a 4-pill dose each. These were inserted into an electronic pill bottle

with a MEMS cap (see Appendix D), along with written instructions regarding the regimen. The MEMS cap on the pillbox containing the ACT electronically recorded the time of each opening of the medication bottle beginning with the first dose. The participant was instructed to return between three days and one week from the distribution date with the electronic pillbox for a health re-evaluation. A pre-paid phone card with 20 kwacha (approximately $3.50) of talk time was presented in appreciation for participation when the bottle was returned.

If the participant was in the control group, the assistant released him/her. If the participant was in the intervention group, the SMS communication was described and reviewed if necessary. The assistant then released him/her and initiated the SMS intervention sequence.

SMS Intervention Sequence

The PI generated an SMS reminder to the participant at the prescribed time each dose of the medication was to be taken - 8 hours after the initial dose and at the prescribed times of 8 a.m. and 8 p.m. for the subsequent 2 days of the regimen (see Appendix A).

Conclusion of Participation

When the participant returned the electronic pillbox, the data were transferred to a designated, secure computer and entered into IBM Statistical Package For The Social Sciences (SPSS) for review and analysis. If the bottle was not returned within one week, an SMS reminder to return the bottle was sent. If the bottle was not returned within the following three days, the assistant followed up with a community visit to collect the bottle and assess the patient's health. The participant was offered a Debriefing Statement following the return of the MEMS (see Appendix E).

Pharmacoadherence Measurement

Pharmacoadherence was measured by comparing electronic pillbox openings to the prescribed times of the treatment regimen. Adherence was defined as having an electronically recorded bottle opening within one hour of the prescribed time for the second dose (8 hours after initial dose), and a recorded bottle opening within two hours of the prescribed time for the next two days' doses (8 a.m. and 8 p.m. on each day) based on dosage recommendations (Lefevre et al., 2001; WHO, 2012). The completion of the regimen was verified by a final pill count (target = 0). If the recorded bottle opening times fell within the designated ranges and the pill count was 0, the patient was considered *probably adherent*. If either requirement is not satisfied, they were classified *probably non-adherent*.

Statistical Analysis

Once all data were collected and summarized, the data were screened for completeness. The PI compared the proportion of those determined to be *probably adherent* in each group to those determined to be *probably non-adherent*, and a Pearson Chi-square test of independence was conducted to determine association between SMS reminders and pharmacoadherence. In addition a Chi-square test of homogeneity was conducted to ensure uniformity of the two groups. Finally, binary logistic regression was used to control for all demographic covariates and determine any factors associated with adherence.

