MOBILE PHONE APPLICATIONS TARGETED TOWARDS MEDICINE ADHERENCE IN AFRICA: A SYSTEMATIC REVIEW

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by

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Declaration

I, Nora Makgwara Masoga, declare that the mini-thesis “Mobile phone applications targeted towards medication adherence in Africa: A Systematic Review” is my own original work and has not been taken from others, except in instances where citation has been noted and acknowledged in context within my thesis.
This thesis has not been submitted in its entirety or in part, to any other university or institution of higher learning to obtain an academic qualification.

Nora Masoga

Signed

Dated 19 November 2020

Glossary of Terms

Adherence- the extent to which a person's behaviour – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider (WHO, 2003).

Mobile Phone Application- application program on a smart phone used to communicate messages to the receiver through mobile phones.

Communicable Disease- Communicable, or infectious diseases, are caused by microorganism such as bacteria, viruses, parasites and fungi that can be spread, directly or indirectly, from one person to another. Some are transmitted through bites from insects while others are caused by ingesting contaminated food or water (WHO).

Non-communicable disease (NCD) - is a disease that is not transmissible directly from one person to another. NCDs include Parkinson's disease, autoimmune diseases, strokes, most heart diseases, most cancers, diabetes, chronic kidney disease, osteoarthritis, osteoporosis, Alzheimer's disease, cataracts, and others. NCDs may be chronic or acute

Intervention- an action taken to intentionally improve poor adherence or prevent non adherence from getting worse

mHealth- is the use of mobile phone technology for health-related purposes

ABSTRACT

Background

According to the WHO (2017), non-communicable diseases (NCDs) which include stroke, cancer, heart disease, chronic respiratory disease and diabetes is the leading cause of death and is responsible for seventy one percent of deaths worldwide. Beaglehole *et al.,* (2009) reported that management of chronic diseases depends primarily on early detection of early disease, identification of high-risk status, interventions including pharmacological and psychosocial intercessions and long term follow up with monitoring and promotion of adherence to treatment.

Adherence to long-term therapy for chronic illnesses in developed countries averages fifty percent according to the WHO (2017). In developing countries, the rates are expected to be even lower. Mitigating risk factors associated with poor adherence to treatment is one of the essential tools in ensuring that the burden of the disease is not high. Primary interventions aimed at improving adherence provide treatment successes and potentially reduce life-threatening risks resulting from poor adherence to treatment of both chronic and acute treatments.

Objective

The objective of this study is to assess through a systematic review of published research and grey literature, whether mobile phone applications have a direct impact on improving medicine adherence in Africa.

Search Methods

Using Boolean strategy, three search engines i.e. Pubmed®, Cochrane ® and EBSCO® databases were searched for journal articles and studies that assessed the impact of mobile phone applications on adherence to treatment of different ailments in Africa. Reference lists of relevant papers were searched, additionally grey literature was searched for articles relevant to this review. No date restriction was applied, only studies published in English and conducted in Africa were considered for this review.

Selection criteria

Original research published in peer-reviewed journals and grey literature that evaluated the impact of mobile phone applications on adherence to treatment in Africa both communicable and non-communicable diseases was considered. Studies which included comparators with no intervention and the "pre- and post" intervention studies were reviewed. No restriction was applied in selecting study design i.e. randomized control trials and non-randomized control trials were included.

Data collection and analysis

Standard methodological procedures prescribed by Cochrane® were considered to evaluate studies that met inclusion criteria. Data was extracted from the studies onto an Microsoft Excel® spreadsheet using a coding system designed by the reviewer which included the following: (i) General information (trial location); (ii) Characteristics of the participants (age and number of patients); (iii) Study design (randomized controlled trials, etc.); (iv) Conditions under treatment (e.g. HIV/AIDS, TB, Diabetes); (v) Duration of the study; (vi) Intervention feature (e.g. SMS, counselling etc.) and (vii) Method and frequency of assessment of adherence.

Results and Discussion

A total of 1077 citations were identified through Pubmed®, Cochrane® and EBSCO®, 13 publications through reference list and two citations through grey literature. Fifteen articles met eligibility criteria. Thirteen of the fifteen studies illustrated a significant improvement in adherence for the intervention group as compared to the control group based on one primary outcome measure. Two of the studies showed no significant difference in adherence between the intervention group and the control group. One study measured adherence through clinical and non-clinical outcomes, clinical outcomes showed no significant difference between the intervention and control group and non-clinical outcomes showed a significant difference between the intervention and control group.

Conclusion and Recommendations

This systematic review revealed that mobile phone application interventions aimed at improving adherence to treatment has the potential to be effective. Seventy three percent of the studies however could not conclusively demonstrate clinically the impact

of mobile phone applications on adherence. As such, additional studies should be performed that illustrate through clinical data the effects of mobile phone applications on adherence.

Key words

Adherence, Mobile phone application, Treatment, Communicable Disease, Non-communicable Disease, Africa

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LIST OF ACRONYMS

Acronym	Description
AIDS	Acquired Immune Deficiency Syndrome
ART	Antiretroviral Therapy
BP	Blood Pressure
CD4	Cluster of Differential 4
CI	Confidence Interval
DOT	Direct Observational Treatment
HIV	Human Immune Virus
ICER	Incremental Cost-Effectiveness Ratio
ITT	Intention to treat analysis
ITU	International Telecommunication Union
MD	Mean Difference
NCD	Non Communicable Disease
NRSI	Non-Randomized Studies of the effects of Interventions
NNT	Number Needed to Treat
QALY	Quality Adjusted Life-Year
RCT	Randomized Controlled Trial
RR	Relative Risk
SMS	Short Messaging Services
TB	Tuberculosis
UK	United Kingdom
USA	United States of America
VL	Viral Load
WHO	World Health Organization

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This work is dedicated to God, my Creator, Comforter and Dad. You have seen me through this long journey and I would like to thank You for carrying me and guiding me.

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CHAPTER 1: BACKGROUND

1.1. Introduction

The burden of non-communicable and communicable disease in developing countries is on the rise and it is estimated that by 2020, seven out of ten deaths will be attributed to non-communicable disease (World Health Organisation [WHO], 2014). Among non-communicable diseases in developing countries, Boutayeb, (2006) pointed out that special attention should be devoted to cardiovascular disease, diabetes, cancer and chronic pulmonary disease.

The demand for access to treatment of communicable and non-communicable diseases in Africa has reached exponential proportions. Simultaneously there are many challenges in meeting the demand. Loewenson and McCoy, (2004) outlined examples of the ever increasing challenges that plague African healthcare systems which include shortfalls in healthcare systems and lack of knowledge about treatments, interruptions in supply of medicines, laboratory capacities, lack of access to counselling and testing, lack of well-trained healthcare workers and scarcity of treatment resources.

These challenges are not surprising as they result from inherited chronic under-resourced healthcare institutions, lack of strategic support and underdevelopment of leaders in the healthcare systems. In addition, Kruk *et al*, (2010) suggest that high prevalence of poverty and civil wars on the African continent have contributed immensely to already poor resource stricken healthcare systems. This picture illustrates a dire situation that requires simplistic and less costly solutions to reduce the economic burden of disease on healthcare systems in Africa.

The WHO, (2003) estimated that fifty percent of patients do not take treatment as prescribed and concluded that the outcome of high quality therapy is based on the patient's level of adherence to treatment recommended by healthcare practitioners. There are however, many factors that contribute to a patient's non-adherence to treatment.

As early as the 1980's, a number of studies, according to Martin, Williams, Haskard and DiMatteo, (2005) have been carried out to identify factors affecting treatment

adherence. Bowen, D.J. Helmes, A. and Lease, E. (2001) evaluated some of the elements that contributed directly to adherence. In summary, Bowen *et al.* (2001) noted cognitive behaviour, interpersonal factors, patient's involvement and participation in decision making regarding therapy, patient attitudes, cultural variations and depression as examples.

In order for a successful treatment programme to be maintained, efforts to improve adherence to a treatment regimen should come from both the patient and the health care professional. Hamilton, G.A. Toberts, S.J. and Johnson, J.M. (1993) and Roter, Hall and Merisca, (1998) agreed that there is not one solution to abate poor adherence in all patients. It is therefore imperative for healthcare professionals to assess patients before providing a specific panacea in a form of interventions to poor adherence. Some of the attributes of non-adherence as described by Mcdonald and Garg, (2002) in developing countries includes access to transportation, side effects of the medicines, lack of social support, forgetfulness and not understanding the instructions on how to take the medication.

The objective of the study is to assess whether there is a direct or indirect impact of mobile phone applications on medicine adherence in Africa. This chapter will lay a foundation on the background and the objectives of the study.

1.2. Background to Research Question

The WHO, (2003) has identified non-adherence as a leading cause to deteriorating clinical outcomes. According to Roebuck, Liberman, Toyama and Brennan, (2011), non-adherence to medication is linked to hospitalisation and increased morbidity and mortality rates.

Many patients, whether on treatment for communicable or non-communicable conditions, experience difficulties in following treatment directions, resulting in poor adherence, WHO, (2003). The WHO (2003) has pointed out that poor adherence in conditions such as Human Immune Virus/ Acquired Immune Deficiency Syndrome (HIV/AIDS) and Tuberculosis (TB) has consequences on development of drug resistance to antimicrobial treatments and ultimately premature death. Nugent, (2008) has observed that the eventual economic burden of poor adherence particularly in state funded programmes is disastrous and in terms of health, may result in adverse implications.

Several interventions, including mobile phone applications, have been developed to counter poor adherence. Bärnighausen *et al.*, (2011) studied and detailed interventions to increase antiretroviral adherence in the Sub-Saharan region. Interventions identified within the systematic review included amongst others "purely behavioural interventions that used directly observed therapy, diary cards, and cell phone short message services (SMS) to remind patients to take their ART medication, (Bärnighausen *et al.,* 2011, p6)."

In-depth studies have been conducted across the globe to establish the impact of mobile phone applications as one of the interventions used to improve adherence to treatment in both communicable and non-communicable diseases. Additionally, evaluations through systematic reviews have been performed to substantiate the impact of research undertaken in this area across the globe. There is no evidence of a systematic review performed to analyse the impact of mobile phone applications on different disease profiles in order to provide a conclusive overview of these interventions on adherence in Africa.

1.3. Overall aim

The overarching aim was to establish, through a systematic review of published and grey literature, whether mobile phone applications are an effective intervention tool to enhance adherence to medicine treatment across the African continent.

1.4. Objectives

- To establish through a systematic review of qualitative studies the impact of mobile applications on treatment adherence.
- To establish through a systematic review of quantitative studies, whether there is an impact on treatment adherence for study groups receiving interventions through mobile phone applications compared with control groups who did not receive any interventions.
- To review available grey literature to assess the impact of mobile phone applications on treatment adherence.

1.5. Research questions

- Do any mobile applications demonstrate dominant utilisation patterns over others?
- Do mobile phone applications improve, hamper or have no impact on adherence to treatment of communicable and non-communicable diseases in Africa?

1.6. Conclusion

The impact of non-adherence to treatment as discussed, can result in devastating outcomes. As such there is a need to improve treatment adherence across the African region. This can be achieved through introduction of effective interventions that have the potential to reduce the burden of disease on the ailing healthcare systems.

CHAPTER 2: LITERATURE REVIEW

2.1. Introduction

In 2017, the WHO reported that non-communicable diseases (NCDs) including stroke, cancer, heart disease, chronic respiratory disease and diabetes were the leading cause of death and are responsible for 71% of deaths worldwide. Cardiovascular disease accounted for most NCD deaths resulting in 17.9 million deaths annually, followed by cancers at 9.0 million, respiratory disease at 3.9 million and diabetes 1.6 million. These four groups of disease account for over 8 of all premature NCD deaths. Beaglehole *et al.*, (2008) reported that management of chronic disease depends primarily on early detection of early stages of the disease, identification of high risk status, and type of interventions for example pharmacological and psychosocial, as well as long-term follow up with monitoring and promotion of adherence to treatment.

