KWTRP

CLINICAL TRIAL PROTOCOL

Evaluation of a Mobile Messaging Service (Text and / or Graphic) in Improving Adherence with Ensured Supply of Anti-seizure Medications in People with Epilepsy in Kilifi and Nairobi, Kenya

1.0 GENERAL INFORMATION

Protocol Number:	**CSC 240**
Trial Registration Number:	**TBD**
Investigational Product(s):	**Short messaging service (text or graphic)**
Funder [name and address:	**National Institute for Health Research**
Tel:	**020 8843 8000**
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1.1 Confidentiality Statement

The information contained herein is privileged or confidential and may not be disclosed unless such disclosure is required by applicable laws or regulations. In any event, persons to whom the information is disclosed must be informed that the information is privileged or confidential and may not be further disclosed by them. These restrictions on disclosure will apply equally to all future information supplied to you, which is indicated as privileged or confidential. This confidentiality statement also applies to data generated during the study.

1.2 SPONSOR'S APPROVAL OF THE PROTOCOL

Evaluation of a Mobile Messaging Service (Text and / or Graphic) in Improving Adherence with Ensured Supply of Anti-seizure Medications in People with Epilepsy in Kilifi and Nairobi, Kenya

Protocol Number: 240

The following personnel has reviewed and approved this protocol [SMS trial], version number 1.4, dated 22nd October 2021.

Signature:	22/October/2021
[Prof Charles Newton, Senior Clinical Researcher at KWTRP and Oxford University]	Date

1.3 INVESTIGATOR'S APPROVAL OF THE PROTOCOL

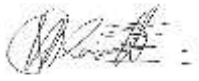
Evaluation of a Mobile Messaging Service (Text and / or Graphic) in Improving Adherence with Ensured Supply of Anti-seizure Medications in People with Epilepsy in Kilifi and Nairobi, Kenya

Protocol Number: CSC 240

The undersigned acknowledge possession of and have read the SMS trials protocol, version 1.4 dated 22/10/2021. Having fully considered all the information available, the undersigned consider that it is ethically justifiable to give short messaging service (text or graphic) reminders to selected participants according to the agreed protocol.

I understand that all information concerning the interventions supplied to me by [KEMRI-Wellcome Trust Research Programme (KWTRP)] - and/or its agents in connection with this study and not previously published is confidential information. This includes the Investigators' Brochure, Clinical Trial Protocol, Case Report Forms, and any other preclinical and clinical data provided by the KEMRI-Wellcome Trust Research Programme or University of Oxford.

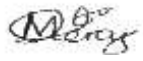
By my signature below, I hereby attest that I have read, understood, and agreed to abide by all the conditions, instructions and restrictions contained in SMS trial Protocol version 1.4 dated 22/10/2021 and in accordance with the most recent Declaration of Helsinki and Good Clinical Practice and all applicable regulatory requirements. I acknowledge that the Sponsor of the study, University of Oxford, has the right to discontinue the study at any time.



22 October 2021

Principal Investigator Signature **Date**

[Dr Symon Kariuki, postdoctoral scientist]



22 October 2021

Co-Investigator Signature **Date**

[Dr Mercy Atieno, Investigator]

Contents

1.4 PROTOCOL SYNOPSIS

Full Title	Evaluation of a Mobile Messaging Service (Text and / or Graphic) in Improving Adherence with Ensured Supply of Anti-seizure Medications in People with Epilepsy in Kilifi and Nairobi, Kenya
Short Title	SMS Trial
Trial Phase	Not Applicable
Objectives	Primary Objective: To examine the impact of sending text or graphic SMS reminders on anti-seizure medication (ASM) adherence people with epilepsy in Kilifi and Nairobi, Kenya Secondary Objectives: To describe the perceptions and perspectives of people with epilepsy (PWE) and their caregivers on the use of text and graphic SMS reminders to improve adherence to anti-seizure medications (ASMs) among PWE in Kilifi and Nairobi, Kenya To compare the effectiveness of text versus graphic messaging service in improving adherence in people with epilepsy in Kilifi and Nairobi, Kenya To identify the factors associated with improvement in adherence, improved quality of life (QoL) and reduction in stigma-associated suffering among PWE and family members. To document the common adverse drug reactions (ADRs) related to commonly prescribed ASMs and the plasma levels associated with these ADRs among PWE in Kilifi and Nairobi, Kenya To evaluate the cost-effectiveness of the interventions in each of the sites
Trial Design	Partially-blinded randomized controlled trial
Sample Size	1200 participants (900 participants in the intervention arm (300 receiving text SMS, 300 receiving graphic SMS, 300 receiving both text and graphic) and 300 in the control arm/receiving non-reminder messages) in each site
Study Population	We will include participants who fulfil the following criteria:

	i. children or adults with a diagnosis of epilepsy ascertained by a clinician at the epilepsy clinic, taking anti-seizure medications at the time of the study, ii. persons living within an area defined as the Kilifi Health Demographic Surveillance System (KHDSS) or the Nairobi Urban Health Demographic Surveillance System (NUHDSS) at the time of the study, or attending the epilepsy clinics in Kilifi or the Kenya Association for the Welfare of persons with Epilepsy (KAWE) clinics in Nairobi iii. persons able to give written informed consent or assent (for children 13-17 years old) iv. persons with access to a basic mobile phone in the household either through direct ownership, a caregiver or a member of the household nominated by the PWE
Intervention (s)	This will be a behavioural intervention with no investigational medicinal product. The intervention will be a mobile messaging service that sends short messaging service (SMS) as texts or graphics to people with epilepsy to remind them to take their medication and to refill their prescription and educational messages to share important messages tackling stigma and tips to improve quality of life We will also engage peripheral health facilities where PWE participating in the study go for ASM refills, in collaboration with the respective county departments of health, to maintain adequate supply of anti-seizure medications through: i. ongoing capacity building studies in Kilifi such as the mental health Gap Action Programme-Intervention Guide (mhGAP-IG) training which is empowering primary healthcare providers at peripheral health facilities to identify and manage epilepsy and other mental health disorders ii. supporting healthcare providers at peripheral facilities through in-person visits, if the COVID-19 situation, permits or by telephone or standard message reminders to restock their ASM supply The participants in the no-intervention group will receive “placebo” health messages not related to epilepsy such as use of bednets.

	The SMS reminders will be sent at a frequency that will be agreed upon during pre-study engagements with potential participants, whether daily, weekly, or monthly. The participants will be able to respond to these texts to report on their health status and any adverse events. To evaluate whether SMS reminders improve adherence, we will use: i. Self-reporting adherence scales- the Morisky Medication Adherence Scale (MMAS-8) ii. Measurement of ASM plasma levels at 3, 6 and 12 months from baseline.
Trial Duration	Each individual participant's participation will take 12 months. The trial itself will last up to three years to account for: i. different enrolment timepoints of participants ii. analyses, close out and dissemination of findings
Safety Evaluation	This trial doesn't involve administration of medicinal products. No adverse events are expected in relation to administration of message reminders. However, we will document any ASM-related adverse events as part of routine pharmacovigilance in the care of PWE.
Outcomes(s)	Primary outcome: Adherence to anti-seizure medications as measured by self-reports and validated by optimal and detectable levels in blood. Secondary outcomes: i. Correct intake of drugs and refill rates- measured by checking record logs for participants attending the study clinics ii. Changes in seizure frequency as assessed by trained clinicians at the study clinics iii. Changes in stigma scores and quality of life scores assessed using standardized scales

1.5 GLOSSARY OF TERMS AND ABBREVIATIONS

APHRC- Africa Population and Health Research Center

ASMs- Anti-seizure medications

DSMB- Data Safety and Monitoring Board

KEMRI-CGMRC- Kenya Medical Research Institute- Center for Geographic Medical Research, Coast

KHDSS- Kilifi Health Demographic Surveillance System

KEBAS- Kilifi Beliefs and Attitudes Scale

KAWE- Kenya Association for the Welfare of People with Epilepsy

LMICs- Low- and middle-income countries

LSM- Local safety monitor

MMAS-8- Morisky Medication Adherence Scale-8

MMS- Multimedia messaging service

NUHDSS- Nairobi Urban Health and Demographic Surveillance System

OxTREC- Oxford Tropical Research Ethics Committee

PWE- People with epilepsy

QoL- Quality of Life

SERU- Scientific Ethics Review Unit

SMS- Short messaging service

USSD- Unstructured Supplementary Service Data

WHOQOL-BREF- World Health Organization Quality of Life Scale

2.0 LAY SUMMARY

Formal Title: Evaluation of a Mobile Messaging Service (Text and / or Graphic) in Improving Adherence with Ensured Supply of Anti-seizure Medications for People with Epilepsy in Kilifi and Nairobi, Kenya

Lay Title: Use of mobile messaging service reminders to improve how people with epilepsy take their medications and how they have access to supplies of medications in Kilifi and Nairobi, Kenya

What is the problem/background?