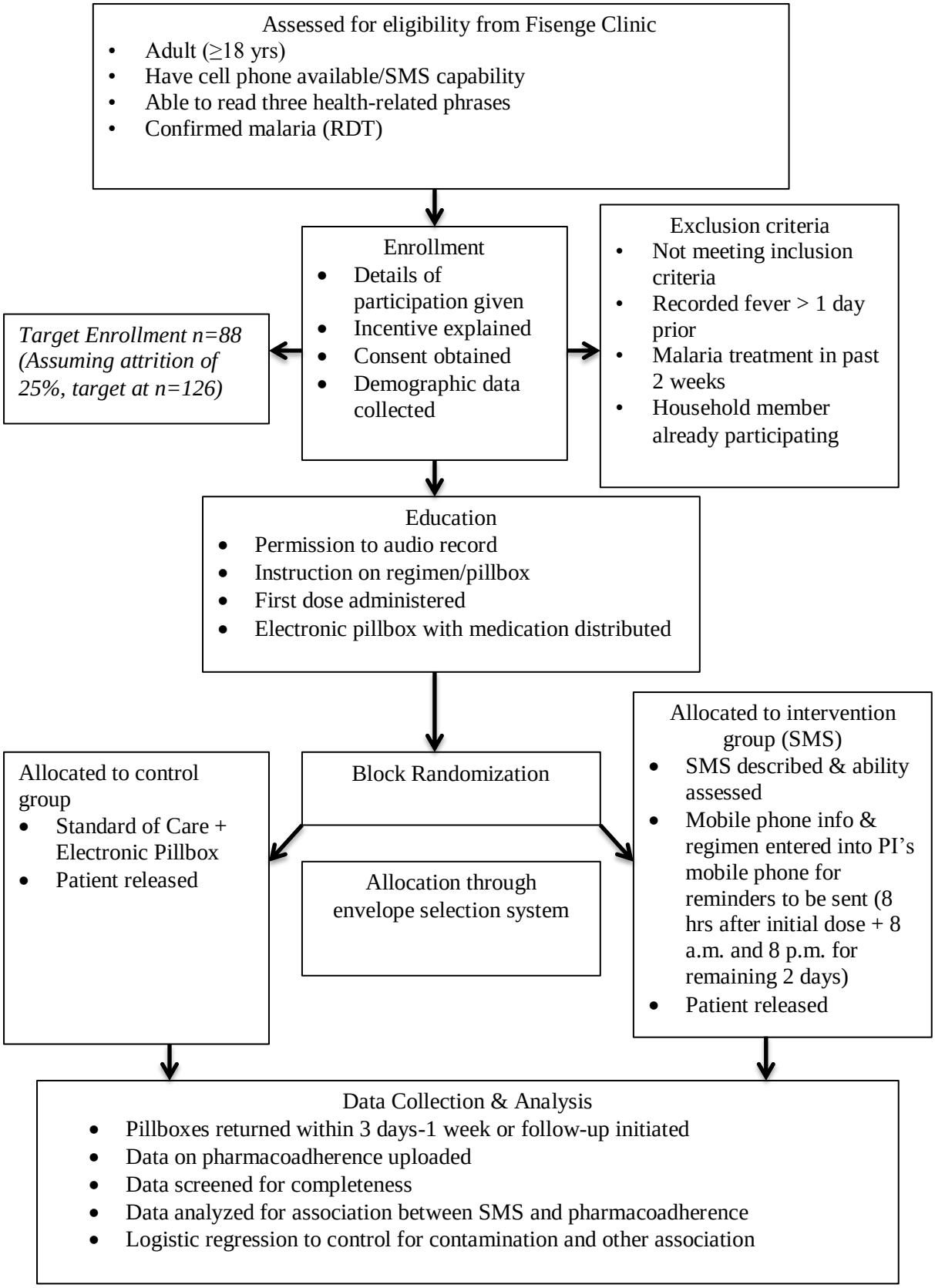


Figure 4: Experimental Methods

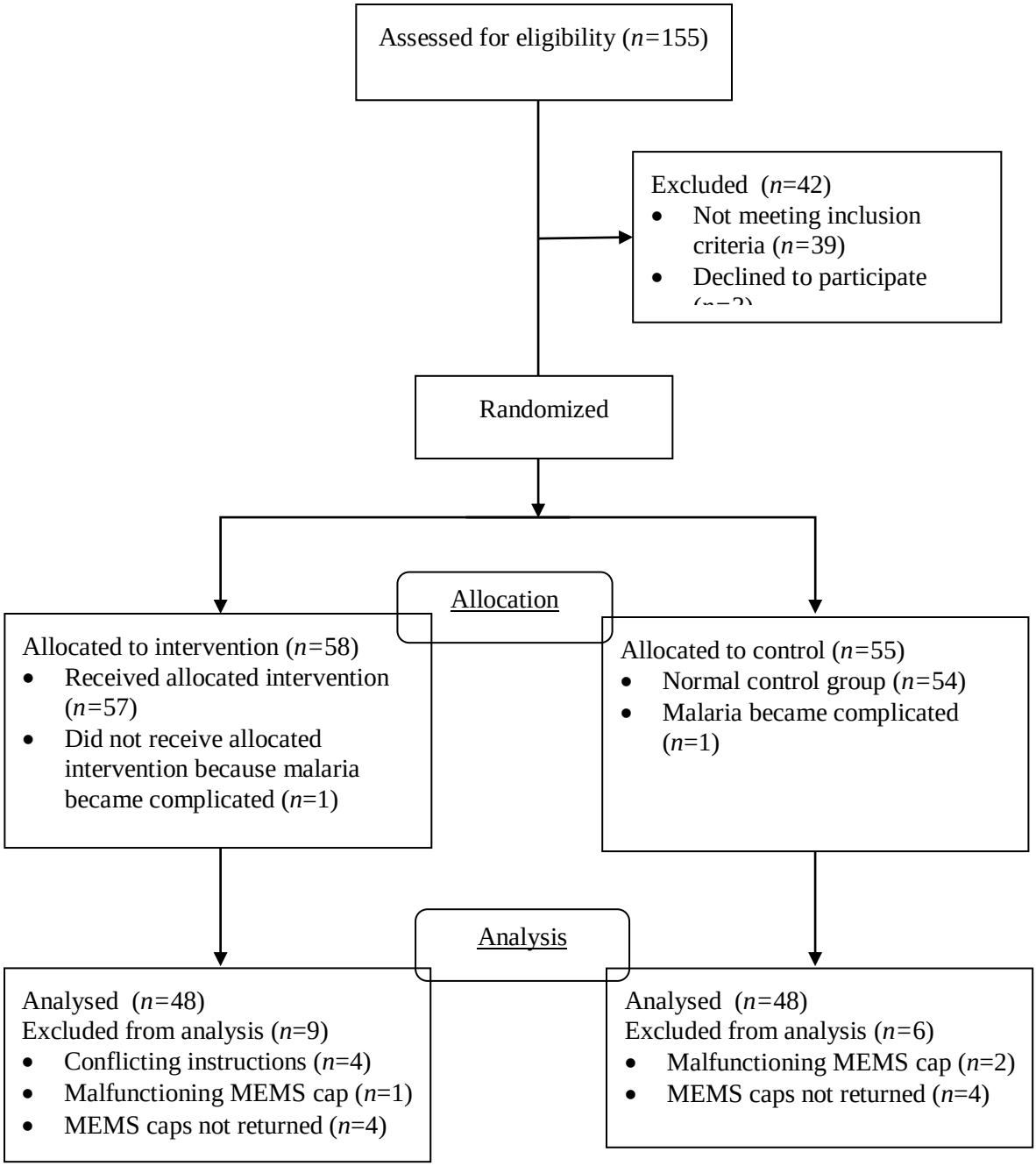


Figure 5: Consort Flow Diagram

Summary

In summary, this chapter reviews the methods used in this study including the design, sample and setting, ethical considerations, procedures and statistical analysis. The methods reviewed are considered appropriate and feasible for the current study to determine the association between SMS reminders and pharmacoadherence.

CHAPTER FOUR: RESULTS

MEMS cap and demographic data were collected over a 2-month period and analyzed using IBM SPSS for Mac version 22.0. All records used in the sample were complete with no missing data.

Characteristics of the Study Population

The study population consisted of those who met inclusion/exclusion criteria at Fisenge clinic from February 21 through April 26, 2014. Though the targeted sample size was 126, data collection was stopped at 113 as more than 88 (target sample size) were able to be included in the analysis. Of these, three were excluded because of malfunctioning MEMS caps; two because their malaria became complicated and they transitioned to alternative treatment; four because of conflicting medication instructions between the clinic staff and research assistant; and eight because the assistant was unable to collect the MEMS cap. The remaining 96 (85%) consented to participate, were randomized to the control or intervention group, and their data were analyzed.

Among participants, 52.1% (*n*=50) were males and 47.9% (*n*=46) were females. The participants ranged in age from 18-64 with 32.3% (*n*=31) of the sample aged 18-25; 28.1% (*n*=27) aged 26-35; 24.0% (*n*=23) aged 36-50; and 15.6% (*n*=15) over 50. A large number of these were unemployed (61.5%, *n*=59*)* and/or had income less than 500 Kwacha rebased (Kr)/month (USD $75) (75%, *n*=72*)*. Additional demographic information is presented in Table 4.

Table 4: Summary of Demographic Characteristics

Variable	Response	# (%)
Age	18-25	31 (32.3%)
	26-35	27 (28.1%)
	36-50	23 (24.0%)
	Over 50	15 (15.6%)
Gender	Male	50 (52.1%)
	Female	46 (47.9%)
Residence	Village	65 (67.7%)
	Rural	31 (32.3%)
Family income	0-100 Kr	63 (65.6%)
	100-500 Kr	9 (9.4%)
	500-1000 Kr	17 (17.7%)
	> 1000 Kr	7 (7.3%)
Employed	Yes	37 (38.5%)
	No	59 (61.5%)
Own radio	Yes	69 (71.9%)
	No	27 (28.1%)
Languages able to write	English	6 (6.3%)
	English and Bemba	53 (55.2%)
	English and Other	5 (5.2%)
	English, Bemba and Other	29 (30.2%)
	Bemba	3 (3.1%)
Languages able to read	English	5 (5.2%)
	English and Bemba	57 (59.4%)
	English and Other	5 (5.2%)
	English, Bemba and Other	29 (30.2%)
	Bemba	0 (0%)
Highest grade completed	1-7	22 (22.9%)
	8-9	31 (32.3%)
	10-12	32 (33.3%)
	College	11 (11.5%)
Taken malaria med before	Yes	87 (90.6%)
	No	9 (9.4%)
Belief in traditional tx (i.e. without medication)	Yes	4 (4.2%)
	No	92 (95.8%)

Groups

Of the total sample (*N=96)*, block randomization resulted in 50% (*n*=48) assigned to the control group and 50% (*n*=48) to the intervention group. After reviewing the data, some variables (age, income, education) were collapsed to increase the *n* for analysis, and a Chi-square test of homogeneity conducted. Where the Chi-square assumption was not met, the Phi value was used. The analysis verified that the randomization successfully achieved balance across observable characteristics with the two groups not differing significantly in any categories (p>0.05) (see Table 5).

Table 5: Chi square test of homogeneity

Variable	Response	Intervention Group	Control Group	*p* value
Age	18-35	31 (64.6%)	27 (56.3%)	.404
	Over 35	17 (35.4%)	21 (43.8%)	
Gender	Male	21 (43.8%)	29 (60.4%)	.102
	Female	27 (56.3%)	19 (39.6%)	
Residence	Village	30(62.5%)	35 (72.9%)	.275
	Rural	18 (37.5%)	13 (27.1%)	
Family income	0-500 Kr	36 (75.0%)	36 (75.0%)	1.00
	> 500 Kr	12 (25.0%)	12 (25.0%)	
Employed	Yes	16 (33.3%)	21 (43.8%)	.294
	No	32 (66.6%)	27 (56.3%)	
Own radio	Yes	31 (64.6%)	38 (79.2%)	.112
	No	17 (35.4%)	10 (20.8%)	
Highest grade completed	1-9	26 (54.2%)	27 (56.3%)	.837
	10-College	22 (45.8%)	21 (43.8%)	
Taken malaria med before	Yes	43 (89.6%)	44 (91.7%)	.726
	No	5 (10.4%)	4 (8.3%)	
Belief in traditional tx (i.e. without medication)	Yes	2 (4.2%)	2 (4.2%)	1.00
	No	46 (95.8%)	46 (95.8%)	

Findings

Pilot Study

Only one adjustment was made following the pilot study. The PI discovered that the clinic nurse was prescribing second and third day dosages at 6 a.m. and 6 p.m., and the SMS reminders were being sent at 8 a.m. and 8 p.m. as initially planned. This caused some confusion in the intervention group resulting in the exclusion of 4 patients from the final results. After consultation with the clinic nurse and the research assistant, the determination was made that the clinic nurse would prescribe the 8 a.m. and 8 p.m. schedule to coincide with the SMS reminder.

Adherence

Only two participants did not complete the regimen resulting in exclusion from the study. Pill counts revealed only one dose left in the returned bottles, which was from a patient's case that was redefined as complicated and excluded. All other pill counts were 0 (zero) as required for the category *probably adherent*.

No significant association was found between SMS reminders and pharmacoadherence among malaria patients being treated with ACT when evaluated with respect to those who received the SMS reminders and those who did not (χ^2=0.19, *df*=1, *p*=0.67). Findings indicated that 64.6% (*n*=31) of those in the intervention group were *probably adherent* compared with 68.8% (*n*=33) of those in the control group (see Table 6). Of the total, 66.7% (*n*=64) were classified as *probably adherent* and 33.3% (*n*=32) as *probably non-adherent*. Of those identified as *probably adherent*, 51.5% (*n*=33) were male and 48.5% (*n*=31) were female.