In terms of communicable diseases, for example TB, HIV/AIDS, malaria and water borne disease such as cholera, the WHO (2015) reported that these diseases were major contributors to a high number of deaths worldwide. The WHO (2015) further reported that a number of people living with HIV worldwide was 36.9 million (11.4 million of which are located in Africa) and that within the same year 2 million people were newly infected. About 1.2 million deaths were attributed to HIV/AIDS. This illustrates the need to improve adherence within the African region.

Adherence to long-term therapy for chronic illnesses in developed countries averages fifty percent according to the WHO (2015), which also estimates that “the rates are expected to be much lower in developing countries”. In another study, Thakkar *et al.*, (2016) concluded that adherence to chronic medication is poor and intense interventions should be established to encourage improvement of adherence of chronic treatment in patients.

Forgetfulness has been cited as one of the reasons for non-adherence as demonstrated through literature review by Mills *et al.*, (2006) and making use of the reminder systems was considered one of the effective tool for optimising adherence in the study.

2.2. Factors affecting adherence

Literature searches yield several contributors associated with adherence to different treatments. Extensive research has been conducted in Africa, particularly in Southern Africa, to establish factors that lead to poor adherence in ART. Mbuagbaw *et al.,* (2012a) categorised these factors into: (i)P*atient factors*, which include substance abuse; gender; mental disorders; lack of education; lack of social support; lack of pain management and no change in health status, (ii) *Medication factors* which include side effects; pill burden; food requirements; dose frequency and the type of medicine and (iii) *Healthcare-provider related factors* which include relationship with patients; lack of participation in decision making by patients and lack of understanding by patients. In addition, (iv) *Disease characteristics* in the form of duration of the illness; symptoms of the illness and opportunistic infections also had a direct impact on adherence.

Shubber *et al.*, (2016) assessed barriers to adherence in ART treatment and categorised these into geographical location, level of economic development and age. The study revealed that *patient barriers* including forgetfulness was higher in adults than in adolescents and children, *being away from home* was higher in adolescents than in adults and children, *a change in daily routine* affected adherence mostly in adults compared with that in adolescents and children. Stigma, feeling sick and proximity to clinics also affected adherence.

A systematic review by Croome, Ahluwaliab, Hughesb and Abasa, (2017) identified 43 barriers and facilitators to adherence. The study identified factors that improved adherence such as social support, reminders, feeling better and a good relationship with the healthcare providers. The review concluded that mobile phones were shown to be good reminder systems for patients and are readily accessible by most patients.

2.3. The burden of non-adherence

The WHO (2017) noted the economic burden of communicable and non-communicable diseases as a major challenge in developing countries. Boutayeb (2010) illustrated the burden of communicable and non-communicable diseases in developing countries. In particular, the author pointed out that high mortality and morbidity rates resulted in economic losses due to lack of productivity. In addition, communicable and non-communicable diseases hamper human development. The impact is particularly observed on education, income, life expectancy and other health indicators.

The financial support required from governments to avail the required medication in developing countries implies that limited resources are focused within the healthcare budget. The WHO (2003) stipulated that poor adherence to treatment amplifies the challenge to improving health in developing countries and contributes to waste and underutilisation of already limited treatment resources.

In 2016, the WHO has estimated that for the time period 2011–2025, cumulative economic losses due to NCDs under a "business as usual" scenario in low- and middle-income countries will tally at US$ 7 trillion. The WHO report reiterated that *"this sum far outweighs the annual US$ 11.2 billion cost of implementing a set of high-impact interventions to reduce the NCD burden"*. It is evident from the report that the consequences of non-adherence are detrimental particularly to developing economies. Additionally these reports demonstrate that the cost of dealing with preventive measures far outweighs treatment costs.

Gill, Hamer, Simon, Thea and Sabin, (2005) rightfully argued that non-adherence to communicable disease treatment for example in the case of HIV/AIDS often leads to failure of treatment, strain resistance development and high costs due to hard to treat diseases. The effect of medication non-adherence on hospitalisation and mortality among patients with diabetes mellitus were studied by Ho *et al.*, (2006) who concluded that non-adherent patients had higher all-cause hospitalisation (23.2 % vs 19.2 %, P<.001) and higher all-cause mortality (5.9 % vs 4.0 %, P<.001). The study further highlighted that non-adherent patients had higher glycosylated haemoglobin, systolic and diastolic blood pressure and low-density lipoprotein cholesterol levels.

A similar trend was established with schizophrenic patients in a study conducted by Gilmer *et al.*, (2004). The study showed that 41% (n =1148) of Medicaid beneficiaries with schizophrenia were adherent to treatment with their antipsychotic medications, 16% (n =448) were partially complaint, 19% (n= 532) had excessive filling of antipsychotic prescription and 24% (n =672) were non-adherent. Medical hospitalisations were lower for those who were adherent. The study did not quantify the cost of hospitalisation; however, it is evident that non-adherent patients incurred extra costs resulting from both psychiatric and medical hospitalisation as compared to adherent patients.

It is clear that the burden of non-adherence to treatment has negative repercussions. The WHO (2003) provided an imperative elucidation that adherence is an important modifier to population health outcomes. It is important to establish measures to detect non-adherence and equally crucial to introduce systems within the healthcare sector, which will mitigate and ultimately eliminate non-adherence.

2.4. The impact of technology on adherence

Maintaining patients on treatment is one of the essential tools that can be considered to minimise the burden of disease. The WHO (2017) highlighted that sixty percent (15.3 million) of HIV infected people in Africa had access to ARV treatment. The WHO, (2003) report on adherence indicated that access to medication is important but insufficient in itself for the successful treatment of diseases.

Primary interventions aimed at improving adherence provide treatment successes and potentially reduce life-threatening risks resulting from poor adherence. There are a number of systems that were developed to prevent non-adherence and mitigate the risks associated with poor adherence over the years. For example, the WHO (2015) developed the directly observed treatment (DOT) approach model for TB. Among HIV-positive people, TB treatment supported by ART averted an additional nine million deaths. The success of this magnitude was driven by adherence through interventions such direct observation treatment (DOT).

The International Telecommunication Union (ITU), reported that mobile phone subscriptions have grown more than twenty percent annually in the last five years. It

was expected to reach 4.3 billion users globally by the end of 2017. Mobile phones have become very affordable worldwide, providing a potential vehicle for communication in the healthcare sphere. Aranda-Jan, Mohutsiwa-Dibe and Loukanova, (2014) has echoed the ITU statistics finding that in developing countries, telecommunication costs are decreasing and network coverage is on the rise. Therefore, there is a wide range of opportunities for mobile phone health applications and other mobile technologies to be explored within the healthcare sector.

Hall, Fottrell, Wilkinson and Byass., (2014) illustrated that interventions, for example the use of mobile applications to improve adherence has been explored and researched in both developed and developing countries since 2009 with some level of improvement to adherence demonstrated in some studies. More evidence has emerged as reported by Hall *et al.,* (2014) that mobile phone health interventions have a direct impact in improving treatment adherence, regular appointment attendance and that it provides a support system for health care. This improvement is driven by an increase in access to mobile phones by patients. This form of communication is a cost-effective way of improving adherence to communicable and non-communicable treatments.

African countries have embarked on implementation of mobile phone applications in an attempt to increase adherence to medication, monitor patients compliance, disease surveillance and intervention monitoring for data collection and reporting. The use of mobile phone applications is seen to be expanding exponentially in Africa as outlined by Aranda-Jan *et al.* (2014) in a study that concluded that mobile phone health applications in Africa "is an innovative approach to delivering health services". Despite challenges faced by health care workers in Africa (e.g. lack of resources), mobile phone applications have a potential to lessen to a great degree the burden on the health care systems.

A systematic review by Aranda-Jan *et al.,* (2014) further established that most of the mobile phone health application interventions undertaken in Africa focused on HIV, Malaria, TB and diabetes. These diseases have the greatest burden on the healthcare systems in Africa. The study revealed that the most implemented type of intervention was patient follow up and medication adherence. The systematic review further showed that there is a "high potential for mobile phone applications to be effective in improving

adherence". However, there were some results reporting no significant effect on the intervention in particular on patient adherence to antiretroviral treatment.

The direct link between implementation of mobile phone applications and improved medication adherence has been studied extensively in developing and developed countries. Hall *et al.,* (2014) established that the area of treatment adherence has received attention within the mobile phone applications system usage area. A study by Finitsis, Pellowski and Johnson, (2014) investigated randomised controlled trials on text message intervention design to promote adherence to ART globally. The study reviewed eight articles which included nine interventions. The meta-analysis concluded that text messaging interventions resulted in higher adherence than controlled conditions (OR=1.39, 95 % CI= 1.18, 1.64). The study further illustrated that the articles reviewed suggested a larger effect when the interventions were sent less frequently rather than daily, included personalised message content and were matched to a participant's ART dosing schedule. Most interventions were associated with improved viral load and/or CD4+ count (k=3, OR=1.56, 95 % CI=1.11, 2.20).

A similar systematic review was investigated by Mayer and Fontelo, (2017) evaluating the effect of text message reminders for HIV-related compliance. The review concluded that a text message reminder was a promising intervention in improving ART compliance based on the thirty-four studies included in the review. For the 20 articles on drug adherence, text message reminders significantly increased adherence (SMD=0.87, 95 % *CI*=0.06-1.68, P=.04, I^2= 99 %), for the 11 studies with physiologic measures (CD4 count and viral load), text message reminders also showed a significant improvement (SMD= 1.53, 95 % *CI*=0.52-2.55, P=.003; I^2=99 %) and for the seven articles relating to non-adherence indicated that text message reminders significantly reduced non-adherence (OR=0.66, 95 % *CI*=0.48-0.92, P=.01, I^2= 52 %).

A systematic review by Gandapur *et al.*, (2016) further illustrated in agreement, the role of mHealth for improving medication adherence in patients with cardiovascular diseases globally. Ten studies were included for the review and these studies were carried out in countries like China, India, USA, UK, France and Malaysia. The study demonstrated that all ten articles unanimously found that mHealth interventions improved adherence, however the magnitude of the benefits was not consistently significant. The mHealth

tools included text messages, blue tooth-enabled electronic pill-boxes, online messaging platforms and interactive voice calls.

On the contrary, few research articles published argue the limitations associated with mobile phone applications. A systematic review by Kaplan, (2006) illustrated that *"there is not enough evidence to support or refute claims that mobile phones work as health care intervention".* It must be noted, however, that at the time of publication of the study, mobile phone access was limited. Furthermore, mobile phone applications were not widely developed and implemented in many African states at the time of the study.

In Pakistan, the impact of a daily SMS medication reminder system on tuberculosis treatment by Mohammed, Glennerster and Khan, (2016) established that there was no significant difference between the intervention group receiving daily a SMS medication reminder and the control group which received none.

The majority of systematic reviews published report a positive outcome on treatment adherence resulting from use of mobile phone applications. The lessons learned during the trials should be transferred to policy development through frameworks, which would be easily adapted for any setting.

Mbuagbaw *et al.*, (2015) proposed a framework for evidence transfer following a review of successful implementation of mobile phone applications on adherence for HIV/AIDS treatment. In the framework, institutions are encouraged to implement two-way text messaging as a tool to improve adherence, follow-up on clinic visits and open communication channels to relay information relating to the health, medication and any other queries to health care workers.

An impact assessment was conducted by Haberer *et al.*, (2017) to provide considerations for programme implementation based on evidence from articles, systematic review, meta-analysis and the WHO Consolidated Guidelines for HIV. Interventions were categorised as: "education and counselling; information and communication technology enhanced solutions; healthcare delivery restructuring and economic incentives and social protection interventions". The report concluded that peer counselling, adherence clubs and short message services were the most effective tools.

Short message services increased adherence and was considered the most cost effective intervention.

Bärnighausen *et al.,* (2011) investigated six types of adherence-enhancing interventions SMS and other reminder devices, treatment supporters, DOT, education and counselling and food supplements. The study concluded that policy makers should consider integrated adherence enhancing interventions. Saberi and Johnson, (2011) concluded a systematic review by pointing out that self-care technology-based methods such as adherence reminders may result in improved antiretroviral adherence. The reminder systems approach however should be designed such that there is periodic communication with health care providers.