Epilepsy is one of the most common conditions that affect the brain, and its impact is enormous, particularly in countries from sub-Saharan Africa (SSA). Many studies focus on the epilepsy treatment gap, which commonly defined as the number of people with epilepsy (PWE) who should be on treatment, often leaving out the people with epilepsy in the community who have never been formally diagnosed (diagnostic gap) and those who do not take their medication correctly (adherence gap). Good outcomes in people with epilepsy rely on an uninterrupted supply of medication and on them taking their medication correctly. In Kilifi County, more than 70% of people with epilepsy are either not on treatment (have never been diagnosed) or do not take their medication correctly due to a variety of reasons, an important one being forgetfulness. In addition, lack of a constant supply of medication and distance to health facilities also contributes to the number of people with epilepsy who receive inadequate care. In Nairobi County, the prevalence of epilepsy, especially in slum dwellings is largely unknown and subsequently data on the adherence gap is also unavailable Text and/or graphic messages sent to mobile phones of people with epilepsy, or their caregivers may be useful in reminding people with epilepsy to take their medications as required and reminding healthcare providers to restock antiseizure medications.

What questions are we trying to answer?

In this study, we plan to test the use of short message service (SMS) reminders sent to remind people with epilepsy to take their medication as prescribed and to engage the Kilifi and Nairobi County Departments of Health to ensure a continuous supply of medications used to manage epilepsy. A previous audit at the epilepsy clinic in Kilifi showed that about 90% of people with epilepsy, either through direct ownership or via a caregiver or a member of the household, have access to basic mobile phones that can receive unique text or graphic messages. After rolling out the SMS reminders, we will compare the different modes of messaging (graphic versus text) to find out which is more acceptable and successful in our local setting.

Where is the study taking place, how many people does it involve and how are they selected?

This study will take place in Kilifi and Nairobi Counties, within two defined areas known as the Kilifi Health and Demographic Surveillance System (KHDSS) and the Nairobi Urban Health and Demographic Surveillance System (NUHDSS). In Nairobi, we will also conduct the study within clinics led by the Kenya Association for the Welfare of People with Epilepsy (KAWE). Before the roll out of the intervention, we will hold about 3 pre-study focus group discussion with about 10 PWE and one of their family members each about the preferred nature of SMS reminders and the timing and frequency. We plan to include 1,200 people with epilepsy (PWE) from each site. In Kilifi, PWE will be randomly selected from a large database of patients attending the Neuroscience epilepsy clinic, of whom majority were identified from previous large-scale community surveys within the KHDSS. In Nairobi, PWE will be randomly selected from those identified through a survey conducted by the African Population and Health Research Center (APHRC) within the NUHDSS and patients attending KAWE-led clinics. At each site, we will randomly divide the participants into four groups of 300 people with epilepsy, to receive either text SMS, graphic SMS, both text and graphic or no intervention/non-reminder SMS (for comparison). Participants will be screened for eligibility by the attending epilepsy clinicians and referred to the field assistant for consenting and/or assenting and recruitment into the study.

What does the study involve for those who are in it?

We will send out reminders to some participants either as a text, a picture, or both a text and a picture to remind them to take their medication. In addition, we will also engage staff at peripheral health facilities where the PWE go for medication refills through ongoing capacity building of all healthcare providers in public health facilities in Kilifi County on management of epilepsy and direct engagement of the respective county Departments of Health to ensure sustained supply and availability of drugs for managing epilepsy. We will ask participants questions regarding how they take their medications, their quality of life and stigmatising experiences before and after they have received message reminders. These sessions will take about 3 hours, including breaks and time spent for clarification and obtaining samples. All study activities will take place at KWTRP in Kilifi and APHRC in Nairobi. Messages will be sent throughout the 12 months for each individual participant and assessment of adherence, quality of life and stigma will be done at the first visit and subsequent follow up visits at 3, 6 and 12 months into the study. To confirm self-reported adherence, we will also collect blood

samples of not more than 5 ml from participants and compare the concentration of antiseizure medications before and after they have received message reminders. Blood samples will be collected at the clinics during the first visit and subsequent follow up visits. All the samples will be stored at KWTRP Main Laboratory and analyses will be conducted at the end of the study at the CREATES Laboratory (https://creates.strathmore.edu/) hosted by Strathmore University. Clinicians attending to PWE in the study will continue to advice all participants on the need for adhering to their medication for good outcomes as part of routine care.

What are the benefits and risks/costs of the study for those involved?

Benefits:

If message reminders are found to be useful, they will help in improving adherence outcomes and quality of life among people with epilepsy while reducing misperceptions about epilepsy and stigma experienced by these people.

Risks:

Message reminders sent on mobile phones of people with epilepsy, or their caregivers may be accessed by other people, thereby, posing a risk of invasion of privacy. In addition, blood draws may be uncomfortable for participants resulting in pain, local swelling, itching, or redness, which gets better after a short while. The questionnaires administered before and after receiving message reminders together with blood draws may take up to 3 hours to administer, including breaks and time taken for clarifications. Therefore, participants will be compensated for out-of-pocket expenses (KES 350), provided with meals or a standard amount of KES 200, in line with the current COVID-19 regulations and reimbursed fare in Kilifi while in Nairobi, APHRC will reimburse participants a flat rate of KSH 1000 to include transport, lunch and out of pocket allowance.

How will the study benefit society?

The community may potentially benefit through improved adherence to medication and quality of life for people with epilepsy and their caregivers. Results from this study may benefit the community by helping health administrators and policy makers in Kilifi and Nairobi and other similar settings optimize care for PWE e.g., improve drug supply for persons with seizures and associated illnesses**.** This intervention along with ensuring adequate

supply of medications may also be applicable for self-management of other chronic conditions in resource-limited settings.

When does the study start and finish?

The study will start as soon as ethics and scientific approvals are granted and will initially run for three years, with possibilities of continuing renewals for subsequent follow-ups.

3.0 LIST OF INVESTIGATORS AND COLLABORATORS

Investigators

Investigators	Institution	Role
Dr Symon Kariuki	KEMRI-CGMRC	Principal investigator
Dr Mercy Atieno	KEMRI-CGMRC	Investigator
Mr. Gilbert Katana	KEMRI-CGMRC	Investigator
Ms Maria Mumbo	KEMRI-CGMRC	Investigator
Mr. Collins Kipkoech	KEMRI-CGMRC	Investigator
Ms Mary Bitta	KEMRI-CGMRC	Investigator
Dr Gershim Asiki	APHRC	Investigator
Dr Damazo Kadengye	APHRC	Investigator
Dr Fredrick Wekesah	APHRC	Investigator
Mr Peter Otieno	APHRC	Investigator
Prof Sloane Mahone	University of Oxford	Investigator
Prof. Arjune Sen	University of Oxford	Investigator
Prof Charles Newton	KEMRI-CGMRC	Co-principal investigator

Collaborators

Collaborators	Institution	Role
Dr Haji Musuko and Dr Nadia Aliyan	Kilifi County	Collaborators
Mr Peter Otieno	Nairobi County	Collaborators

4.0 ABSTRACT

Improved outcomes for epilepsy treatment depend on a continuous supply and daily adherence to antiseizure medications (ASMs). In Kilifi County, the treatment gap which includes both the diagnostic and adherence gap, is greater than 70% and we have found interruption of supply of ASMs to peripheral clinics, distance from clinic and lack of availability of ASMs, to be barriers to adherence. In Nairobi County, factors such as environment hazards, lack of social amenities and correlates of poverty are preponderant in slums, but the prevalence of epilepsy has not been studied in such settings and consequently, the adherence gap remains unknown. Innovative mobile Health (mHealth) strategies including messages delivered by mobile phones have been used to ensure an adequate supply of drugs in health centres, and daily mobile messages have improved adherence to medication in Human Immunodeficiency Virus (HIV) programs, for example. Text messaging requires that the patient has access to a mobile phone and can understand the text message. Multimedia messaging, such as simple pictures, may improve understanding of the necessity to take medication, particularly in people who are illiterate, and we will explore this as an avenue to improve uptake.

We plan to randomize 1200 people with epilepsy at each site, from a defined area in Kilifi and Nairobi County, Kenya. They will be divided into four groups of 300 each, to receive either text SMS, graphic SMS, both text and graphic or SMS on public health promotion not related to epilepsy e.g. use of bednets (for comparison). Our aim is to i) describe the perceptions and perspectives of people with epilepsy and their caregivers on the use of text and graphic SMS reminders to improve adherence to ASMs, ii) compare the effectiveness of text versus graphic messaging service in improving adherence in people with epilepsy and to engage the County Departments of Health through current ongoing training and capacity building studies to maintain supply of ASMs in peripheral clinics iii) identify the factors associated with improvement in adherence, improved QoL and reduction in stigma among PWE and family members and iv) conduct cost-effectiveness assessment for the roll out of the intervention. Besides medication-related messages, there will be other messages, from previous community-based feedback, selected to address stigmatization and improve quality of life. Blood-level monitoring and adherence questionnaires at baseline and during subsequent follow up visits will be used to assess as measures of medication adherence. If

found useful, this intervention may be applicable for self-managing other chronic conditions in under-resourced settings.