Table 6: Adherence Results

	Intervention (SMS) # (% of group)	Control (No SMS) # (%)	Total # (%)
Probably Adherent	31 (64.6%)	33 (68.8%)	64 (66.7%)
Probably non-Adherent	17 (35.4%)	15 (31.2%)	32 (33.3%)
Total	48	48	96

Twenty participants had *probable perfect adherence* as defined by digitally-recorded MEMS bottle openings occurring only during the timeframes of adherence and only the required six openings with one in each timeframe. Of those, 12 (66.7%) were in the intervention group and 8 (33.3%) in the control group indicating that the SMS intervention may have been helpful for staying within the prescribed parameters. However, when these data were analyzed by Pearson's Chi-square test of association, the result was still not found to be significant (χ^2=1.01, *df*=1, *p*=0.32). Though underpowered, these data may provide direction for further research.

Table 7: Probable Perfect Adherence Results

	Intervention (SMS) # (% of group)	Control (No SMS) # (%)	Total # (%)
Probably Perfectly Adherent	12 (25%)	8 (16.7%)	20 (20.8%)
Probably Not Perfectly Adherent	36 (75%)	40 (83.3%)	76 (79.2%)
Total	48	48	96

Binary logistic regression was used to determine if any other independent variables (town, age, gender, belief in traditional treatment, prior treatment, fever time, education, employment status, family income and radio) were associated with adherence. The variables

languages read and *languages written* were excluded due to small sample sizes in some groups resulting in widely varying, insignificant statistical results. To increase statistical power and simplify interpretations the following variables were collapsed into binary variables for the logistic regression: age, education, family income, fever time. A forward step-wise procedure was then executed. Analysis indicated that there were no variables associated with adherence (see Table 8) ($p<0.05$).

Initial binary logistic data were screened and regression results indicated that the overall model fit was questionable (-2 Log likelihood = 115.9) and was not statistically significant in distinguishing between groups ($\chi^2 = 6.31$; $df = 10$; $p = 0.79$). The model correctly classified 64.6% of the cases, a decrease of 2.1% compared to the model without the independent variables considered (66.7%). Regression coefficients are presented in Table 8. Both the *Wald* statistics and the odds ratios indicate little change in the likelihood of adherence based on the SMS intervention.

Table 8: Binary Logistic Regression of Variables

	B	*Wald*	*df*	OR	95% CI	*p*
Town						
Village				1.0 (ref)		
Rural	-0.55	1.0	1	0.58	0.20, 1.7	0.31
Age						
18-35 yrs				1.0 (ref)		
>35 yrs	-0.72	2.1	1	0.49	0.19, 1.30	0.14
Gender						
Male				1.0 (ref)		
Female	-0.28	0.27	1	0.76	0.26, 2.2	0.61
Traditional belief						
Yes				1.0 (ref)		
No	0.63	0.26	1	1.9	0.17, 21.2	0.61
Prior tx						
Yes				1.0 (ref)		
No	-0.28	0.12	1	0.76	0.16, 3.6	0.73
Reported fever time						
<24 hrs				1.0 (ref)		
>24 hrs	-0.33	0.47	1	0.72	0.28, 1.9	0.49
Education						
Gr 1-9				1.0 (ref)		
> Gr 9	-0.65	1.6	1	0.52	0.19, 1.4	0.20
Employed						
Yes				1.0 (ref)		
No	-0.21	0.087	1	0.81	0.20, 3.2	0.77
Family income						
0-500 Kr				1.0 (ref)		
>500 Kr	-0.38	0.21	1	0.68	0.13, 3.5	0.64
Own radio						
Yes				1.0 (ref)		
No	-0.59	1.10	1	0.56	0.19, 1.7	0.30

However when binary logistic regression was run using the same variables against *probable perfect adherence*, three factors were significant: Lower age (OR 0.099, 95% CI [0.024, 0.41], $p<0.01$), owning a radio (OR 0.096, [0.019, 0.47], $p<0.01$), and residing in a village rather than rural (OR 0.116, [0.026, 0.51], $p<0.01$).

In addition, the Omnibus Test of Model Coefficients resulted in $\chi^2=27.04$ ($df=1$, $p<0.01$). Results indicated that the overall model fit using *probable perfect adherence* was better than the fit using *probable adherence* (-2 Log likelihood = 71.2). The model correctly classified 85.4% of the cases, an increase of 6.2% compared to the model without the independent variables considered (79.2%).

In addition, the mean number of bottle openings for the sample ($N=96$) was 7.8 for a regimen that only required six openings. The number of openings ranged from 5 to 15 with the majority of the participants opening the bottle more than the necessary 6 times.

End of Study Questionnaire

The results of 24 self-report end-of-study questionnaires (see Table 9 & Appendix J) provide data for possible further research. Responses to the question regarding awareness of a second group indicated that there was no awareness so contamination is not suspected. When asked what aspect of the regimen was most helpful for taking the medication, results were mixed, but 20 of the 24 (83.3%) included SMS as being one of the most helpful components.

Regarding the helpfulness of the timing of the SMS the 25% who indicated that the evening reminders seemed most helpful suggested that it was because of the many distractions that they faced during that time of day. One participant mentioned that both were helpful "because they were encouraging me showing that they care for my health."

The final question was to gauge whether participants viewed ACT as a primary or a secondary approach to treatment. When asked if they sought help prior to coming to the clinic, only two respondents replied that they had tried alternative treatment. Results indicated that seeking medical treatment from a professional healthcare provider seems to be the primary choice of most of those (92%) presenting to the clinic. Further qualitative studies are necessary to determine true predictors of and factors affecting adherence.

Table 9: End of Study Questionnaire Results

Question	Responses # (%)
What was most helpful in taking the medication?	
Pill bottle	0 (0%)
SMS reminder	8 (33.3%)
Packaging (blister pack)	2 (8.3%)
SMS & packaging	2 (8.3%)
SMS & pill bottle	2 (8.3%)
Pill bottle & packaging	2 (8.3%)
Combination of SMS, pill bottle & packaging	8 (33.3%)
Which SMS messages were most helpful for reminders?	
Morning reminder	3 (12.5%)
Evening reminder	6 (25.0%)
Both equally helpful	11 (45.8%)
No response	4 (16.7%)

CHAPTER FIVE: DISCUSSION

Literature Review and Theoretical Framework

P. falciparum malaria-associated infection continues to burden individuals and public health services in sub-Saharan Africa in the areas of health, longevity and economics. Despite having the best medication available to treat an illness, pharmacoadherence remains an integral key to effective treatment.

While the association between the SMS and adherence were not significant, the rates of adherence for both control (68.8%) and intervention groups (64.6%) were higher than other comparable measures of ACT adherence in sub-Saharan Africa. Best practice methods, such as the pictorial instruction, were intentionally implemented in this study to maximize adherence rates and may have contributed to the higher level of adherence. The Hawthorne effect may also have led to the higher rates. When the definition of adherence included consideration of the medication timing in the literature, *probable adherence* ranged from 38.7% (Lemma et al., 2011) to 48.3% (Gerstl et al., 2010). It was only when factors such as timing were removed that rates of ACT adherence in other studies fell in a similar range to the current study (Cohen et al., 2012; Lawford et al., 2011). The higher rate of adherence may be attributed to the use of the MEMS bottle, which has been found to improve adherence (Fallab-Stubi et al., 1998; Kahook, 2007). The additional attention given to the patients in the research might also contribute, though no base-line adherence rates are available for patients in the Copperbelt Province of Zambia.

Though the literature review indicated an association between SMS and adherence, the current study's data indicated no such association. Most studies measuring SMS direct to patients and indicating association were conducted with ART adherence, but since ACT

adherence is a short-term regimen, results were expected to be similar or better (Horvath et al., 2012; Kunutsor et al., 2010; Lester et al., 2010; Pop-Eleches et al., 2011).