Roebuck, Liberman, Toyama and Brennan, (2011) concluded that irrespective of high pharmacy spending, adherence to treatment by patients on chronic vascular medication provided a substantial medical savings because of reduced hospitalization and emergency department use. By improving treatment adherence; the health of the population and costs associated with health care is intrinsically also improved.

The use of technology to enhance treatment adherence is an effective tool that can be easily adapted by any health care sector. Due to an increase of network coverages in both urban and rural setting, there is no barrier to implementing such systems.

2.5. Smartphone Applications vs Traditional Mobile Phone Applications

A systematic review by Hamine, Gerth-Guyette, Faulx, Green and Ginsburg, (2015) revealed different methods of mobile phone applications used for chronic disease management. More than 40% of the studies across the globe used SMS as an intervention tool of choice. Only 23% of the tools used software applications to improve medication adherence, however, these were in the USA, UK and China. The study further illustrated that SMS communication facilitated patient-healthcare provider interactions, medication reminders, data collection and disease specific measurements. In addition, patient education and motivations were delivered through SMS.

Smart phone applications were widely used in patients with diabetes i.e., in 23% of the studies. The smart phone applications were installed in the patient's smart phone to

facilitate checking of symptoms, maintain food diary plans or to connect patients to educators. The study identified that SMS was a mHealth tool that was widely used to encourage adherence to chronic disease management.

Perera, Thomas, Moore, Faase and Petri, (2014) assessed the impact of smart phone applications on adherence in ART. The study illustrated that participants who received the augmented application showed a significantly higher level of self-reported adherence to ART at 3 months (p=0.03) and decreased viral load (p=0.023) as compared to individuals using the standard version. The study concluded that *"smartphone applications which incorporate personalised health-related visual imagery may have potential to improve adherence to ART"* (Perera *et al.* 2014, p 585).

A study by Hermans *et al.,* (2017) demonstrated no significant difference between the intervention and the control arm on attrition in TB-HIV co-infection in Uganda. Morawski *et al.*, (2018) illustrated that there was no significant difference in clinical outcomes between patients who were randomized to receive smartphone application reminders and those who did not receive reminders. However, the study showed that there was a small improvement with regards to self-reported medication adherence.

Dayer, Heldenbrand, Anderson, Gubbins and Martin, (2013) conducted a study to assess the benefits of using smart phone applications to patients in the U.S.A. Since the technology is widely available in the U.S.A, smart phone applications represent a novel approach to improving adherence in developed countries. Adherence applications can only be used by patients who have access to smart phones which according to Dayer *et al.,* (2013) included 55 % of the adult population in the U.S.A. The study concluded that *"adherence applications represent a low-cost strategy that could be incorporated into a variety of pharmacy services, including medication reconciliation and medication therapy management*" (Dayer *et al.* 2013, p7).

Other types of smart phone applications have been used elsewhere in the world, for example, a prospective single-arm interventional pilot study to assess smart phone based system was conducted in Japan by Molton *et al.*, (2016) which concluded that by using an integrated smart phone and web-based system to provide medication reminders, adherence was improved significantly. The study further concluded that the

system had the potential to supplement and support provision of DOT for TB and improve adherence in other conditions for example, HIV and Hepatitis C.

The studies reviewed above which sought to establish the impact of smart phone applications were conducted in developed countries due to available resources. On the other hand, developing countries have limited resources and therefore the practicality of the smart phone applications on a large scale might be a challenge.

When compared to smart phone applications, Hamine *et al.*, (2015, p2) "SMS interventions require the least sophisticated hardware and can be used to transmit simple information from patients on their personal phones" since all mobile phones are activated to receive and send SMS's. SMS is readily available, inexpensive and can be automated, personalised and systems can be easily put in place to integrate into existing health care systems.

Hamine *et al.,* (2015) noted that in many smaller pilot studies, expensive devices or vouchers were given to study participants. The feasibility of using patients' existing mobile devices to implement at scale, an intervention to improve adherence with smart phone applications has not been assessed. Of particular interest will be a focus within the African context. As developing countries work to address the burden of chronic disease, it is essential to assess the potential of smart phone applications to lessen the burden, reduce the cost of non-adherence and expand outreach. More studies assessing the impact of smart phone applications on adherence from resource-limited settings, especially in Africa are needed. Rigorous cost-effectiveness analyses should also be considered to demonstrate not only the impact on the burden, but also the value of investing in these innovations within the current health care systems.

2.6. Impact of mobile applications on gender and age

Madhvani *et al.*, (2015) reports that mobile phone applications are not always effectively implemented across different genders and ages. Their study showed that there were a number of groups that did not use mobile phones as reminder devices both for attending appointments and for taking medication on time. These groups included gender (women) and age (older than 35 years), of low education level and low income. Therefore, researchers should first seek to identify through a gap analysis any

challenges associated with the designed adherence enhancing interventions on gender and age prior to the implementation.

2.7. The cost of using mobile phone applications to enhance adherence

Cost effective measures are needed to drive programs that seek to improve adherence in Africa. Shubber *et al.*, (2016) concluded that SMS messages are a significantly superior form of intervention compared to other interventions in enhancing adherence. There is a lack of published papers that quantify the cost effectiveness of using mobile phone applications to enhance adherence in Africa.

Detsky and Naglie (1990) emphasized that a cost-effectiveness analysis tool can be used to define priorities for funding health care programmes. According to these authors, for each proposed intervention, the costs implications and clinical outcomes associated with that proposal must be compared with an alternate strategy for treating the same patients. "*If an intervention results in improved outcomes but also costs more, the incremental cost per incremental unit of clinical outcome should be calculated. The incremental cost-effectiveness ratios (ICER) for various programs can be ranked to set funding priorities*" (Detsky and Naglie, 1990). This recommends that when introducing an intervention, the cost implications versus the clinical outcomes should be considered. An adherence enhancing system, when introduced, should result in clinical outcomes outweighing the costs of the intervention. Where an intervention is being introduced to an already existing system, the WHO (2003) recommends that the intervention costs and health benefits be evaluated with respect to current practices. In that case, the numerator in the cost-effectiveness ratio is the change in cost due to the introduction of the intervention and the denominator is the change in health benefit. On the other hand, the results of a newly introduced intervention need to be compared with the cost-effectiveness of other interventions by using league tables.

A study published by Patel *et al.*, (2017) extensively evaluated the cost effectiveness of a mobile phone application to improve ART adherence in Kenya. The study found "*that the base case ICER for SMS interventions was $US 1037/QALY which is below the required WHO cost effective threshold of $US 2154/QALY*". The use of SMS to enhance adherence was an efficient tool for use of funds and provided much needed support to patients to engage with healthcare professionals. SMS interventions can be easily

scaled-up. Table 1 illustrates the cost effectiveness of SMS intervention on adherence and retention of patients on treatment in this study.

Table 1: Cost-effectiveness of SMS intervention on adherence and retention

Incremental cost-effectiveness of SMS intervention: secondary analyses with adherence and retention effects.

Simulation description *	Discounted costs (2016 USD)	Discounted QALY	ICER (USD/DALY)	Undiscounted mean survival time, years
Population adherence under standard care of 40%				
Standard care	$7049	12.52	Reference	22.11
SMS mean effect with retention benefits	$7715	13.32	$834	24.01
Range†	($7602 to $7813)	(13.10-13.51)	($955 to $776)	(23.56-24.40)
Population adherence under standard care of 50 %				
Standard Care	$7147	12.73	Reference	22.53
SMS mean effect with retention benefits	$7802	13.49	$864	24.35
Range†	($7703 to $7877)	(13.30 to 13.64)	($803 to $978)	(23.97-24.66)

ICER= Incremental cost-effectiveness ratio, QALY= quality-adjusted life year, SMS= short messaging service
*intervention cost= $1 5 USD per patient per year. †Range is based on variation of the SMS intervention effectiveness alone.
Source: Patel *et al.* (2017)

Interventions must be considered on merit with respect to ease of access, ease of use and cost. Hirsch-Moverman *et al.*, (2017) has demonstrated that implementation of mobile applications to improve adherence is cost effective. The study revealed that the cost of troubleshooting the application prior to the intervention launching and providing SMS services was $22-$33 per participant depending on the length of the treatment. Despite the cost of implementation of intervention tools like SMS in improving adherence, some challenges have been noted by Chib, Van Velthoven and Car, (2015) when it comes to enrolling on a large scale the interventions. The systematic review illustrated the importance of establishing appropriate project design, participation of all stake-holders, integration of the interventions within healthcare systems and the use of appropriate technology and resources in order to successfully execute the interventions.

On the other hand, the review showed that lack of funds and lack of support by stakeholders resulted in lack of scalability.

2.8. Conclusion

In summary, the literature review acknowledged the barriers associated with adherence to treatment. Poor adherence has dire consequences on the economic landscape of developing countries. The extent of the burden of non-communicable and communicable diseases was highlighted within the review. Adding to the burden on healthcare systems is poor adherence to treatment. Studies that reported on the facilitators of adherence illustrated the long-term benefits resulting from implementation of the interventions. Mobile phone applications were identified as one of the simple, accessible and cost effective tools adapted to mitigate poor adherence.

It must be emphasised however, that no single intervention is sufficient to curb the challenge of poor adherence on its own. Healthcare providers together with patients should consider a more robust and adaptable approach that clearly identifies patient specific factors of poor adherence. Following identification of risk factors, it is essential to establish interventions and support required to overcome barriers to adherence.

CHAPTER 3: METHODS

3.1. Overview

According to Moher, Liberati, Tetzlaff and Altman(2009), a robust critical appraisal of published and unpublished literature implements the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement as the foundation. The PRISMA statement has 27-item check-list and a four-phase flow diagram. Moher *et al* (2009) indicated that PRISMA Statement was developed to assist researchers produce quality reporting of systematic reviews and meta-analyses and to assist in "*critical appraisal of published systematic reviews*". In addition, systematic reviews are defined by Crowther, Lim and Crowther, (2010) as a process of evaluating articles with the "*aim to reduce bias with the use of explicit methods to perform a comprehensive literature search and critical appraisal of the individual studies"*.

Panic, Leoncini, de Belvis, Ricciardi and Bocia (2013) analysed the quality of papers that endorsed PRISMA statement within the gastroenterology and hepatology field. The paper concluded that endorsement of PRISMA resulted in increase of both the quality of reporting and methodological quality. In fact, the study urged medical journals to include PRISMA in the instructions for authors intending to publish.

Smith, Devane, Begley and Clarke (2011) highlighted that within the systematic review of individual studies, the search should be as broad as possible to ensure that all relevant data is captured and to limit possible bias. The Critical Reviews Advisory Group (1996) recommends the search of a variety of electronic databases relevant to the research question. Moher *et al.*(2009) illustrated that before inclusion of the studies in the systematic review and exclusion of other studies, the review team should search relevant literature. Chalmers, Hedges and Cooper (2002) recommends limiting the search criteria to papers published from the early 1990s onwards. This is because researchers only started paying attention to development of methods that reduces biases around the last quarter of the 20th century. Recent studies, according to Smith *et al.* (2011) will ensure that more recent studies of high quality are identified and this is beneficial to the decision makers.

When formulating the scope of the systematic review, the PICOS (participants, interventions, comparators, outcomes and study design) structure can be a helpful tool. Once the scope has been refined, Smith *et al., (*2011) recommends that the planning of the systematic reviews can be undertaken taking into consideration: sources, review selection, quality assessment of the literature, presentation of the results, discussions and recommendations for practice and research. Moher *et al.,* (2009) strategically illustrate the sequence of the structure for PRISMA statement methodology. The inclusion and exclusion criteria is recommended prior to start of the review selection process. Following the study selection strategy development, the selection process can be carried out as follows:

a. **Identification**- identifying records through database and other sources
b. **Screening**- assessment of the retrieved titles, abstracts for relevance and removing duplicates.
c. **Eligibility**- assessment of articles for eligibility and exclusion of articles with reasons
d. **Inclusion**- review in detail the qualitative and quantitative studies (meta-analysis)

Lepage *et al.*, (2001) advised that for data collection, the method of extraction from the studies, i.e. the process of obtaining and confirming the data, ought to be clearly defined. Different methods of data extraction, for example piloted forms, independent evaluation or duplicate reviews among other tools are often used to express the criteria followed to simplify data collected from the studies.