5.0 INTRODUCTION

5.1 Background Information

Epilepsy is one of the most common neurological conditions worldwide with a higher prevalence in low- and middle-income countries (LMIC) and rural communities. In Africa, the burden of the disorder can be ascribed to central nervous system infections and adverse perinatal events (e.g., hypoxic ischaemic encephalopathy). Poor adherence to prescribed medication is considered to be the main cause of unsuccessful drug treatment for epilepsy, increased hospitalization, diminished quality of life (QoL), and a threefold increase in mortality risk (Tang et al., 2013). These factors widen the treatment gap which includes both the diagnostic gap (people with epilepsy who are undiagnosed) and the adherence gap (people with epilepsy who are not on treatment, or whose treatment is inadequate). Not dissimilar to the findings of other resource-poor areas, the epilepsy treatment gap in Kenya is about 60% and ranges from 60 to 90% throughout Africa (Mbuba et al., 2012; Meyer et al., 2010). Adherence to medication (80% rate of total pills taken, medication possession ratio, and days covered by prescriptions filled) (Faught, 2012) is influenced by: (i) patient-related factors, i.e. forgetfulness, stigmatization which is influenced by cultural, socioeconomic, educational and religious affiliation (Fernandes et al., 2007) and being seizure free for a period of time (Tang et al., 2013); (ii) medication-related factors, e.g. cost, side-effects, number of medications prescribed and dosing frequency; (iii) disease-related factors including seizure type, severity, associated risk factors, comorbidity of psychiatric conditions; onset and duration of illness (Sweileh et al., 2011).

In predominantly rural Africa, poor adherence to anti-seizure medications (ASMs) is made worse by the expense of accessing treatment. The medication is the least costly component, compared to the long distances to health facilities (Berhanu et al., 2009), coupled with the financial implications of this; and the influence of cultural beliefs (Mbuba et al., 2012), which compound the challenges relating to adherence or compliance.

A multisite study in Africa showed that the burden of epilepsy in many rural parts of Africa is greater than elsewhere across the globe (Ibinda et al., 2017b). Recent pilot studies in Kilifi of epilepsy (both with convulsive and non-convulsive seizures) revealed a hidden burden of non-convulsive seizures (Kariuki et al., 2021), further widening the treatment gap for these people.

The pooled adherence treatment gap in Kilifi as measured by optimal drug levels has been reported as 79.1% (95% CI; 73.3 to 84.3%), with adherence based on blood levels being more reliable than self-reports using a locally validated and adapted Morisky Medication Adherence Scale (MMAS-8) (Ibinda et al., 2017b). An educational intervention in Kilifi, Kenya resulted in improved adherence in both arms (36% to 85% in cases and 38% to 74% in controls) probably due to sharing of learned information among participants or study staff offering psychosocial counselling to both groups (Ibinda et al., 2014). However, this intervention was costly to sustain and may not improve nonadherence due to forgetfulness associated with epilepsy-related intellectual disability (Mwangala et al., 2018).

Poor compliance has been identified in scientific studies as affecting the concentrations of these medications in blood. These varying concentrations in blood can then affect how a person responds to treatment or whether they experience drug-related side effects including symptoms of psychosis (Chen et al., 2012), weak bones (Zhang et al., 2020) or enlarged gums (Silvado et al., 2018). Other people with epilepsy may also fail to take their medications correctly because of side effects caused by their medications which may discourage compliance. Therefore, we can plan to document drug-related toxicities as reported by patients and in relation to plasma ASM levels.

People are increasingly migrating towards larger cities such as Nairobi, where the disease burden is yet to be determined or compared with the burden in rural areas. Factors such as environmental hazards, lack of social amenities and correlates of poverty are preponderant in slums (Kyobutungi et al., 2008), and can cause substantial disease burden (Kimani-Murage et al., 2015). Lead toxicity from industrial emissions and housing materials in informal settlements in Nairobi may also cause brain damage (Sanders et al., 2009) that can manifest as epilepsy. Data is urgently needed on the epilepsy treatment gap (both the diagnostic and adherence gap) in urban settings such as Nairobi and innovative interventions put in place to improve ASM compliance and adherence.

The Kenya Association for the Welfare of people with Epilepsy (KAWE) is well-established (http://www.kawe-kenya.org/) and is affiliated to IBE. They have initiated many schemes for PWE including advocating for the registration of PWE with the National Council for People with Disabilities, and thus allowing PWE access to support for primary, secondary, and tertiary education, cash transfers for those with more than one form of disability, inter alia.

A study assessing community-level interventions from China (Wang et al., 2008) and the group-orientated Modular Service Package Epilepsy program (MOSES) study in Austria, Switzerland and Germany (May and Pfäfflin, 2002; Ried et al., 2001), illustrated how education helped to improve the understanding of epilepsy and the long-term implications if the disorder went untreated among people with epilepsy. These studies highlight that epilepsy education may only be effective as an intervention to improve adherence if it is continuous. Key information identified by the studies were: information about the symptoms and causes of epilepsy, advice about safety, advice about support within a social and cultural context that address stigma, and, for the service providers, further advice about the treatment. To be effective, interventions should build upon local existing practices, identify, and target the most receptive community members, bolster local skills and priorities, recognize constraints (time, financial, cognitive, and social) on sustained commitment and feature community engagement (Panter-Brick et al., 2006).

Patient-related behaviours, such as irregular medication-taking or dose self-titration are major factors contributing to poor adherence. The consequences of self-management of ASMs may not appear instantly which may induce complacency (Faught, 2012). If a person with epilepsy (PWE) relies on family to help with ASM administration, and the support is misinformed, this can exacerbate the problem. A lack of understanding, made worse by forgetting, could be addressed through more personalized interventions to remind PWE to take their medication, or renew prescriptions. Mobile phone messaging is a potentially powerful tool for behaviour change because it is widely available, inexpensive, and instant (Cole-Lewis and Kershaw, 2010).

Mobile phone health (mHealth) messaging studies that have been conducted predominantly in high-income countries have focused mainly on smoking cessation (Free et al., 2011), self-monitoring of diabetes (Vervloet et al., 2012), and asthma (Strandbygaard et al., 2010). Many of these have involved a small number of participants (<100) and for short periods of time (<6m). The focus of these studies has been on the logistics of sending and receiving text messages to raise awareness; for collecting health behaviour data (Kerr et al., 2012), or to assess the cost efficacy of preventive health care (Marshall et al., 2013), rather than collating high-quality evidence of behaviour change or reduction in health service utilisation (de Jongh et al., 2012).

In LMICs, several studies have considered the effectiveness of text messaging (SMS) interventions to improve health workers' practices (Kallander et al, 2013; Zurovac et al, 2011), as a learning tool, and to improve adherence to medications and care, particularly antiretroviral drugs (de Tolly et al., 2012). To inform policy makers about the feasibility of facility-based SMS messaging interventions, coverage data on mobile phone ownership and SMS use among health workers and patients are needed. More studies are also needed to ascertain the usefulness and potential negative consequences of mobile phone messaging, both SMS and graphic / picture messaging (multimedia messaging service (MMS)), over extended periods of use for self-managing chronic conditions (de Tolly et al., 2012).
It has been estimated that over two-thirds of the population in Africa is covered by a mobile network with a penetration rate of 93%, reaching just under a billion mobile phone subscribers across the continent https://data.gsmaintelligence.com/api-web/v2/research-file-download?id=18809326&file=the-mobile-economy-sub-saharan-africa-2015-infographic-1482139932154.pdf . In 2009, in collaboration with the Kenyan National Bureau of Statistics, the Financial Sector Deepening Kenya survey asked questions about mobile phone usage, ownership, and monthly expenditure on airtime, as well as detailed demographic questions concerning income, education level and housing type (32,748 individuals located at 646 communities: http://www.fsdkenya.org). Based on three cluster surveys, 85% of the population reported using a mobile phone. In rural areas, mean phone ownership was 39% (90% range: 14%–43%) compared to urban regions where it was 58% (90% range: 65%–80%). Ownership was determined by education level rather than gender in urban areas, whereas in the rural areas and among poor urban communities, 20% owned their own phone, while most households shared a mobile phone, and usage was higher among men. InfoDev's findings from a survey of 6 districts in Kenya found no notable gender difference in mobile phone activities, but this did not translate into an absence of a gender disparity in mobile phone ownership (http://www.infodev.org/articles/mobile-usage-base-pyramid-kenya). Both phone owners and phone sharers reported similar monthly expenditure on mobile phones and, surprisingly, both groups spent approximately the same proportion of their income on airtime (13% and 10%, respectively) (Wesolowski et al., 2012). Another finding from both surveys was the deliberate sacrificing of food or bus fare to pay for airtime, in the belief that a call may lead to work. In addition, an audit of mobile phone ownership and usage assessment conducted at the epilepsy clinic in Kilifi in 2013 showed that, of the 222 PWE interviewed,

19% (44/222) owned a mobile phone, and 85% (189/222) could access mobile phones through close caregivers living with them. In Nairobi, the phone ownership rates are likely to be even much higher, considering this is an urban area and the capital city of the Country but PWE may be disadvantaged due to their medical condition leading to other psychosocial consequences such as lack of employment and poor marriage prospects.
This rapid assimilation of mobile phone technology within Africa makes it culturally compelling to help reduce the treatment gap of one of the most common neurological conditions worldwide (Panter-Brick et al., 2006). To our knowledge, no studies have used mobile phone messaging to improve adherence to ASMs and address stigma. The application of text messaging for behavioural change for mental and neurological disorders is at an early stage of research. Randomised controlled trials of such use of text (SMS) or picture (MMS) messaging, and / or with an auditory component are scarce, with few from semi-literate low-resource settings. There are few reported trials on antiretroviral treatment adherence from Kenya (van der Kop et al., 2018) and from India (De Costa et al., 2010). There is also a paucity of studies that assess community-based adherence interventions alongside improved supply of ASMs to health care centres in rural areas to bridge the adherence treatment gap.