The reasons for lack of association between SMS and ACT adherence in the current study may be difficult to discover. SMS may provide simply another tool in the comprehensive, multi-pronged approach that must be tailored to local contexts (Chi & Stringer, 2010). The current study certainly reinforces the ease of implementation and technical feasibility suggested by others regarding the use of the mobile phone for adherence in resource-limited settings (Crankshaw et al., 2010; Haberer & Kiwanuda, 2010; Kamanga et al., 2010). However, the lack of research using mobile phones for malaria leaves little material with which to compare (Kaplan, 2006; Zurovac et al., 2012).

When using the *probable perfect adherence* in logistic regression, several of the factors identified in the literature review were also found to be significant in this study. The three variables, *lower age, owning radio*, and *living in a village* were associated with increased rates of *probable perfect adherence* across all study participants. The *lower age* may be associated due to the young being more open to treatment by medication since they did not live through much of the traditional treatment history that preceded modernity. *Owning a radio* may indicate a higher socio-economic status and/or being exposed to mass media anti-malarial campaigns. *Village life* would bring more exposure to the experience of others who have benefited from medical treatment compared to those living in rural areas. The likelihood of electricity in the village also brings an added level of technology, and with it, education.

The use of the TPB, while helpful, proved problematic to measure as a cognitive model. It is difficult to determine if the SMS intervention was successful in improving *intention to adhere*, one aspect of perceived behavioral control in the TPB. *Intention to adhere* was assumed in this study, and the measurement of this research targeted adherence

behavior rather than intention. Several individuals responded to the SMS with appreciative SMS return responses for the attention and care offered. One responded, "Thanks for your encouragment, i even went for work. May God bless you gudnite [*sic*]." Another, "yes im [*sic*] feeling better now thank you." And another, "Thank you very much. I have taken it im [*sic*] better now." Anecdotally, many patients responded positively to the SMS reminders as the literature suggests (Dean et al., 2012; DeRenzi et al., 2012; Donald et al., 2007; Hoffman et al., 2009; Jones et al., 2012).

The potential barriers identified in the application of the TPB to pharmacoadherence that prevent the planned behavior (i.e. taking prescribed medication according to regimen) from becoming actual behavior were forgetfulness, bad taste, negative side effects and subsiding symptoms. Though the use of the SMS reminder intervention addressed primarily the forgetfulness aspect, it did not address and overcome any barriers to actual control that resulted in improved pharmacoadherence behavior. The reasons for that failure are not readily apparent although multiple challenges existed that may have contributed to the poor association.

Evaluation of Design

Introduction

Every study is only as good as the integrity of its design. One must consider multiple factors that affect both internal and external validity and how they might have influenced the study.

Internal Validity

Multiple factors threatened the internal validity, and the design incorporated measures to address some of these threats. *Randomization, homogeneity* and *standardization* helped to

create a balanced design. One of the primary threats in any experiment is that factors other than the intervention may contribute to the measured difference, and therefore must be considered. *Randomization* was used to assign participants into either the intervention or control group, and both groups contained an equal number of subjects from the same village. Demographic logistical analysis was performed to ensure *homogeneity*, which was verified through the Chi-square test of homogeneity. Thorough training of the assistant and scripting of the educational material *standardized* the interaction with both the intervention and the control group. The script was also worded in such a way as to attempt to eliminate experimenter bias or undue influence by being reviewed by a local consultant prior to implementation. To avoid the possibility of being perceived as coercive, the PI provided vigilant monitoring through a systematic review of random audio recordings of the assistant's interactions with participants that better assured adherence to standardization. The PI found no significant variations from the script. Applying the measures described mitigated the identified threats to internal validity.

In addition, valid statistical analysis requires an adequate sample size. The target sample size (N=88) in this study was determined with G*Power software and was exceeded with a sample size of 96. There are no identified significant threats to internal validity in this study.

External Validity

Additional measures were critical to ensure external validity allowing generalizability to the population of interest. A representative sample design was one necessary measure implemented to enhance external validity. While the convenience sample used in this design was a nonprobability sample, the prevalence of malaria occurrence and the homogeneity of the village help enhance generalizability.

The *Hawthorne effect, novelty effects* and *experimenter effects* may limit generalizability (Polit & Beck, 2004). The *Hawthorne effect* describes the behavior that may result because the participants know that they are in a study, and therefore behave differently than if they are not. This effect was impossible to avoid given the use of the MEMS bottle and the notification requirements of the IRB. Expectancy effects may be motivated by a desire to please the assistant, by being adherent, or by some incentive perceived or actual. According to the clinic staff, the study participants displayed a much higher rate of return to the clinic post-treatment than non-participants thus enabling follow-up and further health assessment. The phone card incentive that was offered to all participants in both groups for returning the MEMS caps and bottle provides a probable explanation for the increased rate of return.

The *novelty effect* refers to the effect that the relatively new technology of SMS and/or the electronic pillbox, might have on patient adherence incentive. Though novelty effects can limit external validity, they are extremely difficult to address and to quantify. However, the advantage of the version of the MEMS cap used in this study is that it is not overtly technological. The appearance is similar to a standardized pill bottle somewhat limiting the novelty effect.

Experimenter effects operating in the assistant and the PI may also introduce some bias. The intellectual and/or emotional investment of desiring an intervention to be successful could lead to misinterpretation or subconscious guiding of the patients. The PI as a white Westerner in an African culture avoided direct contact with the Zambian clients in order to minimize experimenter effects. Careful training of the assistant, script writing, recording, and systematic monitoring of compliance to the script also helped to minimize these concerns.

Methodological Assumptions and Limitations

Methodological assumptions and limitations in this study fall into the categories of design, sampling, measurement, statistical analysis and other challenges.

Design

One study limitation was the possibility of contamination. While participants were masked to the intervention, both experimental and control groups reside in the same highly social community; therefore, information regarding the group differences was investigated to determine significance. Since none of those responding to the end-of-study questionnaire indicated knowledge of the other group, contamination was considered negligible.

A further limitation of the study was that receipt and timing of SMS messages were not confirmed due to the lack of availability of *read receipts* for SMS in Zambia. The participants' phones were not reviewed to determine if and when the messages that were sent were, in fact, received and read. Of course, even if read, there is no means of determining whether the intended participant read them, a reasonable concern recognizing the shared nature of cell phones in low-resource settings.

Other issues that could negatively impact the timeliness of the receipt of the SMS include participants leaving the coverage area, not being in the vicinity of their phone, or having depleted mobile phone batteries without immediate access to electricity to recharge them.

Sampling

Using a convenience sample as opposed to a probability sample can result in selection bias (Oleckno, 2002). Due to the sampling being taken from a single village location, patient demographic characteristics may differ from those in other regions of the country. Those

who participated and/or those who qualified to participate may possibly have differed demographically from those who did not. Those who did not qualify were not asked to complete a demographic questionnaire largely due to linguistic and literacy challenges. Future studies could implement this process in order to better explore generalizability. While all visible observations indicate that Fisenge is a typical rural Zambian village in the Copperbelt Province, clinic and village statistics were not available to justify this assumption, limiting generalizability without further statistical substantiation.

Measurement

The study presents several measurement challenges. The largest challenge to accuracy and precision comes with defining and measuring actual adherence. If a patient consumes the medication within one hour of the prescribed time, is he/she adherent? Are participants adherent if within two or three hours? Precision in measuring adherence proves problematic without clearly defined adherence parameters. The measurement parameters chosen herein are based on an exploration of adherence definitions in malaria research literature and a strict definition was selected for conservative purposes (Lefevre et al., 2001; WHO, 2012).

DOT best assures actual adherence to a prescribed regimen, but multi-day regimens with outpatients render such assurance difficult at best. Electronic monitoring such as the MEMS cap helps, but it records only the opening and closing of the pill bottle, not ingestion of medication. The participants may also save or give away the medication resulting in a false indication of adherence. The best assurance and most precise description of adherence that a researcher is able to achieve given these limits is *probable adherence.*

In this research, the assumption was that if a MEMS cap recorded an opening during the adherence time window *probable adherence* was assumed, even if the bottle was opened

at other times between adherence windows. The excessive number of bottle openings may be due to the novelty of a new dispenser since most medication from the clinic is dispensed in small, clear, plastic medication bags with zip seals. Both groups were using the same type of electronic pillbox and the same standard of adherence, so the precision of the measurement of actual adherence was less critical in this study than the consistency of measurement between groups in order to ensure comparability and to validate the use of the Chi-square statistic. The small number of those identified as *probably perfectly adherent* verifies the difficulty in determining adherence even with the MEMS cap.