The systematic review of mobile phone application interventions used to facilitate adherence to chronic disease management and acute treatment in Africa was performed following the principles above. The search was not limited to a type of disease i.e., both communicable and non-communicable disease profiles were selected to broaden the scope of the search. The systematic review was not limited to adherence to treatment, but incorporated other interventions concomitantly used with mobile phone applications, for example educational tools, medication reminders, appointment reminders and patient-provider communication tools.

The review excluded other forms of interventions, for example video calls, video footage, video conferences and faxes. Using Boolean strategy, three search engines i.e. Pubmed®, Cochrane® and EBSCO® databases were searched for journal articles and studies that assessed the impact of mobile phone applications on adherence to treatment in Africa. Additionally grey literature and references were screened. Medical Subject Headings (MeSH) terms and advanced search-builder features were used for PubMed searches. Duplicates were removed. There was no specified limit to date of publications. The populations, interventions, comparisons, outcomes and study design considered for review are listed in Table 2.

Table 2: Population, interventions, comparisons, outcomes and study design (PICOS) criteria for inclusion

Criteria	Explanation
Study design	Study designs were not limited (both randomised controlled trials and cross sectional studies)
Population	Adults and children, patients on treatment (communicable or non-communicable diseases) in African states
Interventions	Mobile applications implemented for purposes of improving adherence
Comparisons	Intervention arm receiving intervention and control arm not receiving intervention but standard of care Before and after intervention comparisons were also considered
Outcomes	Any measure of adherence for example; clinical outcome such as CD4 counts or BP measurements or self-reporting or filling of prescriptions

3.2. Study site and sample

This study comprises a systematic desktop review of published and grey literature. Original research published in peer-reviewed journals and grey literature which evaluated the impact of mobile phone applications on adherence to treatment in Africa for all diseases i.e. communicable and non-communicable diseases were included.

All mobile phone application interventions aimed at improving disease management with respect to adherence were included. Although content of the interventions was not a focus of the review, these were considered for information purposes.

Inclusion criteria

Studies reporting different outcomes of the interventions like self-reporting, base line and final laboratory results or clinical impact of the assessments were all included as clinical outcomes are considered desired end-points for adherence.

Only mobile phone devices were included, other devices, for example a personal digital assistant, landlines, faxes and computers were excluded. The studies that reported adherence as a primary or secondary interventions were included in the study however, there was no restriction in terms of the outcome measure used to determine adherence i.e. self-reporting or clinical assessment. Only studies published in English and conducted in African states were selected. There was no restriction in terms of date of publication, duration of the study and the population selected was not limited i.e., all genders and age groups were included.

Articles which were completed at the time of publication were considered and where future studies or protocols were published but studies not completed, these were excluded. The study design and sample size were not restricted therefore randomised controlled trials and cross sectional trials were included in the review.

Exclusion criteria

Studies were excluded from the review if: (a) they did not measure adherence, (b) were not conducted in Africa, (c) did not report outcome measures and (d) did not use mobile phone applications as a means to implement the intervention. Studies comparing intervention and control groups, before and after intervention were included in the review.

For effective identification of relevant studies, the following Boolean search terms were used: “mobile phone” OR “cellular phone” OR “text message” OR “application” OR cell phone” AND “treatment” OR “medication” AND “adherence” OR “compliance” OR “medication adherence” or “medication non-adherence” AND “Africa” OR “African States”. Figure 1 shows criteria followed when applying exclusion criteria.

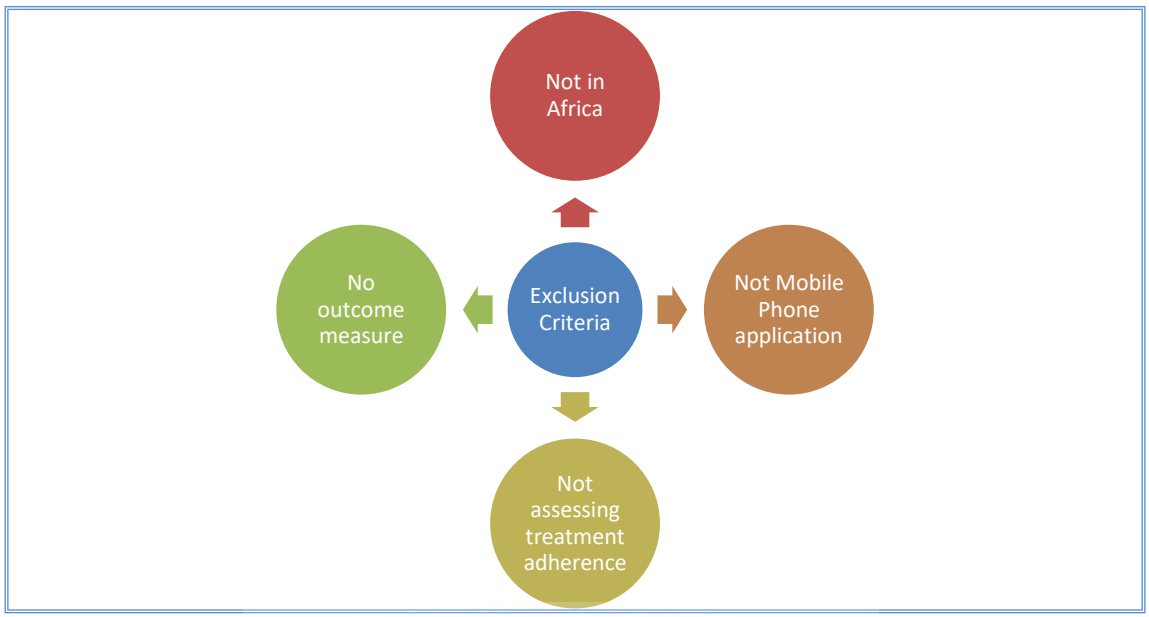

Figure 1: Exclusion Criteria

3.3. Research Method

3.3.1. Data collection process

Publications were screened for possible inclusion based on title and abstract by the reviewer for grey literature and formal research extracted from Pubmed®, EBSCO® and Cochrane®. Grey literature in the context of this study refers to studies that have not yet been published studies, with limited distribution. Table 3 illustrates a search strategy implemented using Boolean search terms when locating relevant studies through Pubmed®. The references of selected relevant studies were searched for additional information and papers that met inclusion criteria.

Table 3: Search Strategy for MEDLINE using Pubmed®

Search set	Search terms (Boolean Phrases)
1	Mobile phone*health application OR mobile health applications OR cellphone* OR mobile app* OR cellular phone* OR smart phone* OR short message* OR text message* OR reminder systems*
2	Disease* OR health condition* OR illness* OR communicable disease* OR non communicable disease*
3	Treatment Adherence* OR medication adherence* OR Treatment compliance OR Medication Adherence
4	#1 AND #2
5	#1 AND #2 AND #3

3.3.2. Data extraction

Information, for example, type of intervention, country where the study was performed, setting, and study sample characteristics, condition under study, outcome measured and results were extracted onto a Microsoft Excel® spreadsheet. The main objective of each study and outcomes measured were the focus when organising the studies for analysis. The studies were organised into the conditions under treatment, country were the study was performed and date of data collection and publication. Data was extracted from the studies using a coding system designed by the reviewer which included the following:

1. General information (trial location and number of participants)
2. Participant demographics (age)
3. Study design
4. Medical condition under treatment and duration of study
5. Outcome Measures
6. Loss to follow up
7. Method and frequency of assessment of adherence
8. Limitations of each study were also assessed based on bias.

Data extraction was performed in duplicate to allow identification of transcription errors and to minimise subjectivity that may occur when interpreting data as per the recommendation from Crowther et.al (2010). Smith *et al.* (2011) illustrated the importance of being specific when reporting the primary outcome of interest for the review. This aspect often results in limiting data extraction to only the results that are relevant to the question.

The primary outcome of each study was extracted i.e. the impact of using mobile phone applications on adherence. The secondary outcomes, where reported, were also extracted onto the spreadsheet for information only.

3.4. Data analysis

Analysis of the data was performed through coding. Following the extraction of the data onto an Excel® spreadsheet, the studies were further subcategorised to allow for ease of evaluation. Qualitative and quantitative studies were segregated onto different tables for ease of analysis. A descriptive summary through the tables was used to analyse the data. Due to the differences in the design of the cohort studies, statistical combination of the results was not performed.

3.5. Validity and reliability

3.5.1. Risk of bias

To validate risk of bias in individual randomised controlled trial studies, PRISMA principles were followed in accordance with Liberati *et al.* (2009). Furthermore, instead of using scales or checklists, a component approach was used to evaluate risk of bias

of individual studies according to Cochrane Collaboration's tool as advocated by Liberati *et al.* (2009).

The component approach by (Jonathan A.C. Sterne et al 2019),recommends assessing risk of bias by evaluating selection bias (allocation concealment), performance bias (blinding of study participants and personnel), detection bias (blinding of outcome assessors), attrition bias (withdrawals or incomplete outcome data) and reporting data (reported and unreported findings).
Higgins, Altman and Sterne, (2011) stated that in order to obtain reliable conclusions when performing systematic reviews, review authors must carefully consider the potential limitations of the included studies.

Selection bias seeks to cover aspects that might arise due to bias such as random sequence generation and allocation concealment. Higgins *et al.,* (2011) provided a description and interpretation of the six domains of bias introduced by the Cochrane Collaborations. A scoring system of low, high and unclear was used, where low depicts less bias allocation to intervention, high depicts biased allocation to intervention and unclear indicates lack of sufficient details to conclude the score.

Higgins *et al.,* (2011) further pointed out that for random sequence generation, risk of bias is considered low if there is adequate generation of a randomized sequence in order to produce comparable groups. The method used to conceal the allocation sequence should be in sufficient detail to determine whether intervention allocations could have been foreseen before or during enrolment. Risk of bias for concealment allocation is considered low if there is adequate concealment of allocation prior assignment.

Higgins *et al.,* (2011) showed that performance bias is used to evaluate risk of bias resulting from blinding both participants and researchers. Risk of bias is considered low if there are measures used to blind trial participants and researchers from knowledge of which intervention a participant received. The effectiveness of the intended blinding should be assessed.

Higgins *et al.,* (2011) further demonstrated that detection bias arises due to knowledge of the allocated interventions by outcome assessment. Detection bias is low if there are measures used to blind outcome assessment from knowledge of which intervention a participant received.

Attrition bias as per the definition provided by Higgins *et al.,* (2011) is a form of bias that arises due to the amount, nature, or handling of incomplete outcome data. This kind of bias is considered low if the study reviewed describes the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. Furthermore, the risk is low if the study reveals whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition or exclusions where reported, and any re-inclusions in analyses for the review. Reporting bias assesses bias arising due to selective outcome reporting. Risk of bias evaluation was conducted for each individual study and is presented in Table 8 for randomized controlled trials.

ROBINS-I ("Risk Of Bias In Non-randomized Studies - of Interventions") tool was used to assess the quality of the observational studies included in the review. Sterne *et al.* (2016) described ROBINS-I as a tool "which is concerned with evaluating risk of bias in estimates of the effectiveness or safety (benefit or harm) of an intervention from studies that did not use randomisation to allocate interventions". The tool is categorized into seven domains through which bias might be introduced into non-randomized studies of the effects interventions (NRSI). The domains include confounding and selection of participants into the study (which address issues before the start of the interventions that are to be compared ("baseline").

The other domains are biases due to deviations from intended interventions, missing data, measurement of outcomes, and selection of the reported result.

Bias due to confounding occurs when one or more prognostic variables (factors that predict the outcome of interest) also predicts the intervention received at baseline (before the start of the interventions that are to be compared).

