CLINICAL MANAGEMENT OF CRYPTOCOCCAL MENINGITIS AMONG HEALTH CARE PROVIDERS AT TWO REFERRAL HOSPITALS IN KISUMU COUNTY, KENYA

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A thesis submitted in partial fulfillment for the requirements of the degree of Master of Science in Advanced Nursing Practice (Medical- Surgical Nursing) of Masinde Muliro University of science and technology

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DECLARATION

This thesis is my original work prepared with no other than indicated sources and support and has not been presented for a degree or an award in any other university.

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CERTIFICATION

The undersigned certify that they have perused and hereby recommend for acceptance of Masinde Muliro University of Science and Technology a thesis entitled **"Clinical Management of Cryptococcal Meningitis among Health Care Providers at two Referral Hospitals in Kisumu County, Kenya."**

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DEDICATION

I dedicate this study to my daughters Silvia and Shirley and their uncle Moffat for their unconditional support throughout the period of my studies. Dedication also goes to my siblings and my parents Mr. and Mrs. Pius Nyamaicho Ogendo for their continuous encouragement and Prayers.

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ABSTRACT

Cryptococcal meningitis is one of the most common and lethal opportunistic infections among human immune virus infected clients/patients before initiation of antiretroviral therapy. It is majorly associated to morbidity and early mortality among human immunodeficiency virus infected patients in resource limited countries. The main objective of this study was to investigate the clinical management of cryptococcal meningitis in adults among health care providers at two referral hospitals in Kisumu County, Kenya. A cross-sectional study using quantitative approach was used targeting 119 health care providers. Collection of data was through pretested self- administered questionnaires to determine clinical management strategies and examine factors influencing clinical management of cryptococcal meningitis. A pre-tested observational check list was used to assess the adherence to World Health Organization guidelines in the management of adults with Cryptococcal Meningitis among health care providers. Data obtained was analyzed using the statistical package for social science version 25. Descriptive analysis was done using frequencies, percentages and means. Inferential analysis was conducted using bivariate logistic regression to determine relationships among the variables, p-values of at or below 0.05 were considered statistically significant. The study established that a satisfactory number of health care providers (55.7% n=65) practiced good clinical management strategies.61 % (n=37) of the health care workers were adhering to World Health Organization recommended guidelines on management of cryptococcal meningitis. The major factor associated positively with clinical management of cryptococcal meningitis was the acknowledgement by the health care providers that the world health organization guidelines lead to a better patient outcome (97%, n=113) and inadequate supplies and resources to facilitate management (78%, n=90) was the major factor associated negatively. Respondents who had experience of five years or less were 80% more likely to practice good clinical management strategies in contrast to those with an experience of six years or more (OR: 1.8; 95%CI: 0.6 – 2.2; p=0.008). Nurses were 40% less likely to adhere to the world health organization recommended guidelines on management of cryptococcal meningitis compared to clinical officers (OR: 0.6; 95% CI: 0.4 – 0.9; p=0.01).Health care providers with an experience of five years or less were 40% more likely to agree that the factors were influencing clinical management of cryptococcal meningitis in contrast to those with an experience of six years or more (OR: 0.6; 95%CI: 0.1 – 0.74; p=0.04).In conclusion a few health care providers practiced good clinical management strategies and adhered to the world health organization recommended guidelines but had inadequate supplies and resources to facilitate the clinical management hence critical aspects in the world health organization recommended guidelines were not carried out. The study therefore recommends that the policy makers in the County government of Kisumu and the hospital management teams to provide periodic and inductive training opportunities on clinical management of patients with cryptococcal meningitis especially those health care providers with years of experience of 5 years and below, scale up timely supportive supervision on adherence to WHO gold standard guidelines on management of cryptococcal meningitis and avail adequate resources, facilities and supplies in the study area, which will promote effective clinical management of cryptococcal meningitis.

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LIST OF ABBREVIATIONS AND ACRONYMS

AIDS	Acquired Immunodeficiency Syndrome
AmpB	Amphotericin B
ART	Antiretroviral Therapy
CFR	Case Fatality Rate
CM	Cryptococcal Meningitis
CNS	Central Nervous System
CPG	Clinical Practice Guidelines
CrAg	Cryptococcal Antigen
CSF	Cerebrospinal Fluid
HAART	Highly Active Antiretroviral Therapy
HCP	Health Care Providers
HIV	Human Immunodeficiency Virus
ICP	Increased Intracranial Pressure
IRIS	Immune Reconstitution Inflammatory Syndrome
JOOTRH	Jaramogi Oginga Odinga Teaching and Referral Hospital
KCH	Kisumu County Hospital
LP	Lumbar Puncture
MR	Mortality Rate
NACOSTI	National Commission for Science and Technology Innovation
OI	Opportunistic Infections
SPSS	Statistical Package for Social Sciences
WHO	World Health Organization

CHAPTER ONE

INTRODUCTION

1.1 Overview

This chapter contains background information, problem statement, objectives, research questions and the justification of the study. In addition, the chapter contains the limitations of the study and the conceptual framework.

1.2 Background of the study

Meningitis is an inflammatory disorder of the meninges, which are structures that cushion the spinal cord and brain to provide protection. Most patients with this infection at least develop fever, severe headache, and neck rigidity and associated altered level of consciousness (Ganiem, 2013).

Inflammation of the meninges of the brain or spinal cord caused by *Cryptococcus neoformans* fungus is termed as cryptococcal meningitis (CM). *Cryptococcus neoformans* is an environmental saprophyte yeast which survives through selective environmental pressure within humans and other mammals. Soil contaminated with pigeon extracts and chicken droppings are the environmental sources of the fungus (Kanji, *et al.,* 2011).

Manga, *et al.,* (2016) defines cryptococcosis as a systemic fungal infection, which is in HIV infected and some patients with deranged body immune system. This systemic infection causes over 600 000 deaths annually in the tropical areas. However, in people with intact immune system, infections of this kind are very rare with a verified incidence of 0.4 to 1.3 cases per 100000 people yearly (Sogbanmu, *et al.,* 2014).

According to WHO (2012), cryptococcal meningitis has a case fatality rate which has remained high ranging between 35%- 65%, in sub-Saharan Africa, comparing with 20%-30% in most developed countries. This case fatality rate is escalated because this infection is the most prevalent opportunistic infection in people living with HIV/AIDS.

The clinical management strategies suitable for the control of cryptococcal meningitis in HIV infected patients by WHO 2018 include, early diagnosis and antiretroviral therapy (ART) initiation in HIV infected patients, early initiation of proper antifungal therapy followed by early and immediate referral for HIV care after diagnosis of cryptococcal disease.

For early diagnosis, clinicians ought to have high index of suspicion for CM in ART naïve patients with clinical manifestations of severe headaches, unexplained fever, nausea, vomiting, neck stiffness, confusion, seizures, and abnormal behavior with new psychiatric symptoms, altered level of consciousness, focal neurological signs, diplopia, unexplained blindness and sometimes coma (Sogbanmu *et al.*, 2014).

The diagnostic approach of CM includes prompt lumber puncture (LP) with measurement of Cerebral Spinal Fluid (CSF) opening pressure, rapid CSF CrAg assay or rapid serum CrAg. CrAg examination of adults infected with HIV who are not yet on ART with a CD4 count lower than 100 cells/mm is required, with immediate initiation of antifungal, if CrAg is positive and when the CrAg is at or more than 3 % is recommended (WHO, 2012).

Abbas, *et al.*, (2016) points out a common diagnostic tool CM to be India ink staining and culture of the yeast as the definitive test for diagnosis of cryptococcal meningitis.

In addition, CSF, serum, or plasma CrAg should be offered for all patients thought to suffer from meningitis. On the other hand, the CrAg lateral flow assay remains a convenient diagnostic test in the point of care.

The clinical standard treatment of HIV/AIDS associated CM for sub-Saharan Africa is, induction phase of 1 mg/kg/day AmpB for two weeks, consolidation period of Fluconazole 800 mg for four weeks, Fluconazole 400mg or 200mg orally for eight weeks, followed by a maintenance phase of Fluconazole 200 mg until CD4 counts were >200 cell/Ml (Mdodo *et al.*, 2010).

Increased intracranial pressure is frequent and the aim of management is to reduce increased cerebral spinal fluid pressure to below 20 cm H20, perform lumber puncture and drain excess CSF for treatment purposes until the clinical presentations related to raised ICP have resolved for 2 days, after every 10 ml of CSF removed, re-check CSF opening pressure (WHO,2018).

Management of AmpB toxicity includes supplementation of electrolytes and fluid therapy administration by infusing 20 mEq of potassium chloride in 1 litre of normal saline solution over 2 hours prior to each regulated infusion of amphotericin B Then administer 8 –m+9Eq potassium chloride tablets 1-2 twice/day. 8-mEq potassium chloride 1 tablet twice/day, increased in the course of the second week, and 2 of 250-mg tablets of magnesium trisilicate supplemented twice/ day, or magnesium chloride 4 mEq twice/ day (WHO,2018).

Management of relapse is done by initiating or recommencing induction treatment and complete the regimen with reinforcement of adherence then initiate HAART if HIV co-infected and has not been started yet. In addition, therapeutic lumber puncture is performed to manage raised intracranial pressure (WHO,2018).

It is acknowledged that organizations and institutions have had a widespread adoption of standard clinical guidelines and precautions but significant omissions by healthcare workers have been noted following barriers such as infrastructure (Correa, *et al.,* 2013). In addition, large numbers of patients with insufficient resources notably escalates the ineffectiveness of clinical practice in basic care provision (Tsiga *et al.,* 2013).

A South African study revealed inadequate observance to the recommended clinical strategies in the control of cryptococcal meningitis, management and prevention of increased intracranial pressure and monitoring for antifungal drug toxicity were not executed, rehydration and renal toxicity monitoring with observations of renal complications were not correctly followed (Sogbanmu, *et al.,* 2014).

Carthey *et al.,* 2011 noted that guidelines with information overload was a hindering factor to clinical management. Clarke, *et al.,* (2010) also discovered that clinicians had problems in embracing new practices in the CPG protocols hence clang to their previous deeds despite the availability of the recommended guidelines.

Studies estimate the prevalence of HIV among adults in Kenya at 7.8% with 1.4 million HIV infected people. Consequently, CM a major opportunistic infection has become a leading cause of diseases and deaths in the country (Mdodo, *et al.,* 2010).

1.3 Statement of the Problem

Cryptococcal infection has remained significant in the last several decades due to the dramatic increase in numbers of patients with acquired immune-suppression from

Human Immune Virus (HIV) infection and immune suppressing medications, such as corticosteroids regimens used in the prevention of organ transplantation rejection (Machiridza, 2014). Study reports reveal close to one million emerging instances of cryptococcosis and nearly 600,000 deaths per annum worldwide.CM related to Cryptococcus neoformans is high in Sub-Saharan Africa and has contributed to 13–44% of mortalities in people infected with HIV in the area (Bitew, *et al.,* 2016).