Another factor limiting the measurement of adherence in this study is the dichotomous nature of adherence chosen in this design when assigning participants to either *probably adherent* or *probably non-adherent*. There is no measurement of partial adherence or analysis of different aspects of adherence like the specifics of timing or number of pills taken other than an end of study pill count. Consistency in the definition and measurement of adherence is critical as related studies are conducted.

Statistical Analysis

One assumption of the Chi-square test is that no cells have a count of five or less. Our analysis and sample size met that assumption, validating the use of Chi-square.

Other Challenges

Every study faces challenges, but those conducted in low-resource settings, such as much of sub-Saharan Africa, face a unique set of challenges, each one an opportunity for further exploration. Factors that influence pharmacoadherence in Zambia likely have a wide application to other sub-Saharan settings.

One of the challenges in this study was the communication barrier between the PI and others involved in the research – the assistant, the clinic nurse and the patients. Though the assistant was fluent in English, miscommunication still occurred. The explanation of randomization, for example, took significant explaining multiple times before the assistant understood the process. This communication barrier even with those fluent in English could potentially impact the study. Recording the assistant's interaction with participants served to mitigate that issue.

Another significant communication challenge is the large number of languages spoken by the clinic's patients. There may be communication and information biases due to interpretation and translation issues, although such bias is most likely insignificant.

Cultural differences also proved to be challenging. Generally members of the community have a clear understanding of the signs and symptoms of malaria and when to seek treatment. However, beyond the signs and symptoms, there continues to be many misconceptions on the etiology of malaria. For example, a significant number of community members reported that malaria can be contracted by eating an unripe mango, or even from being caught out in the rain. Curses and spells are believed to be one of the primary causes of illness in the Copperbelt. Based on these misunderstandings, it seems that better education and knowledge may improve not only adherence, but also prevention of the disease. Though a greater percentage of those over grade nine (72.2%) were *probably adherent* than those under grade nine (62.2%), the difference was not significant (χ^2=1.03, *df*=1, *p*=0.31). An understanding of the importance of adherence to a treatment regimen and its link to the high rate of morbidity and mortality brought on by malaria is crucial to motivate adherence.

Traditional African belief often attributes the causes of diseases to ancestors or witchcraft. Two cases of superstition nearly caused the loss of data and MEMS caps. In one

case, a patient related that her spouse encouraged her to throw the bottle down the outhouse because it must be witchcraft that is involved: "Why else would they want to know how many times you opened the bottle?" A second story indicated that the PI's name (Elinda) was so closely related to the local river goddesses (Linda, Belinda, Brenda) that there must be witchcraft involved. Fortunately in both cases, participants discussed the matter with the research assistant or clinic staff and returned their bottles. In retrospect, the research intervention may have been more successful in an urban setting where education levels are higher, belief in western medicine is widespread, and English speaking is more prevalent. However, such a setting would also further limit generalizability to rural Zambians.

Another concern is the status of the eight who did not return their MEMS caps. It is possible that they were aware of their failure to adhere so retained the caps to prevent measurement. However, since four were from the control group and four from the intervention group, any effect that would present would likely be distributed evenly between the groups.

Some challenges involve the use of mobile phones. The cost of mobile phones and the poverty in sub-Saharan Africa often lead to fixed shared-access mobile phones (Kalba. 2008). These mobile phones are shared among a fixed household or family, which complicates direct and timely communication to individuals. Though the participant may still have access as required for this study, the phone may be in use by another member of the household at the time the SMS is sent. Future studies should consider methods of confirming receipt of SMS reminders by the participant.

In a country where various aspects of the mobile phone industry, such as network coverage, contribute to the use of multiple subscriber identification module (SIM) cards from multiple providers used by each individual, one challenge is knowing to which phone number the SMS is to be sent. Although the assistant only asked for one phone number to which to

send the SMS, the PI would sometimes receive a response from the same participant using a different phone number than the one given. This confusion may have led to missed messages if a different SIM card was installed in the shared-access phone at the time of the SMS. Alternative card use could be due to one SIM card being out of prepaid talk time or cheaper call rates within a specific network resulting in a different SIM card being installed.

Another challenge was the need to reuse MEMS caps for multiple patients, a practice that is discouraged by the manufacturer, Aardex (2013). The primary reason for the discouragement of this practice is the possibility of cross-contamination, however since malaria in a non-contagious disease, and because the pills were in blister packs within the bottles, this objection was not considered substantive. While the multiple use of each bottle did not impede the research, the compilation of the data was slightly more complicated by the reuse of the MEMS caps.

The only economic challenge associated with long-term use of this SMS intervention with the MEMS caps is the expense, which at this time is cost-prohibitive in resource-limited settings. A comprehensive cost analysis would need to be done for any large-scale applications of SMS reminders for adherence. Such costs may include investments in computer equipment and salaries for administrative purposes. However, the costs of all other aspects of the study, including the SMS (approximately USD $0.01/message or a total of less than $10 for all messages in the current study) and the ACT treatment proved negligible due in part to government supply of free ACT to all public clinics, indicating that the intervention is both actionable and practical for future research where similar conditions exist.

Implications for Nursing Practice and Policy

Practice

The study indicates few implications to nursing practice due to the lack of association between SMS and adherence other than to add to the current body of knowledge. However, there are some implications for nursing research. Pharmacoadherence is a multi-faceted concept that will not be easily solved with any individual intervention. The SMS reminder, if found to be associated with adherence in further research, can be used to supplement other adherence strategies in the hope to improve pharmacoadherence not only for ACT and malaria, but also for other long-term illnesses, where forgetfulness may be more prevalent.

The many challenges that the PI faced with communicating clearly to those of another language and culture reinforced the necessity of adequate training and understanding for those involved in research. One is dealing with multiple layers of tradition and traditional understanding, which are not going to be replaced with a scientific understanding in a brief time of training. The more one learns about the culture prior to research, the less likely miscommunication and misunderstanding is to occur. Ideally the researcher would come from the same culture and speak the same language as those among whom the research is conducted. This would minimize undue influence and misunderstanding or miscommunication. However, the assistant used in the current study was the contact person by participants and shared both the same culture and the same language with them.

The PI used best practice standards in the current study such as blister packs and both written and pictorial instructions. The phone card incentive may also have motivated pharmacoadherence. The lack of adherence differences discovered and the higher level of adherence may be due to a combination of these best practices and the incentive provided.

Sixty-two of the participants (65%) claimed that their fever began more than 24 hours prior to clinic arrival, however these were all self-report without thermometer verification. Though only two participants' malaria became complicated, health education must address the need for earlier intervention for treatment initiation or clinic consultation in order to reduce the risk of severe malaria infection and mortality.

Sub-Saharan Africa is in the early-majority stage of the technology adoption curve as determined by Kalba (2008) and defined by Rogers (2003). As mobile phones become more prevalent and the coverage and use more sophisticated, these powerful tools will be able to be utilized in multiple ways to assist healthcare.

Policy

Global policy provides the needed framework to deliver effective healthcare services. The United Nations has established eight Millennial Development Goals, the sixth of which is to combat HIV/AIDS, malaria and other diseases. The third part of this target goal is to halt and reverse the incidence of malaria by 2015 (UNF, 2012). A significant global initiative, the RBM Partnership, was launched in 1998 bringing together the WHO, the United Nations Children's Fund (UNICEF), the United Nations Development Programme (UNDP) and the World Bank in an effort to provide an effective and coordinated global response to malaria. Today RBM embraces over 500 partners including malaria endemic countries (RBM, 2010).

The National Malaria Control Programme of Zambia falls under the Directorate of Public Health and Research in the Ministry of Health and has established the Zambian National Health Strategic Plan 2011-2015 (MOH, 2011). One of the main objectives of this plan is to reduce the annual incidence of malaria to 75 per 1,000 by 2015 exceeding the RBM goal (RBM, 2010). Two strategies in the plan, a focus on health service delivery by

promoting support for health management, and targeting malaria treatment interventions offer opportunities for technology to be used to improve pharmacoadherence (MOH, 2011). However, any such use is affected by mobile network coverage and marginalized areas must be targeted by national policies to ensure the effectiveness of such interventions.