Selection of participants' bias occurs when exclusion of some eligible participants, or the initial follow-up time of some participants, or some outcome events is related to both

intervention and outcome. Bias in classification of interventions is introduced by either differential or non-differential misclassification of intervention status.

Bias due to deviations from intended interventions arises when there are systematic differences between experimental intervention and comparator groups in the care provided, which represent a deviation from the intended intervention(s).

Bias due to missing data that arises when later follow-up is missing for individuals initially included and followed (such as differential loss to follow-up that is affected by prognostic factors); bias due to exclusion of individuals with missing information about intervention status or other variables such as confounders.

Bias in measurement of outcomes is introduced by either differential or non-differential errors in measurement of outcome data. Such bias can arise when outcome assessors are aware of intervention status, if different methods are used to assess outcomes in different intervention groups, or if measurement errors are related to intervention status or effects

Bias in selection of the reported result occurs when results are reported in a way that depends on the findings and prevents the estimate from being included in a meta-analysis (or other synthesis). Risk of bias evaluation was conducted for each individual study and is presented in Table 9 for observational studies.

3.5.2. Publication Bias

Publication bias according to Lipsey and Wilson (2001) occurs when studies that found statistically non-significant findings do not submit their results for publication, or if they do, their manuscript is rejected for publication by reviewers and/or journal editors.
Publication bias threatens the validity of the conclusions of a systematic review, in addition, it is likely that published research papers will have favourable results than unpublished papers. In order to avoid over-estimation of population effect sizes resulting from published studies, grey literature was also included in the search.

3.6. Scope and limitations of the study

This systematic review was restricted to research conducted within the African context. Literature reviewed was confined to articles published in English. Crowther *et al.,* (2010)

pointed out that limiting the studies by language may reduce the number of studies needed to review significantly, especially if there is difficulty in translating the studies. Excluding the studies on the basis of language can be done but Crowther *et al.,* (2010) cautioned that it must be done with care. Depending on the topic of discussion, if the research topic is endemic in specific language areas, the systematic review should seek to identify studies within those affected particular populations. This was not the case with this review.

Studies included reported the impact of the interventions based on self-reports and refill of prescriptions, which assumes that patients took medications as prescribed. There were no further systems to validate this impact in the form of clinical assessments. Therefore, this assumption might not be a true reflection. Furthermore, the study did not take into consideration the content of the mobile phone applications. Therefore, conclusions deducted herewith do not assess the extent of the information that should be contained in mobile phone applications to render the interventions effective.

3.7. Loss to follow up

For the purpose of this study, loss to follow-up refers to patients who, at one point in time were actively participating in a clinical research trial, but have become inaccessible to the researchers. i.e., "lost", (either by error in a computer tracking system or by being unreachable) at the point of follow-up in the trial.

Reliability of studies can be assessed by a loss-to-follow-up quotient. Loss-to-follow up has a potential to result in disguised failures and misleading conclusions. A study conducted by Murray, Britton and Bulstrode, (1997) examined the hypothesis that "*the survival analysis of joint replacement relies on the assumption that surgical procedures in patients lost to follow-up have the same chance of failing as those in patients who continue to be assessed"*. The study concluded that the patients who are lost to follow-up have a worse outcome than those who continue to be assessed. The study further showed that a trial that does not take into consideration patients who are lost to follow-up "is likely to give falsely optimistic results".

A similar conclusion was presented by Dettori, (2011) who published a paper that sought to establish whether loss to follow-up can compromise the validity of the study. In the paper Dettori (2011) emphasizes the fact that incomplete follow-up biases the results

when the drop-out rates are different between the control and intervention group and when the patients who drop out are different from those who do not drop out. For example patients might drop-out because they feel better or patients might drop out because they feel worse or have died. By not assessing the impact of loss to follow-up, risk of bias increased significantly.

Sackett *et al.*, (2000) suggested that a <5 % loss leads to little bias, while >20 % poses serious threats to validity. However, in some cases, a small proportion of patients lost to follow-up might result in significant bias as pointed out by Bhandari, Guyatt and Swiontkowski, (2001). Dettori (2011) suggested, "One way to determine if loss to follow-up can seriously affect results is to assume a worst-case scenario with the missing data and look to see if the results would change".

Another challenge that comes with assessing loss to follow-up within studies is the definition of loss to follow-up.

In their study, Shepherd *et al.*, (2013) illustrated the impact that improper definition of loss to follow-up can have on the estimation of patient retention on treatment, disease progression and mortality. The study concluded that loss to follow up definitions must be based on the study/programmatic outcome of interest, available encounter data, and the cohort visit schedule. The authors did not recommend a universal standard as the definition of loss to follow-up should depend on the intended application and the cohort(s) of study.

3.8. Ethical considerations

Weingarten, Paul and Leibovici (2004) suggested that if the issue of ethics is not considered during systematic reviews, there could be some drawbacks. The systematic review may contain articles with ethical insufficiencies and may be prone to conflict of interest. In addition, Weingarten *et al.,* (2004) pointed out that informed consent given for an original study is not necessarily still valid at the systematic review level. The prime ethical consideration in conducting this review was maintaining accuracy and truthful reporting of reviewed literature. The study was Registered by the UWC Research Committee and conformed to all the protocols of accepted research techniques and considerations. All data sources have been referenced properly and authentic data has been used in generation of the information generated.

CHAPTER 4: RESULTS AND DISCUSSION

4.1. Summary

This chapter focuses on the results of the main outcomes of the review and outlines the study selection, study characteristics, risk of bias of individual studies, additional analysis including study period and loss to follow-up, intervention tools and analysis of individual studies. The results for search strategy for MEDLINE using Pubmed® are presented in Table 4.

Smith *et al*., (2011) recommended that when presenting the results of systematic review, the report should have major conclusions of the review through the provision of answers to the research questions. In addition, evidence of the conclusion should be based on the quality of the evidence supporting each conclusion.

Table 4: Results of the Search Strategy for MEDLINE using Pubmed®

Search set	Search terms (Boolean Phrases)	Results
1	Mobile phone*health application OR mobile health applications OR cell phone* OR mobile app* OR cellular phone* OR smart phone* OR short message* OR text message* OR reminder systems*	104 536
2	Disease* OR health condition* OR illness* OR communicable disease* OR non communicable disease*	3 230 455
3	Treatment Adherence* OR medication adherence* OR Treatment compliance OR Medication Adherence	240 331
4	#1 AND #2	331
5	#1 AND #2 AND #3	614

The overall results were presented in accordance with the PRISMA reporting tool. Summary tables and figures are used in this review to present the results in a structured and clear format that enhances textual commentary. The tables were designed to captivate the summary of each study following the study selection process.

The study selection is presented in Figure 2 flow diagram which illustrates the number of studies screened, the studies assessed for eligibility and the studies included in the review. Study characteristics are presented in Table 5 for quantitative studies and Table 6 for qualitative studies. The tables provide details of the authors and year of publication, sample size, disease under study, country where the study was undertaken, study intervention and the results of the research.

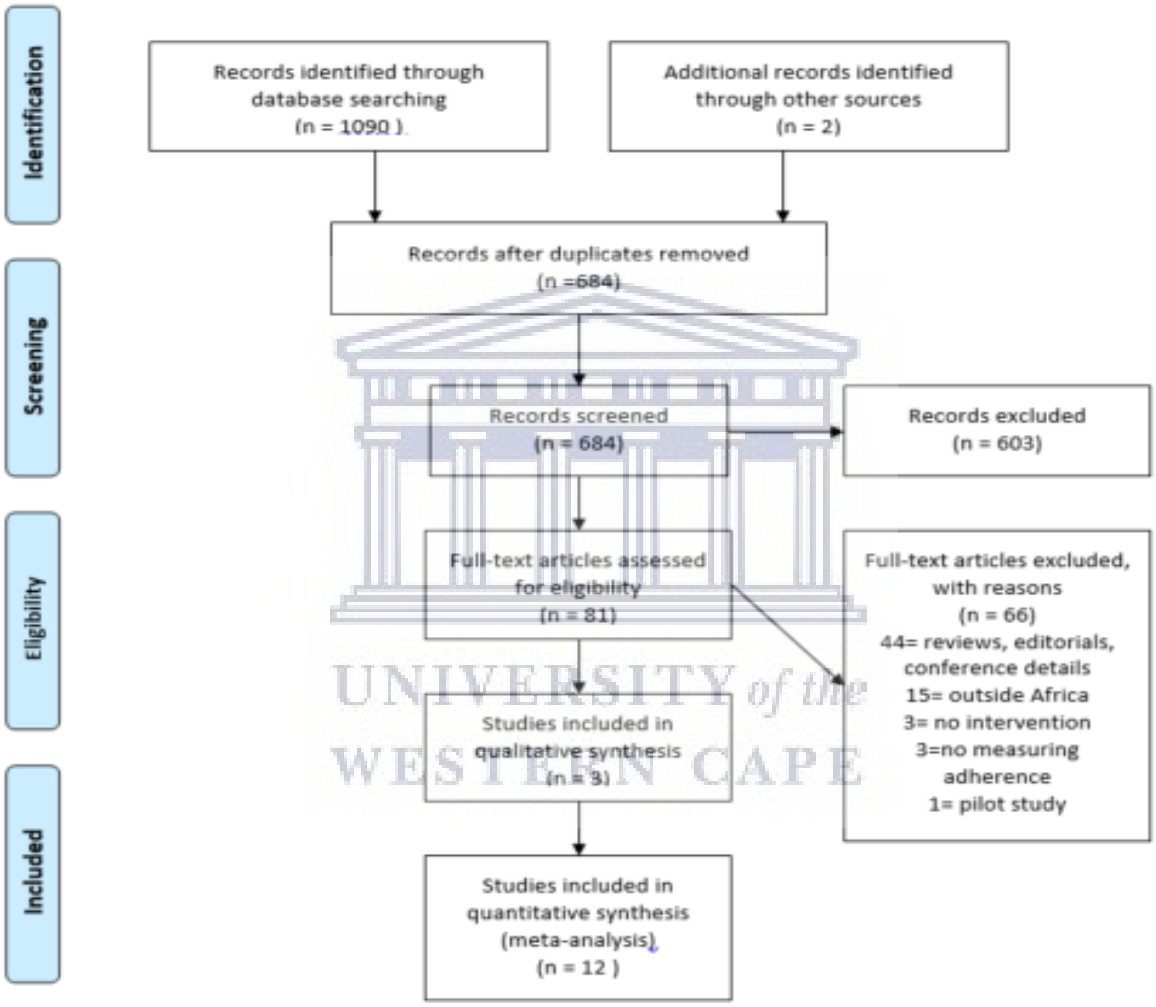

Figure 2: PRISMA Flowchart for Study Selection
Source: *From:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7)

Results were further evaluated with regards to study design. Using a table, each study was presented into a specific study design within each disease. The classification of the study designs included: Randomized Controlled Trials, Descriptive studies, Feasible

Longitudinal studies, Crossover studies, Quasi-experimental studies and Retrospective studies.

Grover and Shroyer (2000) describes randomised controlled trials as studies within which experiment units are randomly assigned to treatments or interventions. Subjects are randomised to an intervention group or a control group. Post the intervention data is collected for analysis.

Cross sectional studies according to Grover and Shroyer (2000) are studies with an outcome based on a sample size. Cohort Retrospective studies encompass data collected prior to the collection date. Quasi-experimental designs with a primary purpose being to investigate cause-effect relationship. In Quasi-experimental approach, the participants are not randomised, instead a comparison group is developed. Table 7 illustrates the study design per disease of the reviewed articles.
The study periods, loss to follow up and limitations of each study were reviewed and are presented in Table 8.

4.2. Study selection

A total of 1077citations were identified through Pubmed®, Cochrane® and EBSCO®, 13 publications through reference list and two citations through grey literature. Six hundred and eighty four records remained after duplicates were removed. Based on title and abstract review, six hundred and three publications were further removed. A full text review was performed on 81 articles for eligibility. Forty four articles were excluded as these were editorials and conference details, fifteen articles were detailing trials conducted outside Africa, three studies did not include interventions of interest, one study was pilot studies, therefore did not provide statistically representative results and three studies did not measure adherence. Figure 2 illustrates study selection process.