Although the gold standard recommended CM control guidelines by WHO are in place, cryptococcal meningitis disease is still the major reason for reported deaths amongst HIV infected patients in underdeveloped areas. The estimated life loss in people infected and living with HIV and associated cryptococcal meningitis is at 70% in underdeveloped countries in contrast with 20–30% for high-income countries (WHO, 2018).

Among people infected with HIV worldwide, the CM burden is estimated at 0.04% to 12% per year, resulting to 625000 deaths (Sogbanmu *et al.,* 2014). HIV infection which accounts for 95% of cases in low-income countries in which Kenya is inclusive, accelerates CM (Sloan *et al.*, 2014).

Prevalence of CM has remained high over the last several decades in line with the HIV/ADS pandemic which has consequently led to the increase of CM associated mortality rates ranging from 17% to 100% in Africa (Muendo & Mutinda, 2012). Prevalence of HIV is unacceptably higher by 3.4 times in Kisumu than at the national level which is 19.9 %, this has resulted to escalated cases of HIV associated cryptococcal meningitis (Kenya HIV Estimates, 2015). The case fatality rate in Jaramogi Oginga Odinga Teaching and Referral Hospital is high at 32 % (JOOTRH Health Records, 2016/2017).

In the absence of treatment, HIV associated CM has 100% case fatality rate hence life threatening (Adeyemi & Ross, 2014). CM treatment with potent antifungal drug combination results in effective cure (Adeyemi, 2014). The current gold standard guidelines in management of CM is by WHO 2018 which include; early diagnosis, prevention, screening and treatment of CM, timing of ART in HIV infected patients, and management and prevention of Amphotericin B deoxycholate toxicity, monitoring for and managing of increased intracranial pressure (ICP), prevention of inflammatory syndrome caused by immune reconstitution monitoring treatment response and managing relapse, (WHO, 2018).

This study therefore was aimed at investigating the clinical management of cryptococcal meningitis in adults among health care providers in JOOTRH and KCRH, in Kisumu County, Kenya.

1.4 Main Objective

To investigate the clinical management of cryptococcal meningitis in adults among health care providers in JOOTRH and KCRH, Kisumu County, Kenya.

1.5 Specific Objectives

i. To determine the clinical management strategies of CM in adults among HCP in JOOTRH and KCRH.
ii. To assess the adherence to WHO guidelines on clinical management of CM in adults among HCP in JOOTRH and KCRH.
iii. To examine factors influencing clinical management of CM in adults among HCP in JOOTRH and KCRH.

1.6 Research Questions

i. What are the clinical management strategies of CM in adults among health care providers in JOOTRH and KCRH?

ii. Are the HCP adhering to WHO guidelines in clinical management of CM in adults among health care providers in JOOTRH and KCRH?

iii. What are the factors influencing clinical management of CM in adults among HCP in JOOTRH and KCRH?

1.7 Justification

Prevalence of CM has remained high in line with the HIV/ADS pandemic which has consequently led to the increase of CM associated mortality rate ranging from 17% to 100% in Africa (Muendo & Mutinda, 2012). With early diagnosis of CM, consistence adherence to the basic principles of clinical guidelines by health care providers, and control of the underlying disease, this infection can successfully be managed in majority of patients (Perfect, *et al.*, 2010). Prompt appropriate diagnostic approaches and therapeutic interventions for CM among health care providers is recommended in patients with cardinal signs and symptoms of CM (WHO, 2011).

This study provides recommendations that will, improve and uphold the quality of health care provided to CM patients in the study area, promote optimal desired outcome of patients and increase patient satisfaction towards management. The recommendations will also assist policy makers and health care planners in improving the clinical management of CM as per the WHO guidelines and greatly contribute towards the attainment of vision 2030. Further, the recommendations from the study will promote professional responsibility and accountability of HCP. In addition, the results can be used as baseline data for other related studies.

1.8 Limitations of the Study

The study design was cross sectional, done at one time in the study area and so the study findings cannot be generalized. Purposive sampling technique, non-probability was used which makes generalization of the study findings limited. Sample size was small, (N=119) although census was used to pick all the HCP in the target population.

1.9 Conceptual framework

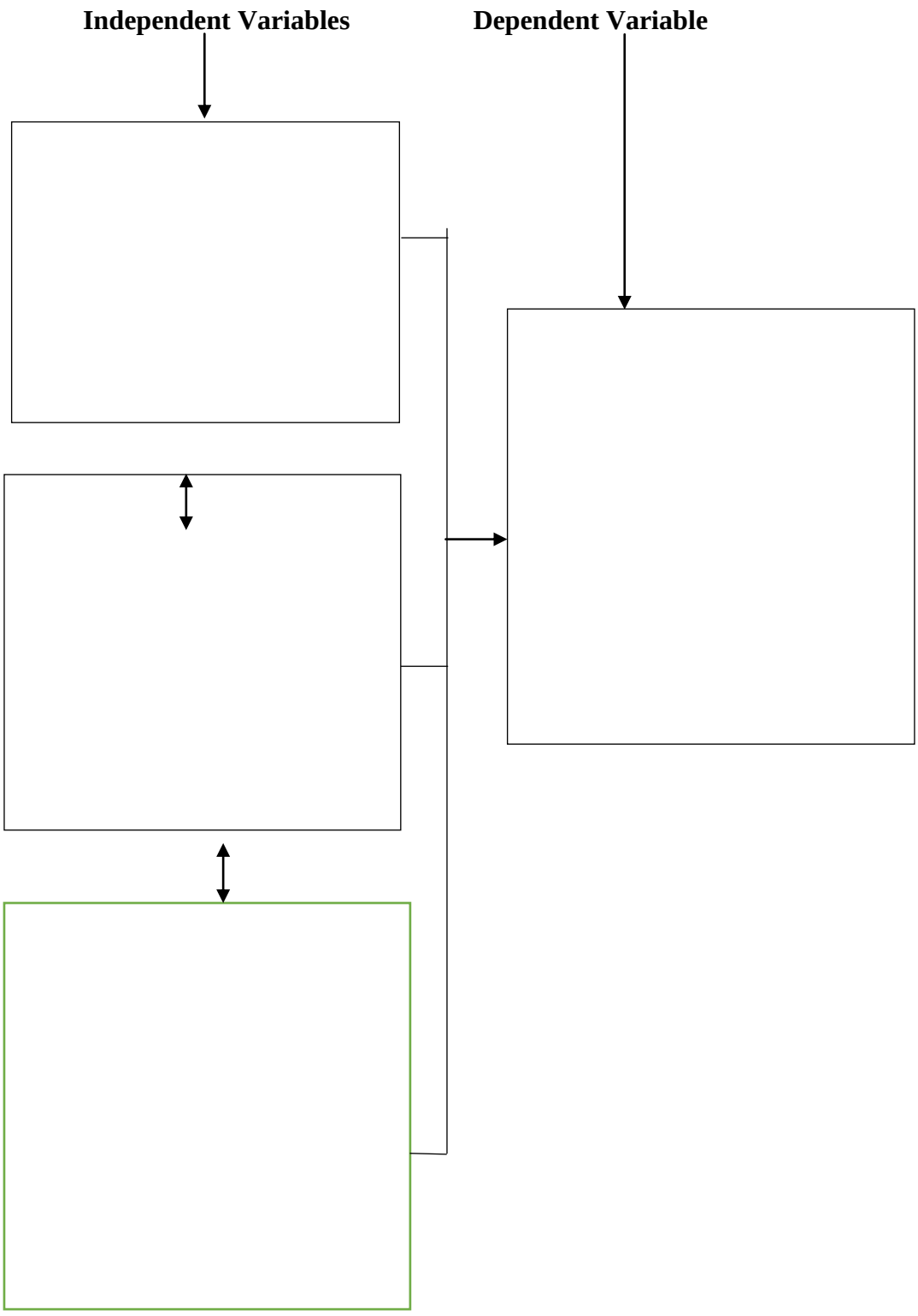

Figure 1.1 Conceptual framework
Source: Researcher, 2019

1.10 Operationalization of Variables

Adherence-Acting according to the recommended clinical guidelines by WHO on management of cryptococcal meningitis in adults.

Case Fatality Rate (CFR) - Number of people who die from a particular disease in all patient diagnosed with a particular morbidity over a time frame.

Cryptococcal meningitis - This is a fungal infection of the meninges of the brain and spinal cord.

Cryptococcal neoformans- An obligate aerobic type of encapsulated yeast that is able to live in both plants and animals.

Facilities – Basic equipment and supplies in the hospitals necessary for provision of quality of care to patients.

Health care providers- Trained, qualified and registered nurses, clinical officers and doctors providing direct care to patients/clients.

Morbidity-This is a state of ill health, disability or disease state

Mortality rate (MR) – The number of deaths measured in a given population

Prevalence- Number of all subjects in a population having a disease or characteristic at a particular time.

Saprophyte- A type of micro-organism that lives on dead or decomposing material.

Strategy-Modality applied to achieve a desired goal

CHAPTER TWO

LITERATURE REVIEW

2.1 Overview

This chapter contains the literature review on the background of CM, clinical management strategies, the conformance to WHO standards and the factors influencing clinical management of adult patients with cryptococcal meningitis.

2.2 Background of cryptococcal meningitis

Cryptococcus exists worldwide in the environment. The organism causing the disease is transmitted through inhalation but rarely causes a flared up clinically significant disease in otherwise healthy individuals. However, exacerbation of latent infection with immunocompromised states occurring months to years as a result of primary exposure leads to a clinically invasive disease (WHO, 2018).

The immune system can heal the body without medical intervention once Cryptococcus reaches the lungs through inhalation, the infection can be localized in the lungs, or can be circulated through blood and spread throughout the body. In health people with intact immunity, infection is self-limiting, and no symptoms are noticed. In patients with deranged immune states, the fungus develops in the lungs and it is distributed further to the CNS causing CM (Kanji, *et al.,* 2011).

Phases of therapeutic management of Cryptococcal Meningitis are 3 and include induction, consolidation, and maintenance phases. For rapid sterilization of cerebrospinal fluid, induction phase is instituted appropriately because retarded rates of clearing the fungus have been connected to increased mortality at week 2 and 10 of therapy (Abbas, *et al.,* 2016).

HIV-associated cryptococcosis is estimated at 1 million cases per year globally. However, the use of ART has reduced the infections incidence especially developed countries, however reported deaths from cryptococcosis are higher in low developed countries where there is inadequate health care services, accompanied by expanding uncontrolled HIV disease (Perfect, *et al.,* 2010).