The local policy strategy involves management of malaria in health facilities, communities and homes using ACT as a first-line drug to increase access to prompt malaria treatment. A challenge to achieving this action point is that, at the provincial and district levels, there are limited human resources to coordinate treatment strategies, increasing the necessity for discovering methods by which to maximize effectiveness (RBM, 2010). Researchers are compelled to continue to explore technological interventions such as SMS to assist in this effort.

Recommendations for Further Research

The additional data collected from the end-of-study questionnaire provides groundwork for further research related to pharmacoadherence. In particular, the data provides a foundation for a follow-up qualitative study on the factors that may influence pharmacoadherence, as well as a study of the contextual traditional assumptions that impede adherence. If some factors could be identified as being associated with non-adherence, research could target those related causes more effectively.

While SMS reminders were not significantly associated with increased pharmacoadherence, addressing some of the other barriers may help overcome the human limitations of poor adherence. Further research could investigate means of addressing these barriers through the use of mobile phones. For example, using a voice call rather than SMS to contact the patient would allow dialogue, possibly enlightening the caregiver to other unidentified barriers. Use of voice reminders as opposed to SMS could be explored to

determine if the social aspect of verbal communication enhances adherence. However, such interventions also increase the time and financial costs involved.

Though the length of SMS has been addressed in some studies (Horvath et al., 2012) the content of the SMS messages is also an aspect that could benefit from further research. Perhaps the wording of the message could be improved or other elements added or the message sent in the local language. Another possibility could explore an SMS response back from the participant with information on the time the medication was taken. However, returned communication increases the cost to the patients as mobile phone charges are applied to the contacting party in Zambia.

A standardized 8 a.m. and 8 p.m. protocol of SMS messages was used for this study, however the exact timing of the SMS could be further tailored to the participant's schedule. When a participant is diagnosed with malaria and offered the ACT, they could be asked what time in the morning and evening would be best for them to take the medication and schedule the SMS reminders accordingly. Since the twelve-hour difference is somewhat flexible, they could , for example, take their morning dose at 7 a.m. and their evening dose at 8 p.m. If automated software were used to initiate the SMS reminders, the additional work to customize the timing of the SMS messages to the lifestyle of the patient would be negligible.

One of the areas ripe for research in sub-Saharan Africa is the dependability of self-report which is the primary method of measurement in many ACT pharmacoadherence studies (Cohen et al., 2012; Lemma et al., 2011; Onyango et al., 2012). In a culture where the intention is to please and time schedules are not a priority, this method has little reliability (Lewis, 2006). One study in Malawi comparing self-report to MEMS and pill count resulted in only 0.8% (n=3) admitting to missing doses on self-report. However 9.4% (n=17) had remaining doses in their MEMS bottles when returned (Bell et al., 2009). In addition, research measuring adherence indicated that MEMS results called into question the 100%

adherence made by SMS self-report (Haberer & Kiwanuda, 2010). Further research is needed possibly using MEMS or virtual DOT to measure the reliability and validity of self-report and to determine ways to more accurately measure actual pharmacoadherence.

MEMS caps offer a more reliable method of measuring/encouraging pharmacoadherence than self-report, however the cost of the caps renders them impractical for widespread use in sub-Saharan Africa and other low-resource settings.

While this study did not determine the satisfaction of the patients with the effectiveness of ACT treatment, further research could explore this area to determine if it is associated with a higher level of adherence.

The MEMS data indicated that in several cases there were substantially more bottle openings than there were doses. Further study could seek to determine the reasons for the multiple openings especially given that part of the briefing by the assistant included a request not to open the bottle except when taking medication. Determining the reason for the extra openings may help identify methods to limit these and thus more accurately measure pharmacoadherence.

Two life-long residents of Africa, one an American, born and raised in central Africa and the other an indigenous leader in the community describe the nature of paradigm shifts and obstacles to behavioral change in this context. Because the culture of central Africa is very resistant to change, Rogers' (2003) Diffusions of Innovations model warrants further exploration as a theoretical backdrop to research implementing new methodologies or modern technological tools. Life in this culture has traditionally been fraught with danger from famine, war, disease and forced migration. Those who were quick to embrace change often died because they gave up their traditional forms of protection and were no longer able to deal with the recurring African dangers. Thinking in terms of inertia and momentum one might say that this culture exhibits a great deal of inertia where change is concerned and

health practices are no exception. Clinics and hospitals see many patients in urban areas, but a large and mostly unidentified segment of the population continues to rely on traditional healing through charms, plants or combinations of both. Many rural communities in Zambia have no access to western medicine so traditional cures are all that is available. Gradually the tide has changed in urban areas and many people now come to clinics for treatment. Momentum seems to be starting to build in favor of western medicine as people experience and witness the effects. The western medicinal approach to the treatment of malaria can be considered a whole new approach to medicine in sub-Saharan Africa and would naturally experience all the normal resistance that the culture exhibits towards innovation. As the incorporation of this method into the normal treatment of malaria continues, the inertia might gradually be overcome and with it momentum might begin to move the culture towards accepting this new medical practice. Once accepted, it would become the new status quo and adherence would be strongly motivated by the same cultural resistance to change that initially made it difficult (J. J. Enright & R. S. Kilembo, personal communication, April 5, 2014).

Another method suggested by the Diffusion of Innovations model to speed up the acceptance of this healthcare model would be to actively recruit the traditional leaders and healers in the community to endorse and advocate this approach (Rogers, 2003). Traditional chiefs' power and authority is limited in urban areas in Zambia, but both are significant in rural areas. A sustained endorsement by the chief and sub-chiefs might have a profound effect on the acceptance of this method. Likewise, bringing the traditional healers in a community on board through dialogue and education would initiate a significant endorsement of the method. Zambia is overwhelming Christian and bringing local pastors, ministers and priests on board would provide another way in which traditional figures of authority would lend their influence to bring about acceptance of this method (J. J. Enright & R. S. Kilembo,

personal communication, April 5, 2014). Clearly, context and culture need to be seriously considered in any study design conducted by westerners in sub-Saharan Africa.

Summary and Conclusion

All study results from this research will be shared with the external collaborator, the Tropical Disease Research Centre, Ndola, Zambia, and with the Zambian Ministry of Health, and submitted for possible publication. The aggregate results will also be made available to the participants at their request.

Preventing malaria is the best strategy for reducing morbidity and mortality. However, once infected the value of ACT pharmacoadherence for treatment justifies continued attempts to improve the statistics in order to combat malaria in sub-Saharan Africa. Though the results of the current study did not find a significant association between SMS and pharmacoadherence, it was the first of its kind using patient-centered communication for ACT adherence in sub-Saharan Africa and was fraught with challenges. The possibilities for further improvement in pharmacoadherence using technology and mobile phones specifically merit further exploration, and offer great opportunity to help bring an end to this deadly disease. Today, 108 countries in the world are free of malaria (Feacham & Malaria Elimination Group, 2009). The hope is to make it 109.

APPENDIX A: SMS MESSAGE SEQUENCE

- Day 1, dose 1: Given at the clinic – no SMS.
- Day 1, dose 2: “Good afternoon (or evening, if appropriate)! It’s time to take your malaria pills.”
- Day 2, dose 1: “Good morning! It’s time to take your malaria medicine.”
- Day 2, dose 2: “Good evening! It’s time to take your malaria pills.”
- Day 3, dose 1: “Good morning! It’s time to take your malaria medicine. I hope you feel better!”
- Day 3, dose 2: “Good evening! It’s time for your last malaria pills.”

APPENDIX B: INVITATION TO PARTICIPATE

EXPLANATION OF RESEARCH

Invitation to Participate

Title of Project: Mobile phone short message service to improve outcomes to malaria treatment

Principal Investigator: Elinda Steury, MSN, RN, CCRN, Doctoral Student at University of Central Florida (UCF)

Other Investigators: None

Faculty Supervisor: Dr. Mary Lou Sole, Supervising Faculty
e-mail: Mary.Sole@ucf.edu
Telephone: 001-407-823-2744

You are being invited to take part in a research study. Whether you take part is up to you.