4.3. Study Characteristics

Fifteen articles met eligibility criteria (fourteen journal articles and one research report). One publication represented a study performed in Ghana, one in Mozambique, four in Cameroon, three in South Africa, two in Kenya, one in Nigeria, one in Uganda, one in

Zambia and one in Botswana. All publications were written in English and published between 2010 and 2018.

Eleven of the studies (73 %; n=11) were randomised controlled trials, three (19 %; n=3) were descriptive/feasible studies and one (6 %; n=1) was a Pre- and Post-intervention study. Table 7 illustrates the profile of study design by disease. Twelve of the studies illustrated an experimental design where intervention and control groups were assessed, one reported before and after intervention and two were a cross sectional and descriptive study. Table 5 demonstrates results analysis for quantitative studies and Table 6 illustrates analysis of qualitative studies.

Eighty six percent (n =12) of the publications were comprised of adult participants only i.e. 18 years or above, with mean values of 32 years of age and, the remaining 24 % (n =3) consisted of a combination of adults and children i.e., between 5 years to 65 years.

Most of the data was collected between May 2007 and December 2014. The studies included 4148 participants of which children made up 15 % (n =622) and adults were 85 % (n =3525) of the population under study. Sample sizes varied between the studies in that five of the studies had a sample size of less or equal to one hundred whilst ten had a sample size above one hundred with a maximum sample size of 1372 participants.

Study characteristics

Table 5: Results analysis for Quantitative Studies

Study and year of publication	Sample size	Condition under study and Country	Study Intervention	Results
Bediang *et al*., (2018)	260(adults only)	TB, Cameroon	Patients in intervention group received daily SMS reminders in addition to usual treatment and those in the control group received usual treatment only.	At 5 months there were 111 treatment success's (81 %) in the intervention group and 106 (74.6 %) in the control group (OR = 1.45 [0.81, 2.56]; p=0.203). At 6 months there were 87 patients cured (63.5 %) in the intervention group and 88 (62 %) in the control group (OR = 1.06 [0.65, 1.73]; P=0.791).
Bobrow *et al., (*2016)	1372(adults only)	Blood Pressure, South Africa	Participants treated for high blood pressure were randomly allocated in 1:1:1: ratio for information only or interactive SMS text-messaging or usual care.	At 12 months the mean adjusted change (95 % CI) in systolic blood pressure compared to usual care was -22 mmHG (-4.4 to -0.04) with information-only SMS and -1.6 mmHg (-3.7 to 0.6) with interactive SMS.
Davey *et al*., (2016)	830(adults only)	HIV/AIDS, Mozambique	Four categories of SMS reminders sent to the intervention group vs control participants who did not receive text messages.	Retention in ART care was higher in the intervention group (93.8 %, 95 % CI= 90.5-95.7) than the control group (91.0 %, 95 % CI= 87.7-93.4).
Kunutsor *et al*., (2010)	176 (adults)	HIV, Uganda	Voice calls and SMS were sent to patients if they missed an appointment or reminded to attend clinic for a refill	Mean adherence [95% confidence interval (CI)] before and after mobile phone recall intervention was 96.3 %(95.2–97.4%) and 98.4% (97.8–98.9%) for the cohort, respectively. The proportion of clients achieving optimal adherence before and after mobile phone recall was 141 (80.1%) and 160 (90.0%), respectively. A paired t test showed a significant difference in

				mean adherence levels before and after mobile phone recall intervention (P = 0.002).
Study and year of publication	**Sample size**	**Condition under study and Country**	**Study Intervention**	**Results**
Lester *et al., (*2010)	538(adults only)	HIV/AIDS, Kenya	Patients received weekly SMS vs control group	Adherence to ART: Intervention group 61.5% and control group 49.81 and suppressed plasma viral load: Intervention group 60.4 and control group 48.3 %
Liu and Modrek, (2016)	728 (adults and children)	Malaria, Nigeria	2 Intervention groups (one basic SMS and one extended SMS) Control Group	A basic SMS increased treatment adherence [OR=1.53, 95 % CI= 0.96-2.44] and decreased use of unnecessary anti-malarial treatment for RDT-negative adults [OR=0.63, 95 % CI=0.0.39-1.00].
(Mbuagbaw (a) *et al.,* (2012)	200(adults only)	HIV/AIDS, Cameroon	A short text message was sent once a week to the intervention group and the controlled group did not receive any text message	At 6 months there was no effect on the number of participants achieving > 95 %adherence by VAS (Risk ratios (RR) 1.06, 95 % CI= 0.89-1.29; P=0.542) or reporting missed doses (RR 1.01, 95 %CI 0.87-1.16; p> 0.999).
Mbuagbaw (b) *et al., (*2012)	30 (adults only)	HIV/AIDS, Cameroon	Discussions were based on open-ended thematic questions pre-specified in the group discussion guide.	Half (15 of 30) of the participants believed that the SMS could help them take their medication but the value of the SMS will depend on the sender.

Study and year of publication	Sample size	Condition under study and Country	Study Intervention	Results
Nsagha *et al.,* (2016)	90 (adults only)	HIV/AIDS, Cameroon	Intervention group received four SMS per week at equal intervals for four weeks vs a control group did not receive SMS.	Adherence to ARVs was 64.4 % in the intervention group and 44.2 % in the control group. (p=0.05). Two (4.4 %) patients in the control group failed to respect their drug refill appointments and all 45 (100%) participants in the intervention group respected their drug refill appointments.
Pop-Eleches *et al.*, (2011)	428(adults only)	HIV/AIDS, Kenya	Patients in the four intervention groups: one group received short text reminders daily, another group received long text reminder daily, another group received short text reminder weekly whilst another received long text reminder weekly.	53 % of participants receiving weekly SMS reminders achieved adherence of at least 90 % during the 48 weeks of the study compared with 40 % of participants in the control group (p=0.03). Participants in a group receiving weekly reminders were significantly less likely to experience treatment interruptions of more than 48 hours during the 48 weeks follow up period than participants in the control group (81 vs 90 %, p=0.03).
Raifman, Lanthorn, Rokicki and Fink (2014)	1140(adults and children)	Malaria, North Ghana	A simple short SMS reminder for antimalarial sent every 12 hours for three days to Group A of treatment group and a long SMS reminder sent every 12 hours for 3 days to Group B of the treatment group vs control.	SMS reminders increased the odds of adherence to treatment as reported by patients i.e. of 538 participants in the control group, 61.5 % reported treatment completion. Of 572 participants in the treatment group, 66.4 % reported treatment completion. A significantly increased the odds of adherence (adjusted OR 1.45, 95 % CI [1.03 to 2.04] p-value 0.033).

Study and year of publication	Sample size	Condition under study and Country	Study Intervention	Results
Reid *et al.,* (2017)	108(adults only)	HIV/AIDS, Botswana	The intervention arm received SMS reminders three days prior, one day prior and the morning of the scheduled monthly pharmacy pickup.	85 % of participants receiving SMS demonstrated 100 % six month timely pharmacy pickup compared to 70 % timely ART pickup in the control group (p=0.0064). There was no significant difference in the CD4 count between the intervention and the control group.

Table 6: Results Analysis for Qualitative Studies

Study and year of publication	Sample size	Condition under study and Country	Study Intervention	Results
Georgette *et al.*, (2016)	100 (adults only)	HIV/AIDS, South Africa	Participants were interviewed on their perception of a weekly SMS adherence support program after implementation	Of the 88 respondents, 86 (97.7 %) participants reported that an SMS helped them remember their medication and 68 (77.3 %) of the participants agreed that the SMS helped them remember their appointments. Fourteen (15.9 %) participants reported that the SMS were reminders that the clinic cares about them.
Leon, Surender, Bobrow and Muller (2015)	(adults only)	Blood Pressure, South Africa	Intervention group that received SMS intervention was interviewed	Adherence support for treatment of raised BP delivered via SMS text message was found to be more acceptable, relevant and helpful to a broad range of participants.

Steury (2016)	96 (adults only)	Malaria, Zambia	The intervention group received SMS messages	No significance association was found between SMS reminders and pharmaco-adherence

4.4. Study periods and outcome measures

The follow up period ranged between sixty-six hours (for Malaria cases) and a month (Malaria, HIV/AIDS, BP and TB) following implementation of interventions. The average duration of intervention was six months (mean= 184 days, range= 3 – 365 days) and the mean number of outcomes reported was two (range = 1-3). The primary outcomes included mean adherence before and after mobile phone interventions (Kunutsor *et al., (2010))*, adherence measured using visual analogue scales (Mbuagbaw (b) *et al., (2012))*, self-report (Mbuagbaw (b) *et al., (2012)*, Liu *et al., (2016),* Leon *et al., (2015),* Georgette *et al., (2016)*, Raifman *et al., (2014)* and Bediang *et al., (2018)),* pharmacy refill data/ pill count (Nsagha *et al., (2016*, Reid *et al., (2017),* Davey *et al., (2016)l,* Raifman *et al., (2014)* and Steury, (2016)*),* education Event Monitoring Systems (Pop-Eleches *et al., (2011))* and biological outcome variables (Bobrow *et al., (2016),* Mbuagbaw (b) *et al., (2012)*, Bediang *et al,. (2018))*.

Table 7: Study Design by disease (n=15)

Study Design	Malaria	HIV/AIDS	TB	Blood Pressure
Randomised Controlled Trial	3 (20 %)	6 (40 %)	1 (6.6 %)	1 (6.6 %)
Descriptive/Feasible	0 (0%)	2 (13 .3%)	0 (0%)	1 (6.6 %)
Longitudinal/ Pre- and Post	0 (0%)	1 (6.6 %)	0 (0%)	0 (0%)
Crossover	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Quasi-experimental	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Retrospective	0 (0%)	0 (0%)	0 (0%)	0 (0%)

4.5. Intervention tools

In terms of tools used, SMSes were used in hundred percent of the studies as a means of delivering interventions in Africa, and in one study this was coupled with voice calls (Kunutsor *et al*.,2010) and coupled with electronic pillbox in another study (Steury, 2016). In all cases standard of care continued for both intervention and control group in the form of usual counselling, health checks and assessments.

The frequency of the text message delivery differed between every twelve hours for three days in Malaria treatment (Raifman *et al*., 2014), two days and seven days before appointments in HIV/AIDS treatment (Davey *et al. ,*2016), every twenty four hours for TB treatment (Bediang *et al.,* 2018), weekly SMS in HIV/AIDS treatment (Lester *et al*.,2010), (Geogette *et al*.,2011), and (Mbuagbaw (a) e*t al., 2012)*, weekly for Blood pressure treatment (Bobrow *et al. ,2016)* and(Leon *et al.,* 2015), daily and weekly for HIV/AIDS treatment (Pop-Eleches *et al*.,2011), daily for Malaria treatment (Liu *et al*., 2016) and (Steury., 2016)), four SMS per week for HIV/AIDS treatment (Nsangha e*t al.,* 2016) and monthly for ARV refills for HIV/AIDS patients (Kunutsor *et al.,* 2010).

The content of the SMS varied from simple, short messages to complex and long messages. Some studies allowed for patient-healthcare provider interactions, whilst others only allowed for a one-way interaction when an intervention was delivered to the patient. Three publications studied effects of interventions on malaria treatment, nine publications on HIV/AIDS, one publication on TB and two publications on blood pressure.

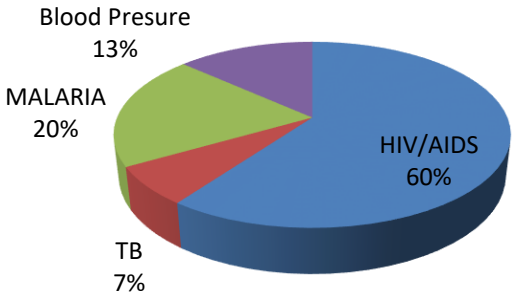

Figure 3: Disease profiles of studies reviewed

4.6. Loss to Follow up

Within studies that reported loss to follow up, a maximum number of total withdrawal from the studies was 36 % (Bediang *et al., (2018).* This was a significantly high number in relation to Kristman, Manno and Côté, (2004) study which recommends that a considerable bias associated with MNAR mechanism with 20 % loss to follow up is significant. Three of the randomized controlled trials did not define loss to follow up although within the statistical analysis there was mention of allowable total loss to follow-up. Two of the observational studies did not report loss to follow-up. Table 10 summarises loss to follow up and limitations of the studies included in this review.