5.2 Name and description of the investigational product(s),

An intervention that utilises a mobile messaging service could serve to remind patients with epilepsy (PWE) to take their medication. This has not been undertaken before and is now feasible because of greater mobile network coverage in rural areas in Kenya and increasing mobile phone ownership and usage in these areas. Use of SMS is more widespread in antiretroviral and antimalarial adherence studies in Africa and has shown great promise in improving adherence to medication and consequently, outcomes. This study will further test the evidence to support the use of graphics in impoverished semi-literate communities such as the study sites to convey health-related messages. These multi-media messages will be designed in a simple format that is compatible with both basic phones and smart phones. However, since the display characteristics of basic phones and smart phones may differ, we will document the type of phone used by the participant and this will be taken into consideration during the analyses and interpretation of findings. It is unclear whether either one of these interventions will improve adherence in a rural population or informal settlements with high rates of illiteracy.

A two-way SMS platform will be implemented such that PWE participating in the study will be able to receive messages from the study team and send messages to the study team via normal text or using an unstructured supplementary service data (USSD) prompt at no cost to the PWE. The SMS platform will also be able to send delivery reports to the study team if the message is delivered to the intended user and a read report once the message is opened by the intended user. During planned follow up visits, we will also check for any issues regarding receiving messages, disruptions in the network service provider or electricity, change of phone number, change of handsets and whether caregivers relay messages to the PWE in the case that they are the ones receiving the SMS on behalf of the PWE. Those who do not relay messages will be encouraged to do so and changes in phone numbers will be updated. Since this is meant to be a pragmatic trial that can be rolled out in a sustainable fashion throughout resource-poor settings, challenges are to be expected and will be taken into consideration when interpreting the findings.

5.3 Justification

Epilepsy is one of the most common neurological conditions in Africa where it is associated with a great degree of stigma. Most people with epilepsy in this setting do not seek biomedical treatment and only a small proportion of those on treatment take their medication correctly. In fact, the precise magnitude of the epilepsy treatment gap (both the diagnostic and adherence gap) as measured from blood is unknown in urban settings such as Nairobi, where data is urgently needed. Poor adherence and denial of the disorder serve to widen the treatment gap and is associated with impaired quality of life (QoL) and premature mortality. These detrimental consequences can be prevented by improving daily adherence to therapeutic doses of anti-seizure medications (ASMs).

An intervention that utilises a mobile messaging service could remind PWE to take their medication, leveraging on recent increase in mobile phone access over the past 20 years and proven benefit of mobile technology in improving drug adherence for other diseases. The service can also be used to monitor the supply of ASMs to peripheral health facilities. Current on-going studies in the Epilepsy Pathway Innovations in Africa (EPInA) studies in Kilifi and Nairobi are aimed at engaging the county department of health to ensure collaboration in improving care for people with epilepsy. As part of the EPInA studies, we plan to train

primary healthcare workers (PHWs) on diagnosis and management of epilepsy and other mental and neurological disorders using the World Health Organisation's mental health Gap Action Programme-Intervention Guide (mhGAP-IG). These PHWs will be selected from public health facilities in both Kilifi, and Nairobi and these capacity building activities will offer a platform for lobbying for consistent supply of ASMs in the peripheral health facilities. SMS platforms have also been used to set up SMS-based stocktaking forms to monitor supply and reordering of antiretroviral medication to health clinics and this is yet to be explored for ASM supply.

Both text (SMS) and picture messaging (MMS) demonstrate strong potential as tools for healthcare improvement for several reasons: these are accessible on almost every model of mobile phone even basic phones; the cost of transmission is relatively low; neither require great technological expertise, and the transmission of brief health-related messages are widely applicable to a variety of health behaviours and conditions. However, since reading text messages requires some level of literacy, we will compare texts versus graphic messages and the impact on ASM adherence. The messaging service also has the advantage of being asynchronous because it can be accessed at any time that is personally convenient. Use of SMS is more widespread in antiretroviral and antimalarial adherence studies in Africa. This study will further test the evidence to support the use of graphics in impoverished semi-literate communities to convey health-related messages. Improved adherence may subsequently improve quality of life among people with epilepsy, reduce accidental injuries, psychiatric comorbidities, and premature mortality. Nevertheless, it is unclear whether either one of these interventions will improve adherence in a rural population with high rates of illiteracy.

6. TRIAL OBJECTIVES AND PURPOSE

6.1 Null hypothesis

Utilising mobile messaging service to send reminders to people with epilepsy to take anti-seizure medications is not associated with a difference in adherence to anti-seizure medications as measured by detectable and optimal drug levels in blood.

6.2 Primary objective

To examine the effect of sending text or graphic SMS reminders among people with epilepsy in Kilifi and Nairobi, Kenya using a randomized controlled trial design on:

i. ASM adherence
ii. Quality of life
iii. Epilepsy-related stigma scores

6.3 Secondary objective(s)

(i) Using qualitative methods, to describe the perceptions and perspectives of PWE and their caregivers on the use of text and graphic SMS reminders to improve adherence to ASMs among PWE in Kilifi and Nairobi, Kenya
(ii) To compare the effectiveness of text versus graphic messaging service or both in improving adherence among people with epilepsy in Kilifi and Nairobi, Kenya
(iii) To identify the factors associated with an improvement in adherence and improved QoL among PWE and reduction in stigma among PWE and their family members.
(iv) To document the adverse drug reactions (ADRs) including neurologic and psychiatric ADRs related to frequently prescribed ASMs types and, where possible, plasma levels among PWE in Kilifi and Nairobi, Kenya
(v) To conduct cost-effectiveness analysis of rolling out the interventions among PWE in Kilifi and Nairobi, Kenya

7.0 TRIAL DESIGN

7.1 Overall Study Design

This study will follow a single-blinded randomized controlled trial design. Participants will be randomly selected from a database of over 3500 PWE. The selected participants will be invited to the clinic for screening against the eligibility criteria and enrolment into the study. The study sample will consist of 1,200 people with epilepsy in each site. Out of the 1200 PWE, there will be 900 participants in the intervention arm (300 receiving text SMS, 300 receiving graphic SMS, 300 receiving both text and graphic) and 300 in the control arm (non-epilepsy related SMS) (Figure 1). The participants will be aware of the intervention status, but the researcher and clinical staff will not. All participants will receive an SMS (cases to

encourage adherence and controls will receive non-epilepsy related messages) for comparability and to reduce the risk of disclosing the blind during follow up visits. Participants will be encouraged to not disclose the content of their messages during follow up visits. As a secondary outcome, ASM-related ADRs including neurological and psychiatric ADRs, will be documented for all participants on ASMs, and where possible, related to type (s) of ASM used.

7.2 Description of the study areas and population

This study is part of the EPInA studies planned in Kilifi and Nairobi. In Kilifi, the SMS trial will take place within the Kilifi Health and Demographic Surveillance System (KHDSS). The KHDSS was established in 2000, covers a defined geographical area of 900km2 located on the Kenyan coast and currently has a population of about 280,000 residents under active surveillance https://kemri-wellcome.org/programme/health-research-linked-to-a-demographic-surveillance-system/. We will approach people with epilepsy currently taking ASMs from a database of over 3,500 patients attending the epilepsy clinic routinely. Written consent and/or assent (for children aged 13 to 17 years old) will be obtained from all participants and the study will be conducted with permission from a local ethics review committee.

In Nairobi County, we are collaborating with APHRC, through their Nairobi Urban Health and Demographic Surveillance System (NUHDSS). The NUHDSS is in Nairobi city comprising two slum communities namely Korogocho and Viwandani, both with a total population of about 65,000 (Beguy et al., 2015). All houses are marked with unique identification numbers making it possible to obtain vital information on not only sociodemographic patterns but also pregnancy outcomes and movement in and out of NUHDSS. Children and adolescents comprise 35% of the total population. In 2012, the crude birth-rate was 28.9/1000 person-years, while mortality rate was 6.2/1,000 person-years. The NUHDSS offers an opportunity to conduct studies investigating the link between urbanisation, poverty, or lack of social amenities on health outcomes (Kimani-Murage et al., 2015). Additionally, participants attending one KAWE-led clinic in Nairobi will also be invited to participate in the study.

8.0 DESCRIPTION OF THE INTERVENTION

8.1 Intervention

The intervention will be a short message service (SMS) reminder sent to the mobile phones of participants in the intervention group reminding them to take their anti-seizure medications. This will be a behavioural intervention with no investigational medicinal product. Each SMS (text or graphic or both) adherence message will be 120–140 characters long. To increase the probability that that the PWE or family member will read the messages and support family members with epilepsy, message will be randomly complemented with a quote (up to 60 characters long) and unrelated to epilepsy treatment, but designed to be motivating, entertaining, or merely attention-getting. This motivational element was used with success in the health workers adherence to antimalarial guideline studies. The graphics will be hand drawn by a local illustrator and the accompanying text of no more than 15 characters will be scanned and sent as low-resolution jpeg files, suitable for the MMS format that is compatible with basic phones.