- **Introduction**: You have been diagnosed with malaria and we would like to help you take your medicine in a way that will help you get better more quickly. We would like you to be a part of a study. Someone will discuss the study with you. Please ask the assistant to explain words or information you do not understand. This study will last until your malaria medicine is finished - about 3 days.
- **Purpose**: The purpose of this study is to help patients at the Fisenge Clinic in Fisenge, Zambia who are taking a six-dose malarial treatment. The outcome of this study will be shared with the Ministry of Health without any names and none of your information will be shared with others.
- **Risks**: There is no health risk to you.
  - One potential risk in the study is the risk of traveling back to the clinic to return the electronic pillbox bottle.
  - All other risks are minimal. There are no procedures to our knowledge that are part of this study that may have unforeseeable risks. If you are pregnant or should become pregnant, no changes will be made since the medication benefits have been shown to outweigh concerns and dangers during pregnancy.
- **Potential Benefits:** We hope that you will benefit from this study by a more successful treatment for malaria that will also benefit your community.
- **Costs/Payments for Participation in the Research:** There are no costs to you for participation in this study.
- **Standard Procedures**: You will be asked to take your malaria medicine according to the standard treatment for malaria. This is: One dose in the clinic, one dose 8 hours later, then 2 doses per day for the next two days at 08:00 and 20:00. This will be requested regardless of your participation in the study.
- **Study Related Procedures:** If you agree to participate in the study you will also be provided with an electronic pill bottle containing your medication. Please remove only the pills that you will be taking for that dose from the bottle at the scheduled time. When your medication is finished, please return your pill bottle

to the clinic within 4 days. Please do not open the bottle except when taking your pills. These are the only additional expectations for participation in this study.

- **Voluntary Participation and Withdrawal from the Research:** Participation in this study is voluntary. You may decide not to participate in this study. Your decision will have no effect on your treatment plan or the care you receive through the clinic. You have the right to withdraw from the study at any time, but if you do so, we ask that you return the pill bottle immediately.

You must be 18 years of age or older to take part in this research study.

Study contact for questions about the study or to report a problem:

If you have questions, concerns, or complaints

-The University of Central Florida Institutional Review Board
e-mail: irb@mail.ucf.edu
Telephone: 001-407-823-2901

-Dr. Mary Lou Sole, Supervising Faculty
e-mail: Mary.Sole@ucf.edu
Telephone: 001-407-823-2744

-Zambia Ministry of Health Tropical Diseases Research Centre
e-mail: MulengaM@tdrc.org.zm
Telephone: 0211613303

The assistant has reviewed the study and this approval with me and I have had a chance to ask questions and receive satisfactory answers. I agree to be a part of this study.

Signed: _____ Date:_____
(If you agree to participate in this study, you will receive a copy of this form for your records.)

IRB contact about your rights in the study or to report a complaint: Research at the University of Central Florida involving human participants is carried out under the oversight of the Institutional Review Board (UCF IRB). This research has been reviewed and approved by the IRB. For information about the rights of people who take part in research, please contact: Institutional Review Board, University of Central Florida, Office of Research & Commercialization, 12201 Research Parkway, Suite 501, Orlando, FL 32826-3246 or by telephone at (407) 823-2901.

APPENDIX C: DEMOGRAPHIC QUESTIONNAIRE

Demographic Questionnaire

Patient's ID#:

1. Interviewer name:
2. Patient's name:
3. Town of residence:
4. Contact information:
5. Age:
6. Gender: (Circle one) Male Female
7. Do you believe that malaria can be treated without medication?
   (Circle one) Yes No
8. Have you taken malaria medication before? (Circle one) Yes No
9. Do you have continuous access to a mobile phone throughout the next 3 days?
   (Circle one) Yes No
   If yes, what is the number?
10. When did your fever begin? (If >1 day ago, patient cannot participate)
    (Circle one) 0-12 hours within 12-24 hours > 24 hours
11. What is the highest grade in school that you have completed?
    (Circle one) 1 2 3 4 5 6 7 8 9 10 11 12 College
12. What languages do you read and write? (Check all that apply)
    READ:___English ___Bemba ___Other: _____
    WRITE:___English ___Bemba ___Other: _____
13. Are you currently employed? (Circle one) Yes No
14. What is your total family monthly income in Kwacha?
    0-100K 100-500K 500-1000K >1000K
15. Do you own a radio? (Circle one) Yes No

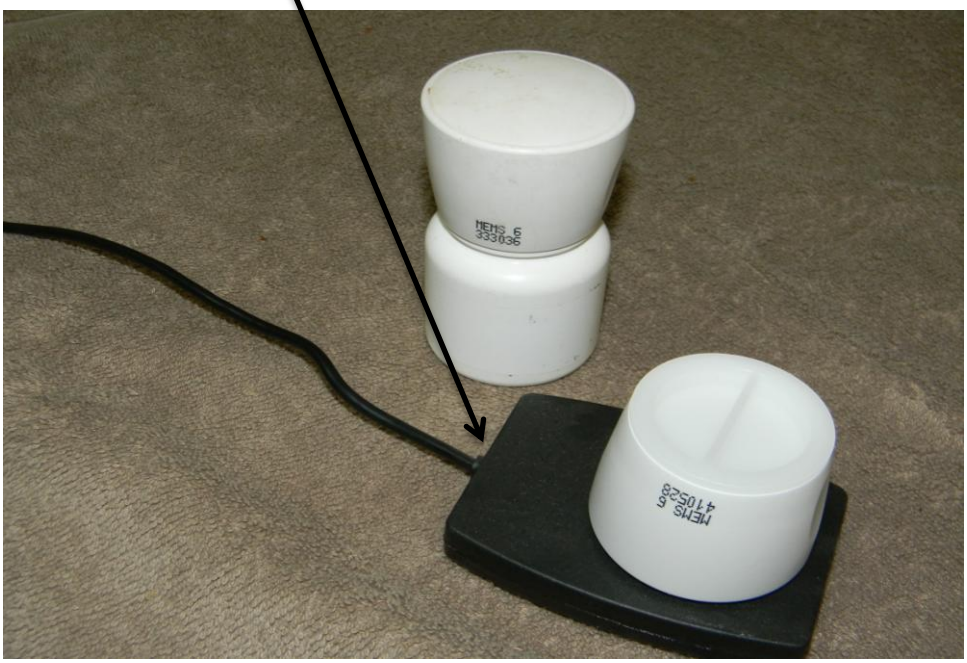
APPENDIX D: DATA COLLECTION TOOL

Medication Event Monitoring System (MEMS): AARDEX Group Ltd, 1950 Sion/ Switzerland; www.aardexgroup.com

MEMS cap version 6

MEMS cap unique reference number

MEMS Communicator/Reader plugged into Windows-based computer with MEMS cap in reading position



APPENDIX E: DEBRIEFING STATEMENT

Debriefing Statement

For the study entitled:

Short Message Service (SMS) reminder intervention for malaria medication adherence in Zambia

Dear Participant;

During this study, you were asked to take your malaria medicine according to the standard treatment for malaria. You were provided with an electronic pill bottle containing your medication and asked to remove only the pills that you would be taking for that dose from the bottle at the scheduled time. You were asked to please return your pill bottle to the clinic within 4 days when your medication was finished, and not to open the bottle except when taking your pills.

You were told that the purpose of the study was to help patients at the Fisenge Clinic in Fisenge, Zambia who are taking a six-dose malarial treatment. The actual purpose of the study was to determine if the use of SMS reminders through mobile phones will increase the adherence rate to a 6-dose ACT antimalarial treatment in Luanshya district, Copperbelt province, of Zambia

We did not tell you everything about the purpose of the study because telling you that we would be using reminder SMS messages may have changed the outcome of the study. By keeping this information from those in the study during the time of the study, we were able to make sure that everyone involved had the same understanding and we were able to prevent someone from, for example, trying harder to remember to take their medicine even if not receiving an SMS. This allows us to reach conclusions about others who may be given reminders in the future, but who will not be in the study.

You are reminded that your original consent document included the following information: *Participation in this study is voluntary. You may decide not to participate in this study. Your decision will have no effect on your treatment plan or the care you receive through the clinic. You have the right to withdraw from the study at any time, but if you do so, we ask that you return the pill bottle immediately.* If you have any concerns about your participation or the data you provided in light of this disclosure, please discuss this with us. We will be happy to provide any information we can to help answer questions you have about this study.