4.7. Validity and reliability

4.7.1. Risk of bias for quantitative studies

Within twelve of the studies, a random sequence generation was used and in ten of the studies, allocation concealment was used. It was not easy to assess selective reporting as there was insufficient information to permit judgement (Cochrane, 2009). In only one of the studies, patients were blinded. Personnel and data collectors were blinded in six of the studies, un-blinded in five of the studies and not clear in one of the study. Detection measurement bias was high in most of the studies as outcome assessors were blinded only in one of the study and un-blinded in nine of the studies and it was not clear from the two studies whether outcome assessors were blinded or not but judging by the study content, it is most likely that the assessors were aware of the participant intervention details. There was a high variability with regards to attrition bias. Reporting bias could not be assessed in eleven of the study and was found high in one study. Further details of quality assessments are illustrated in Table 8.

It was not clear from six of the studies whether all outcomes were completely reported as cases of withdrawals and impact of loss to follow-up was not assessed or detailed in the reports. Lack of information regarding loss to follow-up within some studies made assessment challenging.

4.7.2. Risk of bias for observational studies

The eligibility criteria of all observational studies was detailed and applied equivalently across all participants. In addition the outcome measures were applied similarly to participants. There was no patient lost to follow-up reported in the observational studies. Selection bias was high in all three qualitative studies as a result of confounding in the studies for example, demographics, age, language and experience with technology. Other confounding factors were not documented during recruitment of participants. Bias of outcome measurement was high as assessors were aware of the interventions allocated to specific participants. It was not clear from the studies if there was any missing data as protocols could not be retrieved. Table 9 illustrates further assessment of quality of observational studies.

Table 8: Evaluation of Risk of Bias for Randomized Controlled Trials

Trials	Random Sequence generation	Allocation concealment	Selective reporting	Patients Blinded	Personnel and data collectors blinded	Outcome assessors blinded	Incomplete outcome data
Bediang *et al.,* (2018)	Low	Low	Unclear	High	Low	High	Low
Bobrow *et al* .,(2016)	Low	Low	Unclear	Low	Low	Low	Low
Davey *et al.,* (2016)	Low	Low	Unclear	High	Low	High	Unclear
Kunutsor *et al.,* (2010)	High	High	High	High	Unclear	Unclear	Unclear
Lester *et al.,* (2010)	Low	High	Unclear	High	High	High	Low
Liu *et al.,* (2016)	Low	Low	Unclear	High	Low	High	Unclear
Mbuagbaw (a) e*t al.,* (2012)	Low	Low	Unclear	High	Low	High	Low
Nsagha e*t al., (*2016)	Low	High	Unclear	High	High	High	Unclear
Pop-Eleches *et al.,* (2011)	Low	Low	Unclear	High	High	High	Low
Raifman *et al.,* (2014)	Low	Low	Unclear	High	Low	Unclear	Low
Reid *et al., (2017)*	Low	Low	Unclear	High	High	High	Unclear
Steury, (2016)	Low	Low	Unclear	High	High	High	Unclear

Table 9: Evaluation of Risk of Bias for Observational Studies included in the review

Trials	Selection Bias	Confounding	Deviations from intended interventions	Classification of interventions	Measurement of outcome	Missing data	Reporting Bias
Geogette *et al.,* (2016)	High	High	High	High	High	unclear	unclear
Leon *et al.,* (2015)	High	High	High	High	High	unclear	unclear
Mbuagbaw (b) *et al.,* (2012)	High	High	High	High	High	unclear	unclear

Table 10: Loss to follow up and Limitations of the studies

Study and year of publication	Loss to follow-up	Limitations of the studies
Bediang et al., (2018)	Loss to follow-up = 34.3 % intervention group and 32.4 % in control group	A significant number of total withdrawn patients (lost to follow up, transferred or deceased) was observed throughout the study i.e 35.8 % (n = 49) in the intervention group and 36.6 % (n = 52) in the control group (OR = 0.96 [0.59-1.57]; P = 0.88).
Bobrow *et al.*, (2016)	Loss to follow-up = before 6 months (control = 9%, informative SMS = 8.3%, interactive SMS = 8%), after 6 months (control = 4.8%, informative SMS = 3%, interactive SMS = 6.4%)	1. The measure of adherence used only reflects dispensing in the clinic and not the act of taking medication. 2. Targeting a group of people diagnosed with hypertension rather than those with a diagnosis of poorly controlled pressure may have also limited the extent to which improvements in blood pressure were possible.
Davey *et al.,* (2016)	Loss to follow-up = 8 %	1. Short Time Frame. 2. Only literate patients with mobile phones were included.
Leon, Surender, Bobrow, Muller and Farmer., (2015)	LTF = 0	None could be identified.
Liu et al., (2016)	Loss to follow up =Control 7%, Intervention basic SMS 6% and Intervention expanded SMS 4%	A significant number of patients were lost to follow up i.e. 17 of the control group, 15 of the basic SMS intervention group and 10 of the expanded SMS intervention group were lost to follow up.
Pop-Eleches *et al.*, (2011)	Lost to follow-up = control group (14.4%), short daily reminders group (18.6%), long daily reminders group (16.7%), short weekly reminders group (22%), and long – weekly reminders group (10.8%)	The study did not have HIV-RNA determination and therefore cannot corroborate that the differences in adherence were associated with differences in viral suppression.
Raifman *et al.,* (2014)	Loss to follow-up = 0.4 %	1. Self-selected nature of patients implies that the results do not represent treatment effects for the average population. 2. The effectiveness of the programme may have been limited by mobile phone therapy. 3. The study is limited by its use of self-reported adherence as a primary outcome measure.

Study and year of publication	Loss to follow-up	Limitations of the studies
Geogette *et al.,* (2016)	Loss to follow-up = not reported	This study is limited to self-reported opinions and does not include objective data on adherence or retention in care.
Kunutsor *et al.,* (2010)	Loss to follow up = 0.1% (1 out of 560) after intervention.	The study is limited by drug refill appointments and not by HIV-RNA determination through viral suppression. Therefore the impact of the study could not be established to the pharmaco-therapeutic effect.
Lester *et al.,* (2010)	Loss to follow-up = SMS group 6 % and control group 10 %	A significant number of lost to follow up was experienced.
Mbuagbaw (a) *et al.*, (2012)	Loss to follow-up = 1 % of intervention group	Primary measure of adherence by interviews might have resulted in overestimates of the true adherence rate and the adherence reported for the last week may not adequately reflect adherence behaviours over prolonged periods. Therefore the duration of the trial might not have been sufficient to observe a significant effect.
Mbuagbaw (b) *et al., (2012)*	Loss to follow-up = not reported	Perception of participants was assessed and not HIV-RNA determination and therefore the effect on viral suppression was not established to corroborate the data.
Nsagha *et al.*, (2016)	Loss to follow-up = not reported	The study is limited by drug refill appointments and not by HIV-RNA determination through viral suppression. Therefore the impact of the study could not be established by the pharmaco-therapeutic effect.
Reid *et al.,* (2017)	Lost to follow-up = not reported	1. The sample size was small, therefore limited in ability to detect smaller difference in outcome between control and intervention groups. 2. The time from study completion to publication may limit the relevance of the findings.
Steury., (2016)	Loss to follow up = not reported	The pharmaco-therapeutic and cure rate was not assessed to provide further assurance that there was no impact on pharmaco-therapeutic effect.

4.8. Results of individual studies

4.8.1. HIV/AIDS

Eight studies presented the impact of mobile phone applications on adherence to ART treatment across Africa, i.e., Mozambique, one in Kenya, three in Cameroon, South Africa, Uganda and Botswana.

According to Davey *et al., (2016),* retention in ART care was high in the intervention group (93.8%, 95% CI = 90.5-95.7%) compared with the control group (91.0 %, 95 % CI = 87.7- 93.4 %). The study further noted that retention among urban patients was higher in the intervention group (94.3%, 95% CI= 91.3-96.4 %) than the control group (89.9%, 95% CI= 86.1- 93.1%; rate difference = 4.4, 95% CI= 0.4-8.5, p=0.032). Among rural patients, retention was higher in the control group (96.8%, 95% CI= 87.9-99.2%) than in the intervention group (90.7%, 95% CI= 80.4-95.7%) although this difference was not statistically different (rate difference= -6.1, 95% CI= -14.5- 2.2, P=1.48).

Pop-Eleches *et al.,* (2011) showed that 53% (n =228) of participants receiving weekly SMS reminders achieved adherence of at least 90 % (n=388) during the 48 weeks of the study compared with 40 % (n =172) of participants in the control group (p=0.03). Participants in a group receiving weekly reminders were significantly less likely to experience treatment interruptions of more than 48 hours during the 48 weeks follow up period than participants in the control group (81 vs 90%, p=0.03)

Nsagha *et al.,* (2016) illustrated through a randomised controlled trials that adherence to ARVs was 68% (n =30) in the intervention group and 44% (n =20) in the control group (p=0.05). Four percent (n =2) patients in the control group failed to respect their drug refill appointments and all 100 % (n =45) participants in the intervention group respected their drug refill appointments.

According to Mbuagbaw (a) *et al.,* (2012), at six months there was no effect on the number of participants achieving > 95 % adherence by VAS (Risk ratios (RR) 1.06, 95% CI = 0.89-1.29; P = 0.542) or reporting missed doses (RR 1.01, 95% CI 0.87-1.16; p> 0.999). The mean number of pharmacy refills was also not different between the intervention and the control groups (mean difference (MD) 0.1, 95% CI = -0.23 - 0.43; p=0.617). However, on sensitivity analysis more participants on the SMS group

achieved adherence of > 90 % at six months (RR 1.14, 95 % CI= 1.01- 1.29; P=0.027). In an extended qualitative study, Mbuagbaw (b) *et al.,* (2012) further demonstrated that 50% (n =15) of the participants believed that the SMS could help them take their medication but the value of the SMS will depend on the sender. This outcome illustrated that there was no difference in adherence between the intervention group receiving SMS reminders and the control group.

Georgette *et al.,* (2016) also demonstrated that of the eighty-eight respondents, 97 % (n =97) participants reported that an SMS helped them remember their medication and 77% (n =77) of the participants agreed that the SMS helped them remember their appointments. Fifteen percent (n =15) participants reported that the SMS were reminders that the clinic cares about them.

Lester *et al.,* (2010) showed that adherence to ART was reported in 168 of 273 patients receiving SMS intervention compared with 132 of 265 in the control group (relative risk (RR) for non-adherence 0.81, 95 % CI = 0.69-0.94; P = 0.006). Suppressed viral loads were reported in 156 of 273 patients in the SMS group and 128 of 265 in the control group (RR for virology failure 0.84, 95 % CI= 0.71- 0.99; p=0.04). The number needed to treat (NNT) to achieve a greater than 95 % adherence was nine (95 % CI= 5.0-29.5.) and NNT to achieve viral load suppression was 11 (95 % CI = 5.8-227.3). Patients who received SMS support had significantly improved ART adherence and rates of viral suppression compared with the control group.

Kunutsor *et al., (*2010) showed a mean adherence before and after mobile phone intervention was 96 % (95.2 % -97.4%) and 98 % (97.8 % - 98.9 %) respectively. The proportion of clients receiving optimal adherence before and after mobile phone was 80.1 % (n = 220) and 90 % (n =248) respectively with a significant difference in mean adherence levels before and after mobile phone recall intervention (p= 0.002 using a paired *t*-test).

Reid *et al.* (2017) presented data that showed that 85% (n =92) of participants receiving SMS demonstrated 100 % six month timely pharmacy pickup compared to 70% timely ART pickup in the control group (p=0.0064). The study showed no significant difference in the CD4 count between the intervention and the control group.