2.3 Clinical management strategies of Cryptococcal meningitis

Management of CM effectively, involves prompt diagnosis and initiation of recommended fungicidal drugs, institution of priority interventions to prevent and combat elevated intracranial pressure (ICP), management of inflammatory syndrome related to immune reconstitution and prevention, monitoring and management of hypokalemia and nephrotoxicity (Sogbanmu *et al.*,2014).

2.3.1 Diagnosis of Cryptococcal Meningitis

Oyella *et al.,* (2012) advocates for screening for CM in all patients newly diagnosed, living with HIV infection and have associated low CD4 counts of less than 50cells/mm3 for appropriate plan of action. In addition, those individual patients with compromised immunity secondary to HIV infection and are malnourished with a very low body mass index (BMI) accompanied with clinical presentations of meningitis should equally be screened for CM for prompt management to promote desirable patient outcome.

2.3.2 Antifungal therapy in management of cryptococcal meningitis

According to Cox & Perfect *et al.,* (2018), the most effective therapeutic intervention for the patient with cryptococcal meningoencephalitis in the induction phase consists of amphotericin B plus flucytosine, in consolidation phase, fluconazole is administered and continued throughout the maintenance phase. In addition,

throughout therapy, monitoring of patients for recurrence of clinical symptoms suggestive of increased intracranial pressure, relapse of infection as a result of non-adherence or drug resistance, adverse events following antifungal therapy, and IRIS secondary to antiretroviral therapy.

The treatment management of Cryptococcal Meningitis is divided into three phases: 1) induction, 2) consolidation and 3) maintenance therapy. The goal of induction therapy is the rapid sterilization of cerebrospinal fluid. Slower rates of fungal clearance have been shown to be associated with increased mortality at both 2 and 10 weeks (Abbas *et al.*, 2016).

The WHO (2011) advices administration of a combination of Fluconazole and Flucytocine or high dose of stand-alone Fluconazole during the induction phase in the absence of Amphotericin B, then continue with 8 weeks of consolidation phase of oral Fluconazole and finally provide a maintenance phase of oral fluconazole.

According to John & Pradeep, (2017) the fungicidal therapy goal in HIV co-infected patients with CM is to eradicate and control the infection in acute phase then continue with a longstanding fluconazole regimen to suppress the cryptococcal organism. In patients with cryptococcal infection without HIV comorbidity, the therapeutic goal may differ.

Rothe *et al.,* (2013) noted significant baseline CNS complications and poor clinical outcomes with associated increased deaths and failure of drug efficiency from cryptococcal meningitis in HIV infected adults related to fluconazole monotherapy.

2.3.3 Prevention of drug complications

To prevent hypokalemia following administration of AmpB, pre-emptive hydration and electrolyte supplementation is done with One litre of normal saline solution with 20 mEq of potassium chloride (KCl) over two hours before each controlled infusion of amphotericin B and one to two 8-mEq KCl tablets orally twice daily. An addition 8-mEq KCl tablet twice daily may be added during the second week. This replaces the lost potassium (WHO,2011)

2.3.4 Management of Drug complications

Management of drug complications comprises of the following interventions, initial serum creatinine levels and 2–3 times weekly done in the second week of amphotericin B administration, weekly haemoglobin check after the baseline to detect anemia and transfuse as necessary (WHO 2018).

2.4 Adherence to WHO guidelines on clinical management of cryptococcal meningitis

Failure to adhere to clinical standards results into overtreatment or under treatment leading to a reduction of potential benefits with increased risks. On the other hand, adherence to standards assures provision of recommended care and also minimizes health care costs. In addition, there is a realization of quality of care when recommendations are followed than when they are not (Sidorenkov, *et al.*, 2011).

According to Austad *et al.*, (2015), to improve quality, minimize variations in provision of health care and assist in setting priorities among HCP, clinical practice guidelines are developed. However, in patients with co- morbidities, simultaneous application of several standards for single diseases may result into pill burden and overtreatment

The gold standard recommended clinical guidelines for management of cryptococcal meningitis in adults as per WHO (2018), include the following;

2.4.1 Induction Regimen

Induction therapy of 1-week amphotericin B deoxycholate 1.0 mg/kg/day + flucytosine 100 mg/kg/ day, in four apportioned doses each day, then 1 week of fluconazole 1200 mg per day for adults.

Alternatively;

- Fluconazole 1200 mg daily for 2 weeks plus flucytosine 100 mg/kg/day, divided into four doses / day
- Amphotericin B deoxycholate 1.0 mg/kg/day for 2 weeks plus fluconazole 1200 mg/ day.

2.4.2 Regimen for consolidation

Fluconazole 800 mg for 8 weeks after completion of 2 weeks of induction regimen.

2.4.3 Regimen for maintenance

Administration of Fluconazole 200 mg per day.

2.4.4 AMP B toxicity management and prevention

2.4.4.2 Serum potassium

Done initially then 2-3 times/ week, in the second week of amphotericin B administration.

2.4.4.3 Serum creatinine

Done initially then 2–3 times/ week, in the second week of amphotericin B administration.

2.4.4.4 Haemoglobin

Done as baseline and weekly.

2.4.4.5 Hypokalaemia

Increase the dose of potassium chloride supplementation to 40 mEq by intravenous infusion and/or one to two 8-mEq potassium chloride tablets per oral thrice a day if there is significant hypokalaemia of less than 3.3mol/L.

Perform daily monitoring of serum potassium.

2.4.4.6 Elevated creatinine

Daily serum creatinine monitoring is done

Incase serum creatinine increases by ≥2 fold from the initial measure increase pre-hydration to 1 L every eight hours and consider skipping one dose of amphotericin B temporarily. Once the creatinine levels stabilize, restart amphotericin B at a dose of 0.7 mg/ kg/day and administration of amphotericin B alternate days.

In cases of continuous rise of serum creatinine levels, stop amphotericin B and continue with fluconazole 1200 mg/ day, particularly if seven doses of amphotericin B have been administered.

In significant renal impairment, adjust fluconazole dose.

2.4.4.7 Severe anaemia

For severe amphotericin B–related anaemia, transfusion should be undertaken.

2.4.5 Corticosteroid therapy in during treatment of cryptococcal meningitis

In patients suffering from CM in HIV infection, steroid therapy is not provided especially in the phase of induction therapy.

2.4.6 Timing of ART

Instant ART initiation is not done for HIV co-infected patients until after 4-6 weeks following antifungal drug administration.

ART should be delayed by 4–6 weeks from the commencement of antifungal treatment in HIV infected patients with cryptococcal meningitis comorbidity.

2.4.7 Monitoring for Raised Intracranial Pressure

Perform initial lumbar puncture with the measurement of cerebral spinal fluid opening pressure as baseline to obtain results for comparison with the subsequent repeat measurements. This assists in evaluation of progress.

2.4.8 Monitoring treatment response

During the induction period of 2 weeks, response to treatment is done every day.

2.5 Factors influencing clinical management of cryptococcal meningitis

The aspects that impact on clinical management cryptococcal meningitis include; clinician factors and institutional/organizational factors.

2.5.1 Clinician Factors

A study done by Barth *et al.,* (2015) acknowledged the complexity of what modern medical practice become with interventions of new knowledge. Moreover, existing evidence suggests that those health care providers who adhere to clinical practice guidelines promote better patient outcomes.

According to Flora *et al.,* (2017), diagnosis of CM at an early stage brings about a reduction in CM-related deaths in that better outcomes have been observed on patients who receive early antifungal. CrAg positive patients without signs of cryptococcal disease, who received induction therapy with fluconazole, prevent the development of their disease and hospitalization, with an equivalent decrease in costs.

Almazrou, (2013) explains that although most standards provide clinicians with updated information, the same clinicians may regard these standards to be impractical with volume overload and a challenge to their autonomy. Lack of awareness, insufficient time to study the guidelines and guideline inaccessibility are factors that affect adherence to clinical practice guideline (CPG). However, CPG have been promoted widely but, that health care providers have not incorporated them.

Barth *et al.,* (2015) identified major obstacles to adherence of standards which include health workers inability to embrace change, overconfidence, varied goals for the clinician/ patient and external barriers such human, material, time and financial resources. Tsiga *et al.,* (2013) added that more reasons for non-compliance to clinical practice guidelines were time pressures while Carthey *et al.,* 2011 noted that guidelines with information overload was a hindering factor to adherence to the same guidelines. Clarke, *et al.,* (2010) also discovered that clinicians had problems in embracing new practices in the CPG protocols hence clang to their previous deeds despite the availability of the recommended guidelines

2.5.2 Institutional/organizational Factors

According to Castro-Sanchez *et al.,* (2014), effective institutional structure with strong leadership and an efficient learning culture are facilitate and promote implementation of CPG. The current pressured health care systems involve a multi-disciplinary approach of practitioners in service provision process resulting to fragmentation of care which may result in confusion between different professionals over their job description. This state of uncertainty may result into policy and guideline disregard.

A study done by Forsner, *et al., (*2010) revealed that supporting clinical guidelines adoption and implementation by the head of department in collaboration with a multi-disciplinary team is a successful modality in working with guidelines. On the other hand, lack of financial resources is an important issue of concern that prevents the progress of implementation of CPG.

As pointed out by Francke, *et al.,* (2008), CPG that are easily understood, easy to try and with no prerequisite for particular resources, have better odds of being utilized. However, according to Almazrou, (2013), standards that contradict each other, inadequate resources, motivation, fear of unknown and institutional challenges, are the major basic barriers to adherence of guidelines.

Barth *et al.,* (2015), explains that some CPG contain deeper variations ranging from simple and clear to intricate instructions with multiple rules that may conflict with others. In different occasions some CPG are likely to spell out alternatives which only suit the experienced health care providers but are inappropriate and bewildering for the novice HCP.

Rothe *et al.,* (2017), noted that the gold standard antifungal treatment for CM is often unavailable or difficulty to administer in Sub Saharan Africa. The WHO 2018 confirmed that insufficiency or unavailability of diagnostic equipment leads to delayed diagnosis. In addition, inadequate ability to monitor and manage drug toxicities in low-income countries drastically influence adherence to WHO standards in the management of CM.

Sloan &Paris, (2014), added that non-sustainable supply of the basic antifungal therapy and unavailability of fungicidal drugs in hospitals results in increased case-

fatality rate. Thau *et al.,* (2010) acknowledged that Amphotericin B remains a major ingredient of treatment, while therapy is prolonged, costly and complex to administer.

2.6 Summary of Research Gaps

Following a detailed relevant literature review, the summary and gaps identified with regard to this study are represented as shown in the table below.