The responses in this study are de-identified and cannot be linked to you.

Study contact for questions about the study or to report a problem: If you have questions, concerns, or complaints or think the research has hurt you please feel free to contact any of the following people:

-The University of Central Florida Institutional Review Board
e-mail: irb@mail.ucf.edu
Telephone: 001-407-823-2901

University of Central Florida IRB
IRB NUMBER: SBE-13-09805
IRB APPROVAL DATE: 2/10/2014
IRB EXPIRATION DATE: 2/9/2015

-Dr. Mary Lou Sole, Supervising Faculty
e-mail: Mary.Sole@ucf.edu
Telephone: 001-407-823-2744
-Zambia Ministry of Health Tropical Diseases Research Centre
e-mail: MulengaM@tdrc.org.zm
Telephone: 0211613303

IRB contact about your rights in the study or to report a complaint: Research at the University of Central Florida involving human participants is carried out under the oversight of the Institutional Review Board (UCF IRB). This research has been reviewed and approved by the IRB. For information about the rights of people who take part in research, please contact: Institutional Review Board, University of Central Florida, Office of Research & Commercialization, 12201 Research Parkway, Suite 501, Orlando, FL 32826-3246 or by telephone at (407) 823-2901.

If you have experienced distress as a result of your participation in this study, a referral list of mental health providers is listed below for your use. (Please remember that any cost in seeking medical assistance is at your own expense.)

John Enright, Mental Health Counselor	0967770735
Robert Kilembo, Mental Health Counselor	0969199196

Please again accept our appreciation for your participation in this study.

APPENDIX F: UCF IRB APPROVAL

University of Central Florida Institutional Review Board
Office of Research & Commercialization
12201 Research Parkway, Suite 501
Orlando, Florida 32826-3246
Telephone: 407-823-2901 or 407-882-2276
www.research.ucf.edu/compliance/irb.html

Approval of Human Research

From: **UCF Institutional Review Board #1**
FWA00000351, IRB00001138

To: **Elinda E. Steury** and Co-PIs if applicable:

Date: **February 12, 2014**

Dear Researcher:

On 2/10/2014, the IRB approved the following human participant research until 02/09/2015 inclusive:

Type of Review:	UCF Initial Review Submission Form
Project Title:	Short Message Service (SMS) reminder intervention for malaria medication adherence in Zambia.
Investigator:	Elinda E. Steury
IRB Number:	SBE-13-09805
Funding Agency:	
Grant Title:	
Research ID:	N/A

The scientific merit of the research was considered during the IRB review. The Continuing Review Application must be submitted 30days prior to the expiration date for studies that were previously expedited, and 60 days prior to the expiration date for research that was previously reviewed at a convened meeting. Do not make changes to the study (i.e., protocol, methodology, consent form, personnel, site, etc.) before obtaining IRB approval. A Modification Form **cannot** be used to extend the approval period of a study. All forms may be completed and submitted online at https://iris.research.ucf.edu .

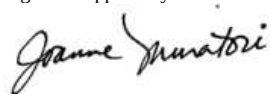
If continuing review approval is not granted before the expiration date of 02/09/2015, approval of this research expires on that date. When you have completed your research, please submit a Study Closure request in iRIS so that IRB records will be accurate.

Use of the approved, stamped consent document(s) is required. The new form supersedes all previous versions, which are now invalid for further use. Only approved investigators (or other approved key study personnel) may solicit consent for research participation. Participants or their representatives must receive a copy of the consent form(s).

In the conduct of this research, you are responsible to follow the requirements of the Investigator Manual.

On behalf of Sophia Dziegielewski, Ph.D., L.C.S.W., UCF IRB Chair, this letter is signed by:

Signature applied by Joanne Muratori on 02/12/2014 02:43:27 PM EST



IRB Coordinator

APPENDIX G: PRELIMINARY TDRC APPROVAL

TROPICAL DISEASES RESEARCH CENTRE
Tel/Fax +260212615444
tdrc-ethics@tdrc.org.zm
P O Box 71769
NDOLA, ZAMBIA

TDRC ETHICS REVIEW COMMITTEE
IRB REGISTRATION NUMBER: 00002911
FWA NUMBER: 00003729

TRC/ERC/04/10/2013

17th October, 2013

Mrs Elinda Enright Steury

NDOLA

Dear Madam,

Sub: Short Message Service (SMS) reminder intervention for malaria medication adherence in Zambia

Reference is made to the protocol entitled **"Short Message Service (SMS) reminder intervention for malaria medication adherence in Zambia."**

I wish to inform you that your research protocol has been reviewed and approved.

This letter constitutes a provisional approval allowing you to start the project.

The Committee will formally ratify the decision at its next full meeting.

We wish you every success in the execution of your study.

Yours Sincerely
TROPICAL DISEASES RESEARCH CENTRE

TROPICAL DISEASE RESEARCH CENTRE
ETHICS REVIEW COMMITTEE
17 OCT 2013
P.O.BOX 71769
NDOLA, ZAMBIA

Eric M. Njunju Bsc, Msc
SECRETARY, TDRC ETHICS REVIEW COMMITTEE

APPENDIX H: MINISTRY OF HEALTH APPROVAL

All Correspondence should be addressed to the
Permanent Secretary
Telephone: +260 211 253040 5
Fax : +260 211 253344

REPUBLIC OF ZAMBIA
MINISTRY OF HEALTH

NDEKE HOUSE
P. O. BOX 30205
LUSAKA

In reply please quote:
MH/101/17/6
No.....

3rd February, 2014

Ms. Elinda Steury
LUSAKA

Dear Ms Steury,

Re: Request for Authority to Conduct Research

The Ministry of Health is in receipt of your request for authority to conduct research on **"Short Message Service (SMS) Reminder Intervention for Malaria Medication Adherence in Zambia."** I wish to inform you that following submission of your request to my Ministry, our review of the same and in view of the ethical clearance, my Ministry has granted you authority to carry out the above mentioned exercise on condition that:

1. The relevant Provincial and District Directors of Health where the study is being conducted are fully appraised;
2. Progress updates are provided to MoH quarterly from the date of commencement of the study;
3. The final study report is cleared by the MoH before any publication or dissemination within or outside the country;
4. After clearance for publication or dissemination by the MoH, the final study report is shared with all relevant Provincial and District Directors of Health where the study was being conducted, and all key respondents.

Yours sincerely,

Dr. D. Chikamata
Permanent Secretary
MINISTRY OF HEALTH

Cc: District Medical Officer

APPENDIX I: TDRC EXTERNAL COLLABORATION AGREEMENT

TROPICAL DISEASES
Tel/fax 260 21 1 613303/602737
Email: MulengaM@tdrc.org.zm

RESEARCH CENTRE
NDOLA, ZAMBIA

OFFICE OF DIRECTOR

Our Ref: TRC/D/PP/04/13

11th April 2013

Elinda Enright Steury
Associate Professor
Brevard Community College
Institute of Nursing, 250 Community College Parkway
Building 1, Room 327B
MELBOURNE, FL 32909
United States of America

Dear Madam

RE: LETTER OF SUPPORT

Project Title: Research Study Exploring the Use of the Mobile Phone through Short Message Service (SMS) to Improve Adherence to Malarial Medication Therapy

We thank you for your letter which we received on 9th April 2013 in which you requested our institution to be an external collaborator to support your research study.

As a research institution mandated to conduct research in this country, we are happy to act as external collaborator with you through the College of Nursing at the University of Central Florida on this project.

We are willing to give advice on all pertinent regulations and policies including Ethics Review Committee approval and any requirements that may relate to this study.

We look forward to collaborating with you.

Yours faithfully
TROPICAL DISEASES RESEARCH CENTRE

Dr Modest Mulenga - MD, DTM&H, MSc, PhD
DIRECTOR

APPENDIX J: END OF STUDY QUESTIONNAIRE

1. Were you aware that there was another group in the study whose conditions were different than yours?
2. What was most helpful for you in taking the medication – the pillbox, the SMS, the packaging, a combination or other?
3. Which SMS messages that you received were most helpful?
4. Did you seek help for your illness from anyone before you came to the clinic and if so, who?

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