8.2 Identity of the SMS

We will use a validated software for the automated bulk SMS service and outsourced tool for the MMS transmission. The SMS company contracted will assist in the setting up and training of the software, plus on-going support. The SMS interface/platform will utilize an android application system for smartphones and Unstructured Supplementary Service Data (USSD) format for basic phones and will be accessible from a web browser and will be integrated into an encrypted central database. All requests and administrative actions made to the program and its responses will be logged chronologically and stored in the database.

8.3 Frequency and timing of sending messages

The messages will be transmitted at a frequency and time, determined during focus group discussions held before the roll-out of the intervention, that is convenient for both the PWE and their caregivers.

8.4 SMS dispensing procedures

Automated reminder messages will be sent out by the KEMRI-Wellcome Trust Research Programme data manager and from a password-protected computer within the Neuroscience Unit in Kilifi. These will be sent as mobile phone texts (SMS) or graphic picture messages (MMS).

8.5 Intervention Compliance

It will be possible to view a delivery report of whether the messages were received or not due to network issues. After the screening visit, all participants will be contacted via phone call to check that their phones can receive the messages. Prior to the commencement of the SMS trial, ongoing EPInA studies will conduct engagements with the respective county departments of health on sustained availability of ASM at the health facilities within the study area where PWE are likely to visit for medication refill. Primarily PWE will visit the study clinics (epilepsy clinic in Kilifi, two APHRC clinics in Nairobi and one KAWE-led clinic in Nairobi). However, due to ongoing capacity building and task sharing studies in Kilifi (the mhGAP study), some PWE may visit any of the 128 public peripheral health facilities already contributing primary health care providers for training. Since adherence may also be affected by availability of medications, we hope to be able to lobby for the set-up of an SMS platform to monitor supply and re-ordering of ASMs in Kilifi and Nairobi County in addition to ongoing engagements with the counties as part of capacity building and task sharing within the EPInA studies.

9.0 STUDY PLAN DESCRIPTION

9.1 Pre-study focus group discussions

We will hold about 3 pre-study focus group discussions. During these FDGs, participants will propose the timing and frequency of the messages during pre-study focused group discussions (FGDs). Perceptions of PWE on use of mobile phone text messages to improve adherence will also be evaluated during the three pre-study FGDs before the roll out of the study. These will involve about 10 PWE and one of their family members in each group. The aim of these FGDs will be to inform the preferred timing and frequency of the messages to be sent out during the study. We will also review the nature of the messages and how best to relay sensitive information, especially for shared phones. Finally, we will establish the content of public health promotional messages (not related to epilepsy adherence) such as use of bednets and the types of messages controls would want to receive. These discussions will be recorded. The audio records will be stored in cabinets under lock and key and destroyed upon transcription. Paper transcriptions will be stored under lock and key until all have been electronically replicated and validated.

9.2 Roll out of the SMS trial

9.2.1 Identification of Participants

Participants will be identified from the epilepsy clinic in Kilifi and three clinics in Nairobi (two APHRC clinics in Korogocho and Viwandani, respectively and one KAWE-led clinic). These PWE will have utilized the clinics more than once and live within either the KHDSS for participants in Kilifi or the NUHDSS for participants in Nairobi. The epilepsy clinic in Kilifi has a database (built under an approved protocol: KEMRI/SERU/CGMR-C/125/3701) that has over 3,500 patients to date, who have accumulated from 30 patient visits a day, 10 of whom are usually new. They will be approached by the study clinician during their routine clinic visit. In Nairobi, participants will be identified from an on-going survey which is part of the EPInA studies. This survey is being conducted by APHRC to identify people with a likely diagnosis of epilepsy living in informal settlements in Korogocho and Viwandani. The diagnosis is confirmed by trained clinicians at two APHRC clinics conveniently located within the study areas. The identified PWE will be added to an epilepsy database from which participants for this study will be identified. Additional PWE will be identified from one KAWE-led clinic in Nairobi.

In Kilifi, record logs usually taken during routine care will be reviewed from the database of those attending the epilepsy clinic and then those at Kilifi County Hospital. In Nairobi, records from participants identified during an on-going epilepsy survey in two slum dwellings conducted by APRHC and records from patients attending KAWE-led clinics will be screened for eligibility.

9.2.2 Eligibility criteria

9.2.2.1 Inclusion criteria

(i) Children or adults with a diagnosis of epilepsy ascertained by a clinician at the epilepsy clinic

(ii) Taking anti-seizure medications at the time of the study

(iii) Living within an area defined as the Kilifi Health Demographic Surveillance System, or the Nairobi Urban Health and Demographic Surveillance System at the time of the study or attending the epilepsy clinic in Kilifi or a KAWE-led clinic in Nairobi

(iv) Able to give written informed consent or assent in addition to parental consent (if aged between 13 and 17 years old) to participate in the study either by themselves or in the presence of an independent witness

(v) Access to a basic mobile phone in the household

9.2.2.2 Exclusion criteria

Participants who meet all the inclusion criteria above will not be eligible for inclusion in the study if they:

i. have intellectual disability
ii. do not have access to basic mobile phones
iii. are currently enrolled in ongoing interventions aimed at improving their health care

9.2.3 Consenting/Assenting and screening for eligibility

Consenting and/or assenting (for children aged 13 to 17 years old) will be done by field workers during initial contact and participants booked for the first study visit. Investigators will emphasize that participation in the study is voluntary. All participants will have the study explained to them including potential risks and obligations before giving written informed consent and/or assent. Once consented and/or assented, participants will be screened for eligibility based on the above-mentioned set of inclusion and exclusion criteria. Screening will be conducted by study fieldworkers in collaboration with the study clinicians. Participants who meet the inclusion criteria at the screening visit will be telephoned by a fieldworker a week prior to sending out the SMS to assess availability of mobile phone access. They will also be asked about any new medical complaints and concomitant medication since their screening visit.

9.2.4 Recruitment and enrolment

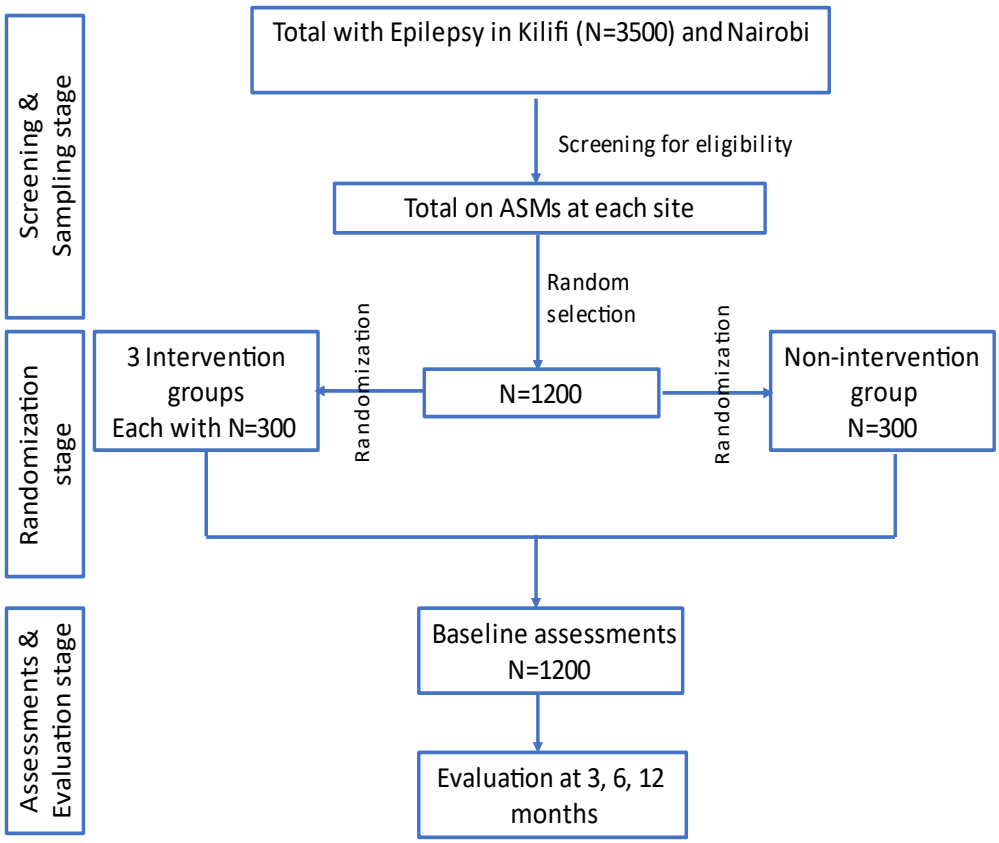
Only participants who are eligible for recruitment and willing to participate in the study through written informed consent/and or assent (for children aged 13 to 17 years old) will be recruited into the study. We plan to recruit a total of 1200 participants for the SMS trial from each site. All screened people with epilepsy will be informed of the inclusion criteria and their eligibility for enrolment. Eligible participants who give consent/and or assent will then be invited for the initial study visit for enrolment into the study and baseline assessments

9.2.5. Randomisation

Participants will be randomized to four groups, with randomisation assigned via a computer-generated sequence by an independent statistician. The database manager will not know details of those SMS are being dispensed to. An allocation ratio of 1:1:1:1 across the 4 arms

will be used. A random sampling technique using computer-generated sequences will be used to ensure epilepsy factors such as focal features, age and gender are balanced between the intervention groups or arms. The SMS randomisation platform will be linked to a central database that stores a pre-generated randomization sequence, which will be generated once at the beginning of the study. Each participant will be randomized once, failure to which the system will alert the data manager and decline the request. The data manager will use an automated system to send out the messages and they will be blinded to participant details. In addition, to prevent cross-contamination due to exchange of information among participants, we will emphasise the need to keep allocation among confidential the participants and schedule follow up visits for participants in different arms on different days. However, cross-contamination may still occur in the community, and this will be considered during interpretation of the findings.