Table 2.1 Summary of Research Gaps

AUTHOR YEAR	TITLE	FINDINGS	KNOWLEDGE GAP
Sogbanmu, John & Lalloo, (2015)	Management of cryptococcal meningitis in adults at Mthatha Hospital Complex, Eastern Cape, South Africa	The researchers used a retrospective study design to identify adherence to clinical practice guidelines.	Study done in South Africa and not JOOTRH or KCRH, Kisumu. Study was retrospective and used charts hence a possibility of missing some information. A cross-sectional study could be an option.
Sogbanmu *et al.,* (2014)	Management of cryptococcal meningitis in adults at Mthatha Hospital Complex, Eastern Cape, South Africa	The researchers majorly reviewed patients' charts hence there was missing data and inappropriate recording of interventions leading to unreliable findings.	Study not done in JOOTRH or KCRH, Kisumu. Observational check list could solve the problem of the missing data in the charts.
Almazrou , (2014)	Anticipated benefits of clinical practice guidelines Factors affecting their adherence and methods of implementation and dissemination	Physicians need awareness, knowledge, guideline accessibility, and reduced workload to modify their practice approaches.	Study not done in JOOTRH or KCRH, Kisumu. Author had more interest in physicians only, ought to have included other health care providers.

CHAPTER THREE

RESEARCH METHODOLOGY

3.1 Overview

This chapter contains the research approach employed in the study, information on area of study, the study design, sampling method, sample size, inclusion and exclusion criteria approached to data collection, processing, analysis and ethical considerations.

3.2 Study Design

Analytic cross-sectional study design using a quantitative approach was used.

3.3 Area of Study

Kisumu County is located in western Kenya, far from the nation's capital city. It's boarders follow those of the regional Kisumu district, one of the former administrative districts of the former Nyanza province. Its headquarters is Kisumu city. It has a population of 968,909 (statistics,2009). Kisumu county's neighbours are Siaya County to the west, Vihiga County to the north, Nandi county to the North East and Kericho County to the East. It is bordered to the South by Nyamira County, and Homabay County to the south west.

The city of Kisumu, on the shores of Lake Victoria, has historically functioned as a major center of Western Kenya commerce. Fishing, sugarcane farming, and rice farming are the county's principal industries. Despite the above economic activities, poverty levels in the region have remained high at 60 % exceeding the national average level of 50 % (World bank 2010).

The research was performed in the medical wards, outpatient departments and the patient support center (PSC) of JOOTRH and KCRH in July – September, 2019.

JOOTRH is located in Kisumu county, Kisumu East constituency, Kondele ward. It is now the largest referral hospital in Western Kenya and serves more than 100 county and sub-county hospitals in the region. Its main mandate is to provide curative, preventive, promotive, diagnostic, teaching and rehabilitative services. It serves a catchment population of 83642 (JOOTRH Hospital Strategic Plan, 2016-2021). Its medical units have a bed capacity of 110.

Kisumu County Referral Hospital is the second largest public hospital in Kisumu County located in Kisumu city center, Kisumu East constituency, Railways ward. Its medical units have a bed capacity of 61. The bed occupancy for the medical wards is 100%. It serves the peripheral facilities and offers diagnostic curative, preventive, promotive, and rehabilitative services. The hospital refers its complicated cases to JOOTRH for further management.

3.4 Target Population

According to Mugenda &Mugenda (2003), the target population needs to comprise some observable features of which the researcher anticipates to generalize the results of the study. The target population was the qualified health care providers offering care to adult patients suffering from CM in the medical wards, patient support center (PSC) and outpatient clinics in the two hospitals. There is a total of 119 health care providers in the aforementioned units in the two hospitals, 37 from KCRH and 82 from JOOTRH, thus;

HCP	KCRH	JOOTRH	TOTAL
Nursing officers	23	56	79
Consultants	3	3	6
Medical officers	2	11	13
Clinical officers	9	12	21
Grand total …….	37……	82……..	119

3.6 Sample Size Calculation

Kothari 2004 explains that a sample size is a portion of the total population employed in the generalization of views of the total population. In this study, the sample size was obtained using census where all the HCP who fell in the target population were recruited in the study participation owing to the fact that the target population was small.

3.5 Sampling Procedure

KCRH

Consultant physicians =3

Medical officers =2

Nurses =23

Clinical Officers =9

Total =37 HCP

JOOTRH

Consultant physicians =3

Medical officers =11

Nurses =56

Clinical Officers =12

Total =82 HCP

The total health care providers in the two hospitals (total sample size) was;

82+37 = 119 health care providers**.**

3.6 Inclusion and Exclusion Criteria

3.6.1 Inclusion Criteria

All qualified health care providers employed in the medical units, outpatient clinics/casualty and the patient support center for at least six months, were involved in the research.

3.6.2 Exclusion Criteria

All the qualified health care providers in the target population who did not consent to participate in the study were excluded.

3.7 Data Collection Instruments

Kothari, (2007), clarifies that self-administered questionnaires are the only way to prompt peoples' attitudes, beliefs, opinions and values. The researcher applied questionnaires in the collection of primary data to determine the clinical management strategies of CM and examination of the factors influencing clinical management of CM among health care providers. In addition, an observational check list was used to assess the adherence to WHO guidelines among HCP.

The research instrument for obtaining data in the study was adopted from WHO 2018 and adjustments were done after extensive literature review. The tool consisted of three parts. Part A obtained demographic features of the respondents, part B solicited for data on clinical management strategies of cryptococcal meningitis and part C probed for factors influencing clinical management of cryptococcal meningitis. An instruction for selecting the responses was provided in all the sections. The

questionnaire consisted of closed ended questions. The observation check list was scored according to individual HCP's performance during observation.

3.8 Validity of the Instruments

Porta, (2014) states that validity is the degree to which inferences drawn from a study are valid. In this study, professional advice was sought especially from my supervisors who are experts in the subject matter. A pilot study was conducted among 20 health care providers, (10% of the sample size) in Ahero County hospital to test the study feasibility and instrument reliability, necessary adjustments were made on the instruments before the main study was conducted.

3.9 Reliability of the Instruments

Porta, (2014), demonstrates that reliability is a measure of stability displayed when a measurement is repeatedly performed under identical conditions. This was achieved through a pilot study that was carried out in Ahero county hospital which confirmed reliability of the tools.

3.10 Procedures for Data Collection

Data was obtained by trained research assistants and the researcher. Self-administered questionnaires were provided to the sampled population, the research assistants and the researcher allowed them time to fill in the questionnaire and collected them when they were through with the filling. An observational check list was used by trained research assistants to evaluate the adherence to WHO guidelines on clinical management of CM, individual HCP were observed as they attended to patients suffering from CM and the observational check list was scored in relation to their performance. Two research assistants who were bachelor of science nurses on

internship were trained on scoring the observational check lists, each was based in one referral hospital.

3.11 Data Management

All the researcher assistants returned the filled questionnaires and observational checklists to the researcher for editing and ascertaining completeness and consistency before processing them. The raw data collected was coded, then analyzed using SPSS version 25.

3.12 Data Processing and Analysis

The Statistical Package for Social Science (SPSS Version 25) software was used in carrying out analysis. Descriptive analysis was done and reported using mean, percentages, and frequencies. For all the objectives Bivariate analysis was done using logistic regression and a p-value of at or below 0.05 was considered statistically significant.

3.13 Ethical Considerations

Ethical approval and permission for the purpose of conducting this research was acquired from Masinde Muliro University's Institutional Research and Ethics Committee (IREC). Permission to gather data in the study area was obtained from the County Government of Kisumu and the National Commission of Science Technology and Innovation (NACOSTI).

Justice: A letter accompanying a questionnaire was written by the researcher to introduce the researcher, make it clear that the data was to be used strictly for academic purposes only and that respondents' information was not to be submitted to unauthorized parties.

Confidentiality: no respondents' names were indicated, information was coded and kept under lock and key.

Autonomy: Informed and signed consent of the willing respondents was sought, and clarifications provided to the respondents.

Respect: No respondents were coerced to take part in the research, the reason for the study was explained to the respondents while assuring confidentiality and anonymity to them.

Beneficence: Participation in the study was free and voluntary hence withdrawal from the study had no penalty. The study findings were to be shared with the participated organizations.

CHAPTER FOUR

RESULTS

4.1 Overview

This chapter outlays the findings of the study done at JOOTRH and KCRH public health hospitals in Kisumu, on clinical management of cryptococcal meningitis in adults among health care providers. The data for this research was obtained through observational check lists and self-administered questionnaires from health care providers working in the two public health facilities in Kisumu County. The chapter is organized by preliminary analyses conducted to check for outliers and evaluate the assumptions of normality and homoscedasticity. The analytical strategy and subsequent findings from the analyses are then presented.

4.2 Evaluation of Statistical Assumptions

The data was tested for outliers. They utilized a box-and-whisker plot within SPSS. No outliers were present for the outcome variable (retention); therefore, no data was required to be eliminated for further hypothesis testing.

4.3 Questionnaire Response Rate

The research targeted a sample size of 119 respondents out of which 116 completed and returned the questionnaires, making a total response rate of 97%. The response rate was judged to be adequate because majority of healthcare providers are constantly engrossed at their workstations and therefore have little time to respond to research questionnaires. Out of the 116 completed questionnaires, 80 were from JOOTRH and 36 of them were from KCRH. A total of 60 observations was conducted in which 36 were done in JOOTRH while the remaining 24 was carried out in KCRH.

4.4 Demographic Characteristics of Respondents

The study sought to obtain information on the respondents' background characteristics based on the gender, job title, experience, age bracket and unit currently working. The analysis of their responses is given in table 4.2.

Table 4.1. Demographic background characteristics of respondents

		n	%
Gender	Male	52	44.8
	Female	64	**55.2**
Age groups in years	Below 30	74	**64.3**
	31-40	24	20.9
	41-50	9	7.8
	51 and above	8	7.0
Job title	medical consultant	5	4.3
	medical officer	14	12.1
	nursing officer	78	**67.2**
	clinical officer	19	16.4
Experience categories	5 years and below	75	**64.7**
	6-10 years	17	14.7
	11-20 years	12	10.3
	20 years and above	12	10.3
Unit of work	male medical ward	52	44.8
	female medical ward	37	31.9
	patient support center	15	13.0
	outpatient clinics	12	10.3

Findings in Table 4.2 gives a summary of the demographic characteristics of the respondents. With regard to their gender profiles, many were females (n=64, 55.2 %). This implied that majority of health workers in public hospital in the study area are female as opposed to males. Distribution of age bracket showed that many (n=74, 64.3%) were aged 30 years or below. Results on their job titles revealed that majority (n=78, 67.2%) were nursing officers while only a few (n=5, 4.3%) were medical consultants. A Greater part of the respondents had experience of 5 years or below (n=75, 64.7%).

4.5 Clinical management strategies of Cryptococcal meningitis

The first question of the research was to obtain the clinical management strategies of cryptococcal meningitis in Kisumu county public hospitals. Firstly, the respondents were asked which method they commonly used to diagnose cryptococcal meningitis. Results showed that 76%(n=88) reported using lumbar puncture with rapid CrAg assay while very few reported using lumbar puncture with rapid CSF India ink test (3%, n=4). When asked which antifungal drugs they commonly used in cryptococcal meningitis during the induction phase, majority (90.5%, n=105) reported using amphotericin B deoxycholate + fluconazole. Their responses are illustrated in table 4.3.