While mean log HIV VL was lowered in the intervention arm at the end of six months (5.31 vs 3.88, p = 0.05), the difference in VL from baseline across the groups was not statistically significant (-0.24 vs 0.09, p = 0.14)

4.8.2. Malaria

Three studies presented the effects of mobile phone applications on adherence for Malaria treatment.

Raifman *et al.,* (2014) *showed that* SMS reminders increased the odds of adherence to treatment as reported by patients i.e., 61 % (n =328) of the participants in the control group, reported treatment completion. Sixty-six percent (n =386) participants in the treatment group reported treatment completion. According to ITT analysis being sent Message A (simple reminder message) significantly increased the odds of adherence (adjusted OR 1.45, 95 % CI [1.03 to 2.04] p-value 0.033)

Liu *et al., (2016)* illustrated that a basic SMS increased treatment adherence [OR = 1.53, 95 % CI = 0.96-2.44] and decreased use of unnecessary anti-malarial treatment for RDT-negative adults [OR = 0.63, 95 % CI = 0.0.39-1.00]. The expanded SMS also increased adherence for adults [OR = 1.42, 95 % CI = 0.97-2.07] but the effects for sick children differed, the basic SMS did not have any measurable impact on treatment adherence [OR = 0.87, 95 % CI = 0.24-3.09], or use of unnecessary anti-malarials [OR = 1.27, 95 % CI = 0.32-1.93] and the expanded SMS actually led to a poorer treatment adherence [OR = 0.26, 95 % CI = 0.10-0.66] and increased use of unnecessary anti-malarials [OR = 4.67, 95 % CI = 1.76-12.42].

Steury, (2016) showed that no significant association was found between SMS reminders and pharmacoadherence (Chi Square= 0.19, df =1, p=.67). Binary logistic regression indicated that there were no variables associated with adherence (p> .05)

4.8.3. Blood pressure

Leon *et al.,* (2015) demonstrated that Adherence support for treatment of raised BP delivered via SMS text message was found to be more acceptable, relevant and helpful to a broad range of participants.

Bobrow *et al., (2016)* illustrated that primary outcome results were available for 92 % (n =457) participants, at twelve months the mean adjusted change (95 % CI) in systolic blood pressure compared to usual care was -22mmHG (-4.4 to -0.04) with information-only SMS and -1.6 mmHg (-3.7 to 0.6) with interactive SMS. Odds ratios (95 % CI) for the proportion of participants with blood pressure <140/90 mmHg were for information-only messaging 1.42 (1.03 to 1.95) and for interactive messaging was 1.41 (1.02 to 1.95) compared to usual care.

4.8.4. Tuberculosis

Bediang *et al., (2018)* showed that at five months there were 81% (n =226) treatment success in the intervention group versus 74 % (n =105) in the control group (OR = 1.45 [0.81, 2.56]; p=0.203). At six months there were 63 % (n =176) patients cured in the intervention group and 62 % (n =88) in the control group (OR = 1.06 [0.65, 1.73]; P=0.791). Very high and similar satisfaction was found for general management of patients in both groups: 99.5 % and 99.2 % (p=0.41)

4.9. Clinical and non-clinical outcomes

4.9.1. Impact of mobile phone application on clinical outcomes

Four of the studies illustrated the impact of mobile phone application on clinical outcomes, i.e., Bediang *et al*., (2018), Reid *et al*., (2017), Bobrow *et al.,* (2016) and Lester *et al*., (2010). Three of the studies showed a significant difference between the intervention group and control whilst one study (Reid *et al.,* (2017)) showed no significant difference in clinical outcomes between the control and the intervention groups.

4.9.2. Impact of mobile phone application on adherence based on non-clinical outcomes

Eleven studies i.e. Davey *et al.,* (2016), Kunutsor *et al*., (2010), Liu *et al*., (2016), Mbuagbaw (a) *et al.,* (2012), Mbuagbaw (b) *et al.,* (2012), Nsagha *et al*., (2016), Pop-Eleches *et al.,* (2011), Raifman *et al.,* (2014), Georgette *et al*., (2016) and Reid *et al.*,2017) measured the impact of adherence based on self-reports, pill counts and

prescription refills. Eight of the studies indicated an increase in adherence within the intervention group vs the control group and two of the studies (Steury, 2016; Mbuagbaw (a) *et al.* 2012) indicated no significant difference. One study (*Kunutsor et al.*, 2010), reporting on a pre- post- intervention showed that mean adherence before mobile phone intervention was lower than after implementation of the intervention.

4.10. Conclusion

This systematic review has demonstrated that implementation of an intervention tool to improve adherence to treatment delivered through mobile applications is essential and may have long-term positive effects. The studies presented were performed over a short and long-term basis (between four days and 17 months). Only two articles illustrated that there was no significant difference between the intervention and control group.

Three of the studies looked at the impact of long or extended text on adherence (Pop-Eleches *et al.,* (2011), Liu *et al*., (2016) and Bobrow *et al.,* (2016). The results showed that the group receiving expanded text messages were less likely to adhere to treatment. In addition, the groups receiving reminders more frequently i.e. daily reminder compared to weekly reminders were likely to experience treatment interruptions. These studies illustrated that extended educational messages in addition to standard of care had no impact on the overall medication taking behaviour. The simpler and shorter messages were established to be effective. Further studies in this area need to be explored to provide a more conclusive recommendation

A conclusion by Mbuagbaw (a) *et al.,* (2012) illustrated that multiple and different reminder methods are more likely to improve adherence than any single method alone. The studies that used a combination of multiple interventions like calls, SMS and an electronic pillbox showed mixed results between the intervention and the control groups. The study presented by Kunutsor *et al., (*2010) used multiple reminder methods i.e., voice calls and SMSes.

The results illustrated that adherence levels were significantly higher using mobile phone intervention compared to prior implementation of interventions. On the other hand, a study conducted by Steury (2016) using an SMS and an electronic pillbox

showed no significant association between interventions and pharmaco-adherence. Similar findings were observed in the literature review. Further research is required to establish which combination methods would be more effective and under which conditions methods would have an impact.

Within the African context, 100 % of the studies conducted used SMS as a tool for delivery of the interventions to assess the impact on adherence. However, in other regions such as the U.S.A and Asia, the primary mode of delivery of the interventions was smart phone applications. This might be because SMS is a basic feature in most mobile phones, the easiest to use and most affordable method of communication. Additionally, the cost of smart phones and affordability of the smart phones might contribute to the selection of SMS as a primary intervention of choice for most researchers. The selection criteria of the intervention tool needs to be justified by researchers in future studies.

Concerning the HIV trials, seven of the nine studies demonstrated a positive impact that mobile phone applications had on adherence. Only one study illustrated no significant difference between the intervention and the control group. Two (Reid *et al.,* 2017; Lester *et al.,* 2010) of the studies measured the effect of the intervention through clinical data. There was a significant difference in suppressed viral load between the intervention and the control group in both the studies. Four studies reported the impact of mobile phone applications based on self-reports and pill counts or appointments attended by patients.

Only one study examined the outcomes of mobile applications on TB treatment adherence. The study results illustrated that there was no significant difference in treatment success between the intervention and the control group. Additional studies need to be performed to evaluate the validity of using mobile phone applications to improve adherence and cure of tuberculosis.

Eight six percent (n =13) of the studies illustrated a significant improvement in adherence for the intervention group as compared to the control group based on one outcome measure. Thirteen percent (n =2) of the studies showed that there was no significant difference in adherence between the intervention group and the control group. One study, Mbuagbaw (a) *et al.* (2012) showed that at six months the mean number of pharmacy refills was not different between the intervention and the control

group (mean difference 0.1, 95 % CI= 0.25- 0.43; P=0.617), however, on sensitive analysis, the study illustrated that more participants on SMS group achieved adherence of more than ninety percent at six months (RR 1.14, 95 % CI= 1.01-1.29; P=0.027). Despite the study reporting that there was no significant difference observed, there was in fact a direct impact of the intervention on adherence. In addition, the long-term impact of the intervention were not established.

Three of the studies looked at the impact of long or extended text on adherence (Pop-Eleches *et al.,* (2011), Liu *et al.* (2016) and Bobrow *et al.* (2016). The results showed that the group receiving expanded text messages were less likely to adhere to treatment. In addition, the groups receiving reminders more frequently i.e. daily reminder compared to weekly reminders, were likely to experience treatment interruptions.

In conclusion, it is clear from both qualitative and quantitative literature review that there is potential to improve treatment adherence through use of mobile phone applications. A simple reminder SMS has been shown to significantly enhance treatment adherence. However, further studies need to be undertaken to provide concrete and conclusive evidence that long-term clinical benefits can be realized when these type of interventions are used to improve adherence.

CHAPTER 5: CONCLUSION AND RECOMMENDATIONS

The WHO (2003) reports that the consequences of poor adherence to long-term therapy include poor health outcomes and increased healthcare costs. The burden of poor adherence on the health status of the population and economy cannot be ignored any further. It is therefore imperative that interventions which improve the effectiveness of adherence are urgently developed and incorporated into policies within healthcare systems in Africa. By integrating these systems, the burden of the diseases on the healthcare system could be significantly reduced.

Mbuagbaw *et al.,* (2012) highlighted different factors associated with adherence including patient factors (substance abuse; gender; depression; socio-economic factors; levels of education), medication factors (dose frequency; pill burden; side effects), provider-related factors (poor patient-healthcare relationship), disease characteristics (symptoms; opportunistic infections) and clinical setting and health system factors (distinct separate clinics for different diseases may influence use of services). It is important that when designing interventions to mitigate poor adherence, that these factors are considered for a more appropriate and effective intervention.

In order for the implementation and scalability of the mobile phone applications to be successful, different stakeholders including policy makers, technologists, health care providers and the private sector need to contribute resources necessary to support such initiatives. Countries that rely on state funded systems should spearhead and support initiatives that seek to improve adherence of medication as this has a direct impact on the overall health of the population and eventually on the burden of disease on the economy.

It is interesting to note that a study (Reid *et al*., 2017) which measured the impact of mobile phone on adherence through clinical and pill counts had two different outcomes. Adherence measured through pharmacy pickup illustrated a significant difference between the intervention and the control group. However, there was no significant difference in the CD4 count between the intervention and the control group.

This study illustrates that trials should seek to illustrate through secondary outcomes i.e., clinical data, the direct impact of mobile phone applications targeted towards adherence.

Thirty three percent of the studies did not report any loss to follow-up. Lack of data pertaining to loss to follow-up results in potentially misleading results. The impact of the loss to follow-up in most cases was not assessed to provide assurance that the results presented were not overestimated. In addition, the papers published that reported on loss to follow-up lacked information on the definition of loss to follow-up. It is recommended that future studies consider reporting loss to follow-up and defining the context of loss to follow-up with respect to the study undertaken.

Cost effectiveness of mobile phone applications has not been extensively studied in Africa to provide policy makers a clear indication of the cost of these intervention. As such it is recommended that more research in this area is conducted to evaluate the economic impact to quantify the cost associated with mobile phone applications in enhancing adherence. Further research is required to establish whether multiple interventions would be more effective in improving adherence to treatment depending on the factors of non-adherence.

There were limitations in these reviews that should be taken into consideration in future studies, i.e. most of the reviewed studies included reported the impact of the interventions based on self-reports and refill of prescriptions, which assumes that patients took medications as prescribed. There were no further systems to validate this impact in the form of clinical assessments. Therefore, this assumption might not be a true reflection of the impact of the mobile phone applications to improve adherence. Furthermore, the study did not take into consideration the content of the mobile phone applications. Therefore, conclusions deducted herewith do not assess the extent of the information that should be contained in mobile phone applications to render the interventions effective.

The results of this review illustrated clearly evidence that text message reminders may improve significantly adherence to treatment of different diseases, particularly in

resource constraints countries. This kind of intervention can be used to improve adherence across wider populations within the African region. A mechanism that seeks to provide a panacea, such as in the case of SMS reminders at a low cost, would be easily adopted by many countries in Africa.

CHAPTER 6: BIBLIOGRAPHY

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