Figure 1. Recruitment strategy and randomization



*All people with epilepsy in the databases will be screened for eligibility

9.2.6. Procedures

(i) Clinical evaluation, assessment of stigma scores and measures of quality of life

During the baseline visit, information regarding epilepsy factors including seizure semiology, electroencephalography (EEG) and medical co-morbidities as well as sociodemographic characteristic will be assessed using tools that have been validated in this setting. Comprehensive clinical examination, and assessment of self-reported sigma and measures of quality of life and collection of blood samples will also be conducted at the baseline visit. Stigma scores will be assessed using standardized Kilifi Epilepsy Stigma Scale and while quality of life will be assessed using the World Health Organization Quality of Life Scale (WHOQOL-BREF). These tools will be validated for the Nairobi site prior to administration.

(ii) Measurement of adherence

Information on adherence to ASMs will also be collected using a validated self-reporting tool, the Morisky Medication Adherence Scale (MMAS-8) and validated using blood samples. Blood will be drawn (not exceeding 5mls) to measure detectable and optimal plasma levels of ASMs at baseline and during three follow up timepoints; at three months, six months and at 12 months (table 1). Optimal and detectable levels of ASMs in blood. All assays for ASMs will be done at the end of the study using a TDxFx analyser and automated VitaLab Selectra E Clinical Chemistry (Abbott Laboratories, Abbott Park, IL, USA) at Centre for Research in Therapeutic Sciences (CREATES), Strathmore University.

(iii)Short message service (SMS) intervention

An automated computer system will be used to generate standard text messages to remind patients to take their ASMs at the prescribed time and to refill their prescriptions. The system will have an algorithm to check time, send the text message and generate a delivery report. Participants will be able to send replies to the messages, either via text or USSD codes at no cost. A three-step verification SMS system will be designed to send a delivery report (which shows if the message has been delivered) and a read receipt (which shows if the message has been opened) back to the service provider and study team and each message will prompt for a USSD or text response at no cost to the participant asking if they have read the message.
The participants in the no-intervention group will receive routine care, including clinic appointment for review of symptoms and medication review and refills and routine electroencephalography (EEG) recordings. For comparability, the control group will receive

public health promotion messages (not related to epilepsy) such as use of bednets. All other data will be collected in the case report forms during scheduled follow up visits at the clinic.

(iv) Anti-seizure medication (ASM)-related adverse drug reactions (ADRs)

Cognisant that this trial doesn't involve administration of medicinal products, we would like to document and describe reported drug-related adverse events of ASM as part of routine care. These data have not been previously systematically documented in relation ASM use in the study population. ASM-related adverse drug reactions will be documented and graded according to Common Toxicity Criteria for Adverse Events (CTCAE), including date and time of onset, severity, and relationship to drug administration. Standardised assessment will be used to measure various emerging ADRs. These data will be used in a secondary analysis to investigate the association of toxicity with ASM concentrations. Any side effects of ASMs will be documented for all the participants and correlated with type of ASM used and where possible, the ASM levels in blood. This will include abnormalities during pregnancy such as congenital abnormalities/birth defects since certain ASMs such as sodium valproate are known to be teratogenic. This information will be collected into case review forms at baseline and during follow up visits.

9.3 Follow-up Visit(s) and End of Treatment Visit

Participants will be invited to the study clinics for follow up visits to examine adherence to anti-seizure medications and assess their quality of life and stigma scores three, six and twelve months from the first visit. The long follow up period per individual of 12 months is selected to ensure high exposure to the intervention to show proof of concept. All other routine clinical assessments will be done during this follow up visit including physical examination, EEG recordings and medication refill. Participants who fail to show up for scheduled follow up visits will be contacted by telephone up to three times and if unsuccessful, followed up at home to remind them to come for their scheduled visits. Participants who are not reached after 3 telephone calls and one home visit will be considered lost to follow up.

Table 1: Study Schedule

	Screening visit 1	**Pre-enrolment screening call**	**Randomisation visit 2 at baseline**	**Follow up visits 1**	**Follow up visits 2**	**End of intervention**
Study Month	**Use available data**	**-1 week**	**0**	**3**	**6**	**12**
Assessment / Procedure						
Provide Patient Information Sheet and Informed Consent Form and/or Assent Form	x					
Obtain written informed consent and/or assent	x					
Call to check phone availability/accessibility		x				
Demography	x					
Medical history	x					
Physical examination	x		x	x	x	x
Vital statistics e.g., heart rate and blood pressure	x		x	x	x	x
12-lead EEG	x					x
Blood for adherence levels	x		x	x	x	x
Morisky self-reported scale	x		x	x	x	x
Stigma scores scale	x		x	x	x	x
Quality of life scale			x	x	x	x

10.0 ASSESSMENT OF EFFICACY

10.1 Specification of the efficacy parameters.

10.1.1 Primary efficacy variable

The primary outcome measures will be adherence to anti-seizure medications as measured by self-reports and validated by optimal and detectable levels in blood.

10.1.2 Secondary efficacy variable(s)

(i) Correct intake of drugs and refill rates- measured by checking record logs for participants attending the epilepsy clinics and identified in the surveys in NUHDSS
(ii) Changes in seizure frequency as assessed by trained clinicians at the epilepsy clinics and identified in the surveys in NUHDSS
(iii) Changes in stigma scores and quality of life scores assessed using standardized scales
(iv) Unwanted drug-related adverse events as reported by participants and confirmed using standardized questionnaires.

11.0 EVALUATION OF COST EFFECTIVENESS OF THE INTERVENTION

The impact of measures to address the epilepsy treatment will be used to inform economic modelling that we will undertake to calculate the return on investment from investing in management. A decision analysis model will be constructed by collating data on the resources required for treatment strategies in epilepsy care.

In addition, we shall draw on existing analyses of the costs of epilepsy, to estimate economic benefits from a health and societal perspective of averting epilepsy. The costs of treating epilepsy will be estimated by adapting existing resource use and cost estimates from Ethiopia so that they match the local Kenyan context using the WHO's One Health Tool. Threshold analysis to identify the minimum level of effectiveness and/or costs needed to generate a positive return on investment. Drawing on data on the QoL benefits associated with preventing epilepsy a net monetary benefit approach to determining the economic case for action will also be conducted.

Crucial to the sustainability of the project, although initially tailored to the local context in Kenya, the economic model will be made available in Excel format as a legacy of the proposal. Decision makers in SSA would then be able to look at the potential return on investment in their own contexts. They would be able to vary assumptions on

population reached, effectiveness, coverage, resource requirements and the short and longer-term costs of both treated and untreated epilepsy.

12.0 STATISTICS

12.1 Determination of sample size

The minimum sample size determination will be based on reducing the adherence treatment gap from the current estimates of 62% in Kilifi ((Ibinda et al., 2017a) aiming for a proportion of improvement of 40%-50%. Previous studies have shown non-adherence of >60% even among clinic attendants, especially when symptoms subside. Assuming a refusal/non-consent/ attrition rate of 10% and design effect of 1.5 (assuming possibility of modest clustering), if we recruit 300 patients at each arm, i.e., total of 1200 patients, we will have 95% power to detect a 50% improvement in adherence. Therefore 1,200 PWE will be randomized into 4 arms as follows: text SMS (N=300), graphic SMS (N=300), both text and graphic SMS (N=300) and control/non-reminder SMS (N=300). An allocation ratio of 1:1:1:1 across the 4 arms will be used. Since no prevalence estimates exist for the Nairobi site, we will utilise a similar sample size for each site. This sample size determination will account for these unprecedented withdrawals by recruiting a surplus of participants, assuming a proportion of 20% loss to follow up.