Table 4.2 Clinical management strategies of cryptococcal meningitis among health care providers

		n	%
Method commonly used to diagnose cryptococcal meningitis	lumber puncture with rapid CrAg assay	88	**75.9**
	lumber puncture with rapid CSF India ink test	4	3.4
	lumber puncture with CSF culture	22	19.0
	serum CrAg	2	1.7
Antifungal drugs commonly used in the treatment of cryptococcal meningitis during the induction phase	amphotericin B deoxycholate + flucytosine + fluconazole	8	6.9
	Fluconazole + flucytosine	3	2.6
	amphotericin B deoxycholate + fluconazole	105	**90.5**

When asked if they perform monitoring, management and prevention of amphotericin B deoxycholate toxicity, 95.7% (n=111) accepted, 83%(n=96) reported to be doing monitoring and management of raised intracranial pressure, 90%(n=104) reported to be timing ART initiation in HIV infected patients, 62%(n=72) reported not using adjunctive corticosteroids in the management of cryptococcal meningitis in HIV infected patients, 94%(n=109) reported to monitor treatment response, 85%(n=98) reported to do monitoring and management of immune inflammatory reconstitution syndrome while 86%(n=100) reported to be doing management of relapse for cryptococcal meningitis. Table 4.4 below portrays an evaluation of the responses

Table 4.3 Clinical management strategies provided for the patient suffering from cryptococcal meningitis

	YES		NO	
	N	%	N	%
Prevention, monitoring and management of amphotericin B deoxycholate toxicity	111	**95.7**	5	4.3
Monitoring for and management of raised intracranial pressure	96	82.8	20	17.2
Timing of ART initiation in HIV infected patients	104	89.7	12	10.3
Use of adjunctive corticosteroids in the management of cryptococcal meningitis in HIV infected patients	44	37.9	72	62.1
Monitoring of treatment response	109	**94.0**	7	6.0
Monitoring and management of immune reconstitution inflammatory syndrome	98	84.5	18	15.5
Management of relapse for cryptococcal meningitis	100	86.2	16	13.8

Respondents answered a total of seven closed ended questions. Each response was given a mark based on the level on the dichotomous scale with the anchors being No=0 to Yes=1 and vice versa for questions that were reverse coded. Scale scores were computed by adding responses to the seven questions leading to a minimum possible score of 0 and a maximum of 7. Respondents who scored below the mean score of 3.8 were classified as having poor management strategies and those that scored above the mean score were classified as having good management strategies.

- Good management strategies (above mean score of 3.8)
- Poor management strategies (Below mean score of 3.8)

From the results, many of the health care providers had good management strategies (n=65, 55.7%), while 44.3 %(n=51) had poor management strategies (figure 4.1)

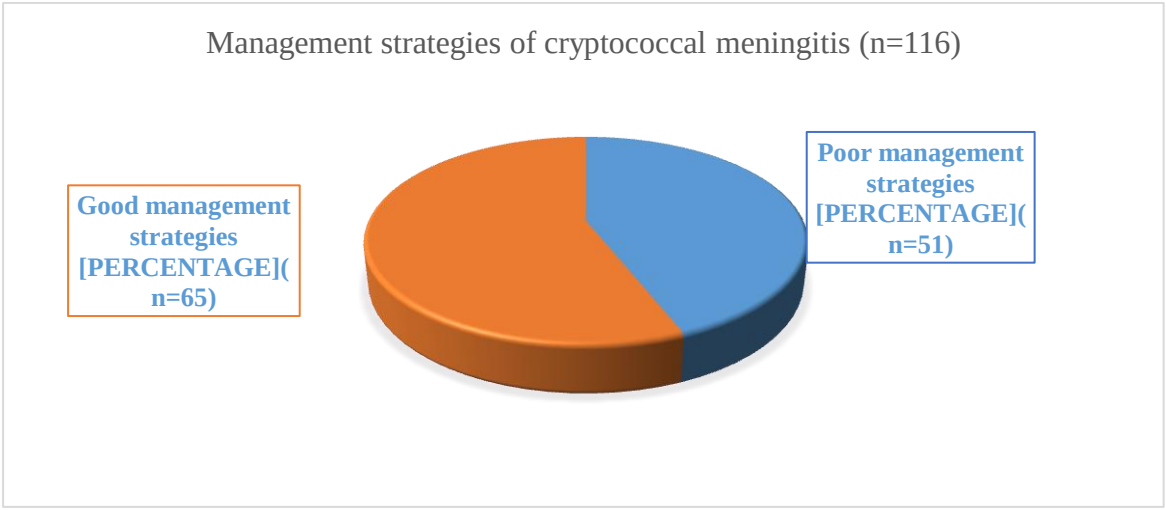

Figure 4.1. Management strategies of cryptococcal meningitis

4.6 Bivariate analysis of demographic characteristics associated with management strategies of cryptococcal meningitis

Bivariate analysis on demographic factors that are associated with clinical management strategies for cryptococcal meningitis shows that there was a borderline significant correlation between age and management strategies in the study area (OR: 0.7; 95% CI: 0.7 – 1.5; p=0.06) as portrayed in table 4.5. The respondents aged 30 years and below were 80% less likely to have poor management strategies compared to respondents aged 31 years and above.

Males were 1.3 times more likely to have poor management strategies compared to women (OR: 1.3; 95% CI: 0.7 – 2.3; p=0.97).

Job titles was not statistically significant with management strategies with the results showing that respondents who were medical consultants/medical officers being 1.7 times more likely to have poor management strategies compared with their counterparts nursing officers/clinical officers (OR: 1.7; 95% CI: 1.5 – 3.0; p=0.14).

Similarly, respondents who had an experience of five years or less were 80% more likely to have poor management strategies in contrast to those with an experience of six years or more (OR: 1.8; 95%CI: 0.6 – 2.2; p=0.008).

Table 4.4 Demographic characteristics associated with CM clinical management strategies

	n	Management strategies		Overall OR	95% CI	p-value
		Poor	Good			
Age						
<=30	74	85.3(157)	14.7(29)	0.2	0.7 – 1.5	**0.06**
>31	42	93.2(111)	6.8(8)			
Gender						
Male	52	61.7(66)	38.2 (41)	1.3	0.7 – 2.3	0.97
Female	64	61.2 (121)	38.8(77)			
Job titles						
Medical consultant/Medical officer	19	73.5(193)	26.5 (69)	1.7	1.5 – 3.0	0.14
Nursing officer/clinical officer	97	54.4 (23)	45.6(20)			
Experience						
<=5	75	58.8(62)	41.2 (44)	1.8	0.6 – 2.2	**0.008**
>6	41	33 (66)	67(43)			

4.7 Adherence to WHO guidelines on clinical management of cryptococcal meningitis

The second research question of the study was to find out adherence to WHO standards on clinical management of cryptococcal meningitis. The information was obtained via observation checklists. Firstly, with regards to methods of diagnosis of cryptococcal meningitis, it was observed that 100 % (n=60) did history taking of the patient and physical examination. An analysis of feedback is shown on Table 4.6 below.

Table 4.5 Adherence to WHO guidelines on clinical management of cryptococcal meningitis

	Yes		No	
	N	%	n	%
History taking	60	100.0	0	0.0
Physical examination	60	100.0	0	0.0
Diagnostic tests;				
Lumber puncture with measurements of CSF fluid opening pressure	0	0.0	60	**100.0**
Lumber puncture with rapid CSF CrAg assay	60	100.0	0	0.0
Lumber puncture with CSF India ink test	40	66.7	20	33.3
Rapid serum/whole blood CrAg assay	60	100.0	0	0.0
Induction phase of treatment				
Two weeks amphotericin B 1mg/kg/day + fluconazole 1200mg/day	60	100.0	0	0.0
Fluconazole 800mg daily for 8 weeks following induction phase	44	73.3	16	26.7
Preventing, monitoring and managing of amphotericin B toxicity				
Serum potassium:				
Initial Serum potassium	60	100.0	0	0.0
Serum potassium 2-3 times/week in the second week of amphotericin B administration	20	33.3	40	66.7
Hypokalemia				
Daily serum potassium measurement	4	6.7	56	**93.3**
20 mEq of potassium chloride infused in 1 litre of normal saline over two hours before each dose of amphotericin B	60	100.0	0	0.0
8-mEq potassium chloride 1-2 tablets orally twice daily	0	0.0	60	**100.0**
8-mEq tablet may be added twice/ day during the second week	4	6.7	56	**93.3**
Supplement magnesium 2 of 250-mg tablets of magnesium trisilicate twice / day, or magnesium chloride 4 mEq twice/ day	4	6.7	56	**93.3**
Serum creatinine				
Initial serum creatine measurement	60	100.0	0	0.0
Serum creatine 2-3 times weekly in the second week of amphotericin B therapy	16	26.7	44	**73.3**
Timing of ART In HIV positive patients				
Withhold ART 4-6 weeks from the initiation of antifungal drugs	56	93.3	4	6.7
Give blood transfusion in severe Amphotericin B related anemia	32	53.3	28	46.7
Monitoring for raised intracranial pressure				
Have an initial lumbar puncture	60	100.0	0	0.0
Measurement of CSF opening pressure	0	0.0	60	**100.**
Perform repeat lumbar puncture with measurement of CSF opening pressure	0	0.0	60	**100.0**
Management of raised intracranial pressure				
Therapeutic lumbar puncture	16	26.7	44	**73.3**
Persistent raised intracranial pressure				
Perform lumbar puncture if possible every day with measurements of CSF opening to evaluate progress	0	0.0	60	**100.0**
Monitoring treatment response				
Performed every day in the period of induction therapy	60	100.0	0	0.0

With regards to diagnostic tests, none (0%, n=0) did LP with measurement of CSF fluid opening pressure, all (100%, n=60) did the rapid serum/whole blood CrAg assay and LP with rapid CSF CrAg assay, majority (67%, n=40) did lumbar puncture with CSF India ink test.

In the induction phase of treatment all (100%, n=60) gave two weeks amphotericin B 1mg/kg/day + fluconazole 1200mg/day while a majority (73%, n=44) of them gave Fluconazole 800mg daily for 8 weeks following induction phase.

With regards to monitoring, preventing and managing of amphotericin B toxicity, all (100%, n=60) did serum potassium baseline, majority (67%, n=40) did not perform serum potassium 2-3 times every week in the second week of amphotericin B drug therapy.

In management of hypokalemia, majority (93%, n=56) did not monitor potassium daily but all (100%, n=60) administered 1 liter of normal saline infused with 20 mEq of potassium chloride beyond two hours prior to each infusion of amphotericin B. 93%(n=56) did not administer two of 250-mg tablets of magnesium trisilicate, or magnesium chloride 4 mEq twice/ day for supplementation of magnesium.

In monitoring of serum creatinine, all (100%, n=60) measured initial serum creatinine levels but 73% (n=44) did not measure 2-3 times/ week during the second week of amphotericin B drug therapy.

In timing of ART, in HIV co- infected patients, 93% (n=56) withheld HAART for 4-6 weeks following the initiation of antifungal regimen

In monitoring for raised intracranial pressure, all (100%, n=60) did not measure CSF opening pressure and also did not carry out a repeat lumbar puncture with measurement of CSF opening pressure to for monitoring of patient progress.

In management of raised intracranial pressure all (100%, n=60) did not do repeat daily therapeutic lumbar puncture (with measurements of CSF opening pressure where available. With regards to monitoring treatment response, all (100%, n=60) assessed patient response to treatment every day during the first two weeks of induction treatment.

The observation checklist had a total of twenty-five items. Each response was given a mark based on the level on the dichotomous scale with the anchors being No=0 to Yes=1 and vice versa for items that were reverse coded. Scale scores were computed by adding responses to the 25 items causing a minimum possible score of 0 and a maximum of 25.

Respondents who scored below the mean score of 20.6 were classified as not adhering to WHO guidelines and those that scored above the mean score were classified as adhering to WHO guidelines.

- Adhering to WHO guidelines (above mean score of 20.6)
- Not adhering to WHO guidelines (Below mean score of 20.6)

From the results, many of the health care workers were adhering to WHO guidelines (n=37, 61%), while 39% (n=23) did not adhere to WHO guidelines (Figure 4.2)

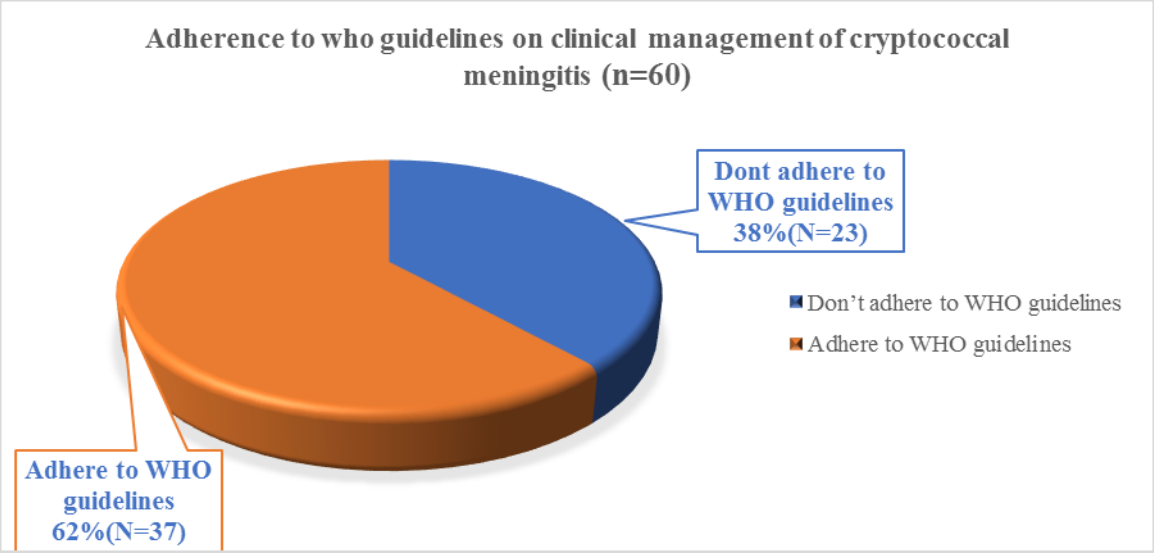

Figure 4.2. Adherence to who guidelines on clinical management of cryptococcal meningitis

4.8 Bivariate analysis of socio-demographic characteristics associated with adherence to WHO guidelines on CM management

Bivariate logistic regression was done to evaluate the relationship amongst adherence A and socio demographic characteristics. Nurses were 40% less likely to adhere compared to clinical officers (OR: 0.6; 95% CI: 0.4 – 0.9; p=0.01). Males were 1.2 times more likely to adhere compared to females (OR: 1.2; 95% CI: 0.8 – 1.9; p=0.3). This is shown in the table 4.10 below

Table 4.6 Socio demographic characteristics associated with adherence to WHO guidelines om management of CM

		Adhere		Don't Adhere		Overall OR	95% CI	p value
		N	%	n	%			
Job Titles	Nurses	14	45.1	18	54.9	0.6	0.4 – 0.9	**0.01**
	Medical officers	3	33.3	7	66.7	0.7	0.2 – 2.7	0.7
	Clinical officers	7	40.9	11	59.1	*	*	*
Gender	Females	18	46.4	21	53.6	1.2	0.8 – 1.9	0.3
	Males	4	16.7	17	83.3			

*** Reference category**

4.9 Factors influencing clinical management of cryptococcal meningitis

The third research question of the study was to find aspects that influence clinical management of Cryptococcal meningitis. Firstly, the respondents were asked if they were aware of the WHO guidelines on the management of cryptococcal meningitis, 89% (n=103) accepted that they were aware of the WHO recommended standards on management of CM. When asked if they have ever been trained on WHO guidelines on clinical management of cryptococcal meningitis, 55% (n=64) reported to have been trained. When asked if adherence to WHO to guidelines leads to better patient outcomes, 97%(n=113) accepted, 95%(n=110) agreed that WHO standards are useful source of advice to them, 88%(n=102) agreed that WHO guidelines are based on sound evidence and 56%(n=66) declined that adherence to WHO standards was part of their annual performance appraisal objective. When asked if WHO guidelines are not available in their unit of work, 68%(n=79) agreed, 65%(n=75) noted that WHO guidelines have information overload hence very complex to use, 87%(n=101) disagreed that WHO guidelines have multiple rules and are not easy to comply, 99%(n=115) disagreed that WHO guidelines are outdated and unrealistic, 53%(n=62)

declined that there was increased workload hence no enough time to comply with the WHO guidelines, 83%(n=96) did not accept that WHO standards conflict with other clinical practice standards and 78%(n=90) acknowledged that there were no adequate supplies and resources to facilitate adherence to the WHO guidelines. Table (4.8) below gives an analysis of the responses.

Table 4.7 Factors influencing clinical management of Cryptococcal meningitis

		n	%
Iam aware of the WHO guidelines on the management of CM	Yes	103	88.8
	No	13	11.2
I have been trained on WHO guidelines on clinical management of CM	Yes	64	55.2
	No	52	44.8
Adherence to WHO to guidelines leads to better patient outcomes	Yes	113	97.4
	No	3	2.6
WHO guidelines are a useful source of information to me	Yes	110	94.8
	No	6	5.2
The WHO guidelines are based on sound evidence	Yes	102	87.9
	No	14	12.1
The adherence of WHO guidelines is part of my annual performance appraisal objective	Yes	50	43.1
	No	66	56.9
WHO guidelines are not available in my unit of work	Yes	79	68.1
	No	37	31.9
The WHO guidelines have information overload hence very complex to use	Yes	41	35.3
	No	75	64.7
The WHO guidelines have multiple rules and are not easy to comply	Yes	15	12.9
	No	101	87.1
The WHO guidelines are outdated and unrealistic	Yes	1	0.9
	No	115	99.1
There is increased workload hence no enough time to comply with the WHO guidelines	Yes	54	46.6
	No	62	53.4
The WHO guidelines conflict with other clinical practice guidelines	Yes	20	17.2
	No	96	82.8
There are no adequate supplies and resources to facilitate adherence to the WHO guidelines	Yes	90	77.6
	no	26	22.4

4.10 Scoring of factors influencing clinical management of CM

Respondents answered a total of nine closed ended questions. Scale scores were computed by adding responses to the nine questions resulting in a minimum possible score of 0 and a maximum of 9. Respondents who scored below the mean score of 6.7 were classified as agreeing that the factors had a considerable influence on clinical management and those that scored above the mean score were classified as disagreeing that the factors had considerable influence on clinical management.

- Agreed (above mean score of 6.7)
- Disagreed (below mean score of 6.7)

From the results, a larger number of the respondents were in conformity that the factors had a major influence on adherence to WHO guidelines (n=67, 57.9%), while only 42.1 % (n=49) disagreed that the factors had a considerable effect on adherence to WHO guidelines (Figure 4.3).

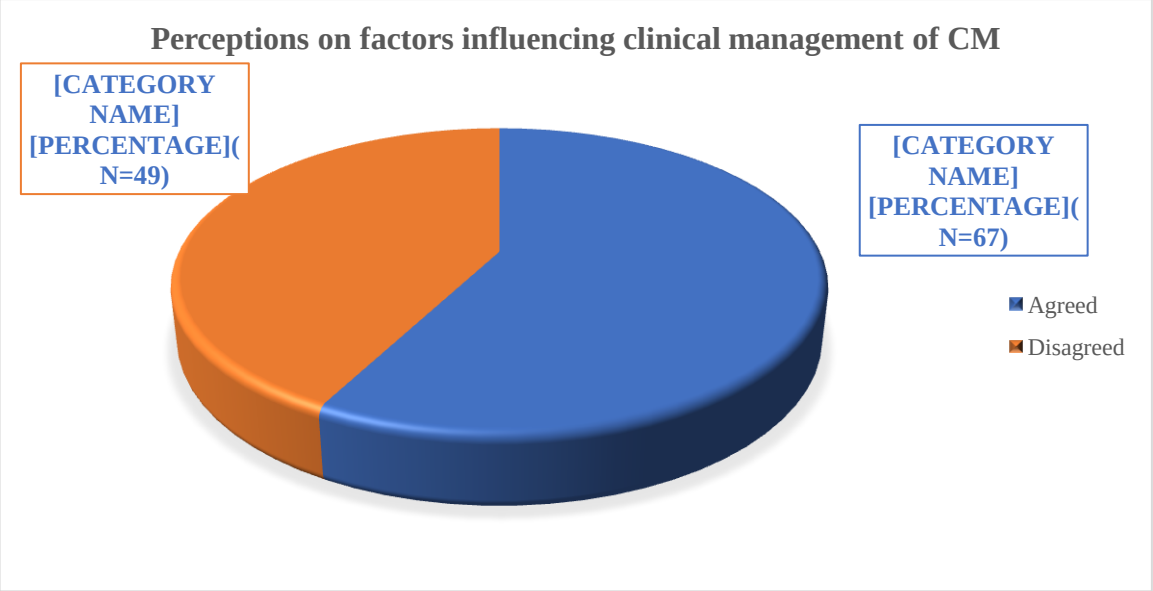

Figure 4.3 Summary on scoring of factors influencing clinical management of CM

4.11 Bivariate analysis of socio-demographic characteristics associated with factors influencing clinical management of CM

Bivariate analysis on socio-demographic aspects that are associated with perceptions on factors influencing clinical management shows that there was a major association between age and perceptions on factors influencing clinical management of CM (OR: 7.3; 95% CI: 1.5 – 35.7; p=0.01) as shown in table (4.9).