Table 2. Sample size adjusted for 10% attrition at varying improvements and powers

	Power			
Improvement		**80%**	**90%**	**95%**
	40%	588	786	971
	45%	268	358	442
	50%	154	205	253

12.2 Statistical and analytical plans

12.2.1 Data management

Audio records from focus group discussions and the hard copy files will be stored in cabinets under lock and key for the duration of the study and for use in future publications and training of master's and PhD students. All data will be stored in KEMRI computers protected by passwords. The SMS company will set up and test an SMS/MMS gateway for the study and

provide on-going support. The data manager at Kilifi (CK) will be trained by the SMS company to utilize the software and ensure that the messages are sent out as planned.
All analyses will be done on Stata Version 17 (College Station TX: StataCorp LP). We will use paired sign-rank tests to compare continuous scores of stigma and quality of life, and Man-Whitney U tests for cross-sectional comparisons during follow up. Analyses will be sub-based on either outcomes (binary or continuous) or evaluation timepoints (cross-sectional or across all time points i.e. at baseline, 3, 6 and 12 months). For evaluation timepoints across all time points, generalized estimating equations will be used to analyse adherence binary status in panel or long data format with appropriate link functions (i.e. specifying binomial family and log link). For cross-sectional evaluations at different timepoints (i.e., evaluation of either baseline, 3, 6 or 12 month- timepoint), we will calculate the relative risk (RR) using generalised linear models with appropriate link functions (i.e. specifying binomial family and log link). Relative risks will be used to efficacy by subtracting the RR ratio from 1.
Adherence will be determined by comparing detectable ASM levels in blood against proportion of prescribed doses correctly taken. We will conduct interim analysis at the halfway mark to assess performance of the intervention. Multivariable logistic regression will be performed to investigate association between type and ASM blood levels and incidence of psychiatric comorbidity.

12.2.2 Planned statistical methods

All quantitative analyses will be done on Stata Version 17 (College Station TX: StataCorp LP). We will use paired sign-rank tests to compare continuous scores of stigmas and quality of life and Man-Whitney U tests for cross-sectional comparisons during follow up. Adherence (which is the primary efficacy variable) will be determined by comparing detectable ASM levels in blood against proportion of prescribed doses correctly taken, with a binary variable for adherence generated from established detectable and optimal levels of ASM in blood. Generalized estimating equations, with appropriate link functions (i.e. specifying binomial family and log link), will be used to analyse adherence binary status in panel data format, across the follow-up periods of baseline, 3 months, 6 months and 12 months. For cross-sectional evaluations at each follow-up period e.g. at 3 months, will be done using generalised linear models with appropriate link function (i.e. specifying binomial family and log link). Both generalised estimating equations and generalised linear models will produce Absolute relative risks (RR) which will be subtracted from one to compute efficacy (i.e. efficacy=1-

RR). We will conduct interim analysis at the halfway mark to assess performance of the intervention. For secondary efficacy variables, specifically stigma scores and quality of life scores, we will first generate discrete variables of improvement by subtracting baseline scores from follow up scores and repeat efficacy analysis using the approaches described for primary efficacy variable i.e., adherence. All levels of efficacy analysis will be done including Full Analysis Set (FAS), Intention-to-treat population (ITT), and Per Protocol population (PP). Multivariable logistic regression will be performed to investigate association between type and ASM blood levels and incidence of adverse events.

For qualitative studies, standard analysis approaches, will be used including transcribing verbatim, coming up with a preliminary thematic framework through reading a sample of the transcripts. The thematic framework will be used to create a coding structure in NVivo, the software that will be used for final analysis including inter-rater coding and data management/filing.

13.0 STUDY MANAGEMENT

13.1 Protocol deviations and violation(s)

A protocol deviation will be any failure to adhere to the defined procedures or intervention plans outlined in the protocol version approved by Scientific Ethics Review Unit (SERU) and Oxford Tropical Research Ethics Committee (OxTREC). A protocol violation is any planned or inadvertent changes that may impact safety of study participants, affect integrity of the study data and/or affect study participants willingness to participate in the study previously approved by the SERU or OxTREC. Any unforeseen and unavoidable deviations from the protocol will be documented and filed in a protocol deviation folder, with explanation and reported to the relevant ethical and regulatory authorities during the annual reports to ethical review boards while violations will be reported immediately.

13.2 Discontinuation of the study

The study in its entirety may be discontinued prematurely by the Sponsor, or the Ethics Committee with oversight responsibilities at any time. All arms of the study may be discontinued by the sponsors in the event of the following but not limited to:

i. occurrence of an unanticipated health or technological problem
ii. evidence of serious and/or continuing noncompliance.

iii. safety or human rights concerns raised by the ethics committees in Kenya and Oxford.

13.3 Withdrawal of Study Participants

Participant may opt to withdraw from the study at any point. The study team may withdraw them from the study if it is established that they are not accessing SMS, have missed two of the follow up periods, have stopped taking anti-seizure medications following advice by the attending clinician or those who have emigrated or died. Participants may terminate their participation prematurely, or have their participation terminated by the Investigator

13.3 Direct access to source data/documents

The regulatory agency, and other authorised representatives of the sponsor will have direct access to source documents to permit trial related monitoring and audits.

13.4 Quality control and quality assurance

The quality assurance manager at the trial site will conduct internal audits to check that the trial is being conducted, data is being recorded, analysed, and accurately reported according to the protocol, trial SOPs, and in compliance with ICH GCP. The audits will also include laboratory activities for the collected blood samples according to an agreed audit schedule. The Clinical Trials and Research Governance Office in Oxford may carry out an audit to ensure compliance with the protocol, GCP and appropriate regulations.

13.5 Trial Registration and Monitoring

The trial will be registered on the clinical trial registry before participant enrolment into the study. The trial will be monitored as a behavioural intervention by the monitoring department of the Clinical Trials Facility (CTF) at KEMRI-Wellcome Trust Research Programme (KWTRP). Regular monitoring will be performed according to International Council for Harmonisation (ICH) Good Clinical Practice (GCP) and a Monitoring Plan. Monitors will check whether the clinical trial is conducted, and data are generated, documented, and reported in compliance with the protocol, GCP and the applicable regulatory requirements.

14.0 INTELLECTUAL PROPERTY

Any intellectual property rights that arise from the work will be safeguarded according to the current KEMRI guidelines and the Industrial Property Act of 2001, sections 32, 58 and 80 and

APHRC guidelines. The scientific and intellectual contributions of all persons involved in the research will be appropriately acknowledged in all publications and presentations arising from the work.

15.0 TIME FRAME/DURATION OF THE TRIAL

Activities	2022				2023						2024	
	Q3		Q4		Q1		Q2	Q3	Q4		Q1	
Protocol development and internal review												
Engagement with the Kilifi and Nairobi County Department of Health and the SMS company												
Ethical board reviews (SERU, PPB, NaCOSTI, OxTREC) and trial registration												
Pre-study focus groups and community engagement												
Audit of phone ownership and ASM availability, enrolment, and randomisation												
Roll out the SMS trial: sample collection and assessment												
Data cleaning, entry, and analysis												
Report writing and close out												

16.0 ETHICS

Ethical approval will be sought from the Oxford Tropical Research Ethics Committee (OxTREC), KEMRI Scientific & Ethics Review Unit (SERU), Pharmacy and Poisons Board and NACOSTI.

16.1 Human Subjects

The SMS trial will be conducted in accordance with the latest version of the Declaration of Helsinki, ICH Good Clinical Practice and all local regulatory requirements. The safety of the participants will be monitored throughout the trial. All patients will have access to routine care at the study clinics in Kilifi and Nairobi. Since the ASM plasma levels will be determined at the end of the study, the investigators will not be aware of any non-adherence based on optimal or detectable levels, but all participants will be informed of the importance of adhering to their ASMs during clinic visits as part of routine care.

16.2 Informed Consent and/or Assent

The consent/assent form (for children aged 13 to 17 years old) will be explained to the participant and / or their carer by a fieldworker. The participant and / or their carer will be asked to sign the form or use an ink stamp to provide a thumb print. The consent forms will be in English and translated into Swahili and Giriama (for the Kilifi site). Adults will give individual consent, unless the participant is unable to, in which case a close caretaker/parent/guardian will be approached to give consent on behalf of the participant or as a witness. Parents will give consent on behalf of participating children, with those between 13-17 years allowed to give assent in addition to parental consenting.

16.3 Compensation

It may take the participant at least 3 hours for clinical and neurological assessments at the epilepsy clinic, including the informed consent/assent process, undergoing clinical evaluation to determine seizure semiology, neurological and physical exam and to record EEGs; and answering questions related to stigma experiences and perceived quality of life. Participants invited to the clinics will be provided with meals (or KSH 200 if the COVID situation is restrictive) and reimbursed transport (based on individual place of residence) and out of pocket expenses (KSH 350) for the Kilifi site. Transport will be reimbursed based on travel and meals will be provided. In the Nairobi site, APHRC will reimburse participants with a flat rate of KSH 1000 to cover all expenses.

16.4 Patient Data Protection/Confidentiality

Participants will be assured about confidentiality of the personal details obtained from them since seizure disorders are associated with stigma in most rural areas of Kenya (Mbuba et al., 2012b). We will deliberately explain to community members and PWE that epilepsy is not a

mental health disorder in all communications and that people with either conditions should not be stigmatised. Any clinical interviews will be carried out in private rooms. The messages will not have any personally identifiable information to ensure privacy of the participants. Caregivers/members of the household, especially those who receive messages on behalf of PWE will also be encouraged to handle the messages with confidentiality to prevent access of the messages by others outside the household which may lead to stigmatisation or breach of confidentiality. We are also running community awareness studies as part of the EPInA studies to reduce the enacted and perceived stigma around epilepsy. All current COVID-19 mitigation protocols will be adhered to during clinic visits including wearing of masks, social distancing, sanitising and temperature checks in line with the Ministry of Health guidelines. Participants will be provided with contact details of investigators for any enquiries and clarifications.