The respondents aged 30 years and below were 7.3 times more likely to agree that the factors were influencing clinical management compared to respondents aged 31 years and above (OR: 7.3; 95% CI:1.5-35.7; p=0.01).

Males were 80% less likely to agree that the factors were influencing clinical management compared to females (OR: 0.2; 95% CI: 0.03 – 1.2; p=0.02). Job titles was not statistically significant with perceptions on factors influencing clinical management with the results showing that respondents who were medical consultants/medical officers being 80% less likely to agree that the factors were influencing clinical management compared with their counterparts nursing officers/clinical officers (OR: 0.2; 95% CI: 0.06 – 0.8; p=0.3).

Similarly, respondents with an experience of five years or less were 40% more likely to agree that the factors were influencing clinical management of CM in contrast to tho*se* with an experience of six years or more (OR: 0.6; 95%CI: 0.1 – 0.74; p=0.04).

Table 4.8 Demographic characteristics associated with perceptions on factors influencing clinical management of CM

	N	Perceptions on factors influencing clinical management of CM		Overall OR	95% CI	p-value
		Agree	Disagreed			
Age						
<=30	74	60.8(45)	39.2(29)	7.3	1.5 – 35.7	**0.01**
<31	42	43.9(18)	56.1(24)			
Gender						
Male	52	60.0(31)	40.0 (21)	0.2	0.03 – 1.2	**0.02**
Female	64	54.5 (35)	45.5(29)			
Job titles						
Medical consultant/Medical officer	19	55.7(11)	44.3 (8)	0.2	0.06-0.8	0.3
Nursing officer/clinical officer	97	45.2 (44)	54.8(53)			
Experience						
<=5	75	54.4(41)	45.6 (34)	0.6	0.1-0.74	**0.04**
<6	41	42.3(17)	57.7 (24)			

CHAPTER FIVE

DISCUSSION

5.1 Introduction

This chapter addresses a synopsis of findings in regard to the purposes of the research. The study's aim was to evaluate the clinical management of cryptococcal meningitis among health care providers in selected hospitals, Kisumu County. The study determined the clinical management strategies of cryptococcal meningitis, assessed the adherence to WHO guidelines on cryptococcal meningitis and examined the factors influencing clinical management of cryptococcal meningitis among health care providers.

5.2.1 Clinical management strategies of cryptococcal meningitis

This study findings show that a satisfactory number of the health care providers (55.7%, n=65) had good clinical management strategies. However, although the WHO standards, 2018 does not recommend steroid use among HIV infected CM patient during the period of induction phase, this study identified that 37.9% (n=44) of HCP carried out this strategy indicating the need for prompt updates for the HCP on the most current WHO gold standard guidelines.

Majority of the HCP (95.5%, n=111) monitored and managed amphotericin B deoxycholate toxicity which is in line with the WHO guidelines. This finding differs with a research carried out in South Africa on cryptococcal management in adults by Sogbanmu *et al.,* (2014) which identified that while managing patients with cryptococcal meningitis, effective measures such as renal toxicity monitoring and documentation of fluid administration were not done.

Respondents who had an experience of five years or less were 80% more likely to have poor management strategies in contrast to those with an experience of six years or more (OR: 1.8; 95%CI: 0.6 – 2.2; p=0.008).These findings support a study done by Barth *et al.,* 2015, which revealed that there is a difference in practice over the generations and clinicians who are in their second half of their career, practice as individuals according to their knowledge and experience.

The study identified that males were 1.3 times more likely to have poor management strategies compared to women (OR: 1.3; 95% CI: 0.7 – 2.3; p=0.97). Majority of health care providers were females (55.2%, n=64) and this possibly explains why there was fairly good clinical management strategies in the study area.

5.2.2 Adherence to who guidelines on management of cryptococcal meningitis

This study results show that, 61% (n=37) of the health care providers were adhering to WHO guidelines, the results further reveals that nurses were 40% less likely to adhere to the WHO recommended guidelines on management of CM compared to clinical officers (OR: 0.6; 95% CI: 0.4 – 0.9; p=0.01),in addition, males were 1.2 times more likely to adhere compared to females (OR: 1.2; 95% CI: 0.8 – 1.9; p=0.3). The study also realized 100% (n=60) history taking and physical examination of patients by the HCP, this is consistent with the WHO 2018 guidelines which recommends that earlier diagnosis, and prompt treatment of cryptococcal malaise and its complications, is required to lessen the incidence and related high death rate in resource limited settings.

All the HCP (100%,n=60) performed rapid serum/whole blood assay and lumbar puncture with rapid CSF CrAg assay while 67%,(n=40) of HCP performed lumbar puncture with CSF India ink test to diagnose CM .This is in line with the WHO 2018

guidelines and a study done by Oyella *et al.*, 2012 which encourages clinicians to be cautious in diagnosis of cryptococcal disease in vulnerable patients who present with meningeal irritation, neck pain, a low BMI, and a recent HIV diagnosis before ART initiation for suitable intervention.

It is established from this study that all the health care providers (100%, n=60) gave two weeks amphotericin B 1mg/kg/day + fluconazole 1200mg/day in the induction phase of treatment while a majority (73%, n=44) of them gave Fluconazole 800mg daily for 8 weeks following induction phase. This finding indicates that the HCP in the study area instituted appropriate therapy in the induction phase according to the WHO guidelines 2018 on clinical management of cryptococcal meningitis and a study done by Govender et al, 2013.

Although this study realizes that all the HCP (100%, n=60) did administer 20 mEq of potassium chloride infused in 1 litre of normal saline over two hours before each infusion of amphotericin B, all HCP (n=60) never monitored potassium daily and only 67% (n=40) checked the serum potassium levels 2-3 times weekly. This practice contradicts the recommended WHO guidelines, 2018. This finding proves that the monitoring of AMP B toxicity was not sufficiently performed in the study area hence increasing the risk for mortality from preventable AMP B toxicity. In addition, 93% (n=56) did not administer Magnesium to counteract AMP B complications. This outcome is commensurate to those of a comparable research done in South Africa by Sogbanmu *et al.,* 2014 which revealed that preload and potassium supplementation were not done during the management of patients with CM.

It is noted from the study that all the health care providers (100%, n=60) measured serum creatinine at baseline but a large number of the HCP (73% n=44) did not measure 2-3 times weekly as stipulated in the WHO recommended guidelines. Majority of the HCP (93% n=56) of HCP did timing of ART, in HIV patients, through withholding it 4-6 weeks following antifungal treatment hence prevention of IRIS as a result of ART. This latter finding is in line with a study carried out by Cox & Perfect, 2018 on clinical management of CM.

On the other hand, all the HCP (100%, n=60) neither measured CSF opening pressure nor performed any subsequent lumbar puncture with measurement of CSF opening pressure as recommended by WHO 2018 to monitor patient progress in regard to raised ICP. In addition, all the HCP (100%, n=60) did not perform repeat daily therapeutic lumber puncture and CSF opening pressure measurement as a means of managing raised ICP. These results agree with a study carried out in 2014 by Adeyemi & Ross which noted that previous studies had shown critical disparities in clinicians' compliance to recommendations on management of CM. However, all the HCP (100%, n=60) assessed the patients for response to treatment on a daily basis during the induction phase of regimen, this practice is line with the WHO 2018 recommended guidelines.

5.2.3 Factors influencing clinical management of cryptococcal meningitis

The study finding indicate that a good number of HCP (89%, n=103) were aware of the WHO standards on the administration of cryptococcal meningitis and a satisfactory number (55% n=64) reported to have been trained on WHO guidelines on clinical management of cryptococcal meningitis. This finding outcome is commensurate to a study done by Castro-Sanchez *et al.,* 2014, who stated that a learning culture that is powerful promotes adherence to clinical practice guidelines.

There was a substantial relationship between age and perceptions on factors influencing clinical management in the study area (OR: 7.3; 95% CI: 1.5 – 35.7; p=0.01).Study results additionally showed that respondents who were medical consultants/medical officers were 80% less likely to agree that the factors were clinical management compared with their counterparts nursing officers/clinical officers (OR: 0.2; 95% CI: 0.06 – 0.8; p=0.3).

Similarly, respondents having an experience of five years or less were 40% more likely to agree that the factors were influencing clinical management of CM patients in contrast to those with an experience of six years or more (OR: 0.6; 95%CI: 0.1 – 0.74; p=0.04).

The study findings establish that the major motivating factor for effective clinical management of cryptococcal meningitis was the acknowledgement by the HCP that WHO guidelines lead to a better patient outcome (97%, n=113).Other motivating factors included WHO guidelines are useful source of advice to HCP, 95% (n=110), and WHO guidelines are based on sound evidence, 88% (n=102). These findings tally with those in a research by Barth *et el.*, 2015 which showed that clinical guidelines promote good practice and improve patient outcome.

On the other hand, the major hindering factor to clinical management of CM was inadequate supplies and resources to facilitate adherence (78%, n=90). This was followed closely by unavailability of WHO guidelines in the unit of work, (68% n=79). These research results concur with a study done by Almazrou, 2013 on barriers to adherence to clinical guidelines. In addition, 46.6 %, (n=54) of HCP stated that there was increased workload hence were not able to adhere to WHO guidelines, this

finding also tallies with a study done by Tsiga *et al.*, 2013 which identified time pressure and excess workload as factors influencing clinical management negatively.

CHAPTER SIX

CONCLUSION AND RECOMMENDATIONS

6.1 Conclusion

The study concludes that a satisfactory number of health care providers (55.7%) had good clinical management strategies. The HCP's age (p- value 0.06) and years of experience (p-value 0.008) greatly influenced the clinical management strategies of cryptococcal meningitis.

Critical effective aspects in the WHO recommended guidelines in the management of CM such as measurement of CSF opening pressure, daily observation of serum potassium levels, monitoring of serum creatinine 2-3 times weekly and daily repeat of therapeutic lumber puncture in management of raised intracranial pressure, were not done in this study during the study period. This finding can be associated with the increased CM mortality rate in the study area.

55% (n=6) of HCP reported to have been trained on WHO guidelines on clinical management of cryptococcal meningitis. Major motivators of effective clinical management of CM were; HCP's acknowledgement that WHO guidelines lead to better patient outcome (97%), WHO guidelines are a good source of advice (95%), and guidelines are based on sound evidence (88%). On the other hand, inadequate resources and supplies to facilitate adherence to the WHO guidelines (78%), unavailability of WHO guidelines in the unit of work (68%), and increased workload (46.6%), were the major hindrances of effective clinical management of cryptococcal meningitis.