16.5 Data Sharing

Individual-level anonymized data will be shared with the Sponsor. Summary-level statistical analyses will be shared with wider stakeholder engagement and the medical community. Information collected or generated during this study may be anonymised for use to support new research on epilepsy. Any future research using information from this study must first be approved by a local or national expert committee to make sure that the interests of participants and their communities are protected. Data will be managed by the data governance committee of KEMRI CGMRC.

16.6 Safety

The study team will employ epilepsy clinicians to provide medical care to participants during the study follow-up period for epilepsy-related complicated managed in epilepsy clinics in Kilifi and Nairobi. The study team will not become responsible for long-standing chronic conditions that were present before vaccination, or those that are unrelated to epilepsy and psychiatric comorbidity.

16.7 Stakeholder and community engagement

Community members will be informed and educated about the study through local radio announcements and chief's meetings (observing COVID-19 containment measures). Public engagement in Kilifi will be conducted through KEMRI Community engagement Advice for STudies (CAST) of which Community Liaison Group (CLG) is a member.

The following groups/offices will be targeted for community engagement:

(i) The Sub-County Health Management Team (SCHMT).
(ii) The County health research office.
(iii) The Chiefs and Assistant chiefs within the KHDSS and
(iv) KEMRI Community representatives – to be informed about the study as they are community representatives.

The aim of these engagements will be to establish buy-in on the use of mobile technology to improve adherence to ASMs. We will be keen to deduce pre-study community perceptions on epilepsy and adherence to treatment as well as type, frequency, and timing of the messages. During the study, the CLG and CAST groups will be useful avenues for targeted community engagement or sensitizations to ensure the planned engagements do not increase stigmatization against people with epilepsy who have poor response to treatment or unwanted side effects.

17.0 COVID-19 MITIGATION

All study staff will follow COVID-19 safety measures as described below:

(i) Ensure attendance of all trainings on rational use of Personal Protective Equipment (PPE) and infection prevention and control as regards COVID-19 as scheduled by the study coordinator

(ii) Sit only at designated marked areas at their workstation and ensure 2-meter physical distance between themselves and others during field visits

(iii) Invite a limited number of participants for interviews on allocated days as per an agreed schedule for studies sharing space workspaces.

(iv) Ensure participants invited to the clinic are seated at a designated tent outside when waiting their turn to avoid overcrowding with patients at the waiting areas.

(v) Disinfect all frequently touched surfaces after each participant assessment

(vi) Disinfect hands frequently with available sanitisers and carry extra sanitisers to offer to potential participants during field visits

(vii) Adhere to Programme COVID-19 measures of temperature checkpoints at entry points

(viii) Wear their mask correctly at all times

(ix) Carry extra masks during field visits to offer to participants who inadvertently do have their own

(x) Do not exceed more than 5 people (including the driver) in Programme vehicles during field visits

(xi) Set off early when planning to visit far-flung sites to ensure KWTRP and APHRC vehicles are back on campus by 3PM to allow for disinfection as per current KWTRP and APHRC COVID-19 containment measures

(xii) Plan reconnaissance visits for studies with activities outside KWTRP to identify suitable venues that will allow for adherence to KWTRP, APHRC, County and National COVID-19 guidelines

Study participants will also be expected to always wear masks during study activities and those who show up without masks will be offered disposable masks. Participants visiting the clinics will be expected to adhere to institutional guidelines of handwashing, sanitizing, social distancing, and temperature checkpoints.

The study coordinators and site investigators will be in-charge of ensuring these measures are adhered to and KWTRP and APHRC Health and Safety teams will conduct spot-checks to ensure compliance.

18.0 ARCHIVING AND RECORD RETENTION

The PI, co-investigators, and clinical research staff will have access to records. The investigators will maintain appropriate medical and research records for this study, in compliance with ICH E6 GCP, GDPR, regulatory and institutional requirements for the protection of confidentiality of participants. The investigators will permit authorized representatives in Oxford, and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety and progress. The master files including a copy of the final completed CRFs, as well as all source documentation will be maintained at KEMRI CGMRC retained by the PI and one copy will be maintained by the Sponsor, who will ensure that it is stored with other study documents, such as the signed informed consent/assent forms, protocol, the investigator's brochure, and any protocol amendments, in a secure place following local regulations. The final study database will be securely kept with all archive tables for at least 25 years. Paper CRFs and study files at KEMRI CGMRC will be archived following local laws.

19.0 FINANCING AND INSURANCE

19.1 Budget for each site

	USD $	Ksh
a) Personnel, salaries, and benefits disbursements	100,575.00	10,561,974.00
b) Patient costs, travel, food, accommodation and/or supplies	52,060.00	13,338,000.00
c) Equipment (SMS software and support)	132,294	297,000
d) Supplies		
Laboratory consumables: blood draws and analyses at CREATES	60,718.00	22,494,600.00
Clinical consumables: at epilepsy clinic	24,278.00	432,000.00
e) Travel and accommodation		
Local (Nairobi)	5,750	782,000
International to Oxford	20,110	3,950,000
f) Transportation, vehicle repairs and field visits etc	26,540	4,700,000
g) Operating expenses postage, printing etc.	4,850	1,500,000
h) Contingency fees (15% of above)	64,076.25	8,708,400
Total	427,175.00	66,763,974.00

19.2 Justification of the Budget

Salaries are required for the project coordinator for the study, who will help with the study implementation, 3 clinicians to help with screening and clinical care for participants, and 4 fieldworkers to help with recruitments, administration of questionnaires and household visits. The project will generate enough data for use in PhD studies, but there will be separate arrangements to fund this beyond the period of data collection. Some costs will go towards EEG consumables and MRI scans for routine investigations. We will contract a SMS software company to develop, set up and support the SMS messaging application system. Tablets and computers are needed for online data collection and capture. Meals and reimbursements for fares will be provided. Fuels for motorbikes and a car are needed for recruitment of participants, and for doing follow-ups in the community. Stationeries are needed for record keeping and for making reports. This work is funded by a NIHR grant.

19.3 Insurance

The University of Oxford will sponsor the study and provide insurance for the trial. The University of Oxford has a specialist insurance policy in place which would operate in the event of any participant suffering harm because of their involvement in the research.

20.0 REPORTING, DISSEMINATION AND NOTIFICATION OF RESULTS

The findings of this study will made available through publications in scientific journals. We will feedback individual results with clinical relevance to participants in real-time. Summaries of the outcomes of the trial will be provided during community meetings in the areas from which participants are recruited This work will also be presented at local and international conferences as posters or platform presentations and at key policy meetings concerning epilepsy. In addition, we will upload videos on a YouTube channel and other online platforms to help dispel epilepsy-related stigma. Positive messaging on epilepsy will also be shared through barazas (community meetings), local newspaper articles and discussions on the radio and television based on information from oral histories. Caution will be taken to ensure participants are not remotely identifiable through face blurring and voice masking technologies.

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22.0 APPENDICES

22.1 Roles of Investigators

Symon Kariuki: the principal investigator for the study will be involved in the overall supervision of implementation of the study, will identify a contact to provide the pen and ink line drawings for the scanned graphics, and writing up of the findings for publication.

Mercy Atieno: EPInA study project coordinator who will help with study implementation; statistical analyses; and writing up of the findings for publication.

County Department of Health representative: to be the contacts / liaison persons for the MoH.

Gilbert Katana and Maria Mumbo: will provide the clinical data for study participants.

Collins Kipkoech: will select the participants, send out SMS and manage data.

Mary Bitta: She has experience in public mental health and will share her experiences setting up and running the mhGAP trial.

Gershim Asiki- is a research scientist with interests in Public Health, Health systems, Maternal and Child Health, non-communicable diseases, and HIV

Damazo Kadengye- is a Biostatistician and Research Epidemiologist with over 17 years of multidisciplinary experience in public health and educational sciences. He is mostly interested in research projects that espouse Implementation Science or Impact Evaluation theories, and making effective use of data and data systems to enhance evidence-informed policy-making processes that inform development investments. He will be involved in data analyses and modelling in the Nairobi site.

Fredrick Wekesah- is a chronic disease epidemiologist and a postdoctoral research scientist at APHRC. His research interests span non-communicable diseases and adolescent mental health. He will be involved in project implementation in the Nairobi site.

Peter Otieno- is a PhD candidate and a Research Officer at APHRC based in Nairobi, Kenya. His interests are in implementing studies on health system strengthening through the development of evidence-based decision models to inform public health policy. He will be involved in project implementation in the Nairobi site.

Sloan Mahone – historian with extensive experience of working in Africa and other LMICs, specific expertise in acquiring oral histories, keen interest in studying neurological illness. She will be involved in the post-study questionnaire and the writing up of the findings for publication.

Arjune Sen– head of Oxford Epilepsy Research Group, topic advisor to NICE epilepsy guidelines, ILAE Council member, and consultant epileptologist. He is leading the project from Oxford including coordination of activities of collaborating institutions. .

Charles Newton: the co-principal investigator and concept originator will continue to facilitate the communications between KEMRI, University of Oxford; assist with study proposal writing, contribute to design of the text and graphic messaging content; and the writing up of the outcomes for publication.