6.2 Recommendations

- The County government of Kisumu in collaboration with the two hospital management teams in the study area, to organize and provide periodic and inductive training opportunities for the HCP especially those with years of experience of 5 years and below to promote capacity building on clinical management strategies of CM whose prevalence is high in this region.
- In addition, the HCP in the two hospitals should be encouraged to work towards accessing and acquiring knowledge and skills to appropriately equip themselves in managing patients suffering from cryptococcal meningitis using the WHO guidelines through attending available scheduled continuous education programmes, special trainings e.g. on job trainings, workshops and seminars so as to facilitate, attain and sustain optimal adherence to WHO recommended guidelines on the management of CM.

  The hospital management teams with the medicine departments in the two hospitals should consistently avail current recommended clinical guideline protocols in all the medical departments to ease reference, hence promote adherence. In addition, they should include the aspect of adherence to WHO guidelines on management of cryptococcal meningitis, as one of the yearly appraisal objectives and provide timely supportive supervision in order to promote and streamline optimal adherence to the WHO guidelines on CM management.
- Considering the disease burden in the study area and the wake of the National Universal Health Coverage strategy, the policy makers at the ministry of health in the County government of Kisumu to provide adequate resources, facilities and supplies to facilitate clinical management of CM management.

REFERENCES

Adeyemi, B.O., &Ross, A. (2014). *Management of cryptococcal meningitis in a district hospital in Kwazuru-Natal*: A clinical Audit .Afr j prm Health care fam Med.2014; 6(1), Art.//672,6 pages.

Almazrou Mazrou S.H. (2013). Expected benefits of clinical practice guidelines: *Factors affecting their adherence and methods of implementation and dissemination*. J Health Spec; 1:141-7.

Ali Mohammad Mosadeghrad (2014). *International Journal of Health Policy and Management*, 3(2), 77–89

Babbie, E. (2004). *The practice of social research* (10th Ed); Thomson Belmont CA: Wadsworth Publishing Company.

Britz, E., Perovic, O., von Mollendorf, C., von Gottberg, A., Iyaloo, S., &Quan V. (2016). The Epidemiology of Meningitis among Adults in a South African Province with a High HIV Prevalence, 2009-2012. PLoS ONE 11(9): e0163036.doi:10.1371/*journal.pone*.0163036.

Carthey, J., Walker, S., Deelchand, V., Vincent, C., & Griffiths, W.H. (2011). Breaking the rules: understanding non-compliance with policies and guidelines. *Br Med J;* 343:d5283.

Castro-Sanchez, E., Charani, E., Drumright, L.N., Sevdalis, N., Shah, N., &Holmes A.H. (2014). *Fragmentation of care threatens patient safety in peripheral vascular catheter management in acute care – a qualitative study*. PLoS One 2014; 9:e86167.

Chau, (2010). *A prospective descriptive study of cryptococcal meningitis in HIV uninfected patients in Vietnam - high prevalence of Cryptococcus neoformans var grubii in the absence of underlying disease* BMC Infectious Diseases 2010,10:199.

Clarke, A., Blundell, N., Forde, I., Musila, N., Spitzer, D., & Naqvi, S. (2010). *Can guidelines improve referral to elective surgical specialties for adults?* A systematic review. Qual Saf HealthCare; 19:187-94.

Concha-Velasco F, GonzaÂlez-Lagos E., Seas C., &Bustamante, B. (2017). *Factors associated with early mycological clearance in HIV-associated cryptococcal meningitis*. PLoS ONE 12(3): e0174459. https://doi.org/10.1371/journal. pone.0174459

Corrêa, I., Moralejo, D., Barretti, P., &El Dib R.P. (2013). *Interventions to improve adherence to guidelines on 'Standard Precautions' for the control of healthcare- associated infections*. Cochrane Database of Systematic Reviews 2013, Issue 10. Art. No.: CD010768.DOI:10.1002/14651858.CD010768.

Forsner, T., Hansson, J., Brommels, M., Wistedt, A.A., & Forsell, Y.(2010). *Implementing clinical guidelines in psychiatry*: A qualitative study of perceived facilitators and barriers. BMC Psychiatry; 10:8.

Francke, A.L., Smit M.C., de Veer A.J, &Mistiaen, P. (2008). *Factors influencing the implementation of clinical guidelines for health care professionals*: A systematic Meta review. BMCMed Inform Decis Mak 2008; 8:38.

Ganiem, A.R., Indrati, A.R., Wisaksana, R., Meijerink, H., &Van der Ven A. (2014). Asymptomatic cryptococcal antigenemia is associated with mortality among HIV-positive patients in Indonesia. *J Int AIDS Soc* 17: 18821.

Govender, N.P, Meintjes, G., Bicanic, T., Dawood, H., Harrison, T.S., Jarvis, J.N. (2013). Guideline for the prevention, diagnosis and management of cryptococcal meningitis among HIV-infected persons: 2013 update by the Southern African HIV Clinicians Society. *S Afr J HIV Med.*; 14(2):76±86.

Guidelines for the diagnosis, prevention, and management of cryptococcal disease in HIV- infected adults, adolescents and children, March 2018. Geneva: World Health Organization. License: CC BY-NC-SA 3.0 IGO.

Jean Louis F., Andre J.A., Perrin, G., Domercant, J.W., &Francois, K. (2016) Low Prevalence of Cryptococcal Antigenemia among Patients Infected with HIV/AIDS in Haiti. *J AIDS Clin Res* 7: 577. doi:10.4172/2155-6113.1000577.

Julian, H., Barth, Shivani Misra, Kristin Moberg Aakre, Michel R…, & Oosterhuis. (2015). *Why are clinical practice guidelines not followed?* DOI 10.1515/cclm-2015-0871e

Kothari, C. R. (2007). *Research Methodology: Methods and Techniques.* New Delhi: New Age International Publishers

Lee (2012): *Correlation of anti-fungal susceptibility with clinical outcomes in patients with cryptococcal meningitis*. BMC Infectious Diseases; 12:361.

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Manga, N.M, Cisse-Diallo, V.M.P., Dia-Badiane, N.M. (2016). Prevalence and Factors Associated with Positive Cryptococcal Antigenemia among HIV Infected Adult Hospitalized in Senegal. *J HIV Retrovirus*; 2:2:

Mdodo, R., Moser, S.A., Jaoko, W., Baddley, J., Pappas, P., Kempf, M.C. (2011). *Antifungal susceptibilities of Cryptococcus neoformans cerebrospinal fluid isolates from AIDS patients in Kenya*. Mycoses; 54(5):e438–42.

Mugenda & Mugenda (2003), Research Methods: *Quantitative and Qualitative Approaches.*

Oyella (2012): Prevalence and factors associated with cryptococcal antigenemia among severely immunosuppressed HIV infected adults in Uganda: a cross-sectional study. *Journal of the International AIDS Society;* 15:15.

Perfect, J.R., Dismukes, W.E, Dromer, F., Goldman, D.L., Graybill, J.R., Hamill, R.J. (2010). *Clinical practice guidelines for the management of cryptococcal disease:* update by the infectious diseases society of America. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America.; 50(3):291– 322.

Rothe, C., Sloan, D.J., Goodson, P., Chikafa, J., &Mukaka, M, (2013). *A Prospective Longitudinal Study of the Clinical Outcomes from Cryptococcal Meningitis following Treatment Induction with 800 mg Oral Fluconazole in Blantyre,* Malawi. PLoS ONE 8(6): e67311.doi:10.1371/journal.pone.0067311.

Sawadogo, S., Makumbi, B., Purfield, A., Ndjavera, C., Mutandi, G., &Maher, A., (2016). Estimated Prevalence of Cryptococcus Antigenemia (CrAg) among HIV-Infected Adults with Advanced Immunosuppression in Namibia Justifies Routine Screening and Preemptive Treatment. PLoS ONE 11(10): e0161830. doi:10.1371/*journal.pone.*0161830.

Sidorenkov, G., Haaijer-Ruskamp, F.M, de Zeeuw, D., &Denig P. (2011). A Longitudinal Study Examining Adherence to Guidelines in Diabetes Care According to Different Definitions of Adequacy and Timeliness. PLoS ONE 6(9): e24278. doi:10.1371/*journal.pone*.0024278.

Sloan, D.J, &Parris, V. (2014). *Cryptococcal meningitis:* Epidemiology and therapeutic options. Clin Epidemiol 6: 169-182.

Tsiga, E., Panagopoulou, E., Sevdalis, N., Montgomery, A., &Benos, A. (2013).The influence of time pressure on adherence to guidelines in primary care: an experimental study. *Br Med J Open*; 3:e002700.

World Health Organization (2011). *Rapid Advice- Diagnosis, Prevention and Management of Cryptococcal Disease in HIV-infected Adults, Adolescents and Children*. Geneva: World Health Organization.

WHO, (2012). *Rapid advice: Diagnosis, prevention and management of cryptococcal disease in HIV infected adults, adolescents and children*. 2011.

Yamane, T. (1967): *Statistics: An Introductory Analysis*, 2nd Ed., New York: Harper and Row.

APPENDICES

APPENDIX I: INFORMED CONSENT FORM

INFORMATION SHEET

Dear respondent,

Iam Robina Ogendo, a scholar at the school of Nursing, midwifery And Paramedical Sciences (SONMAPS) in Masinde Muliro University of Science and technology (MMUST). Iam required to conduct a research study as part of the university requirement. The topic for my study is; *Clinical management of Cryptococcal Meningitis among health care providers in JOOTRH and KCRH in Kisumu County, Kenya.*

Benefits: There is no any financial benefit for participation but this study's results will be useful in understanding the clinical management of cryptococcal meningitis

Risks: No risks are associated with participation of this study.

Confidentiality: No name shall appear anywhere in this study, all the information provided by you will be kept confidential and private.

Participation: This study entails voluntary participation. Unwillingness to participate or withdrawal from participation in the study will not result in any penalty.

Compensation: There is no compensation for participating in the study.

Conflict of interest: The researcher and the supervisors confirm that there is no conflict of interest amongst them.

CONSENT FORM

If you Consent to Participate in the study please sign below;

I hereby consent to participate in this study. I have been informed of the nature of the study being undertaken and potential risks explained to me. I also understand that my participation in the study is voluntary and the decision to participate or not to participate will not affect my employment status at this facility in any way whatsoever. I may also choose to discontinue my involvement in the study at any stage without any explanation or consequences. I have also been reassured that my personal details and the information I will relay will be kept confidential. I confirm that all my concerns about my participation in the study have been adequately addressed by the investigator and the investigator have asked me questions to ascertain my comprehension of the information provided.

Participant's Signature ……Date……..

Researcher's name…….....Date……

Researcher's Signature…… Date ……

For any Clarification, please contact;

Robina Ogendo (Researcher),

Mobile No. 0716903215.

Email ogendorobina@yahoo.com

APPENDIX II: OBSERVATION CHECK LIST ON ADHERENCE TO THE WHO GUIDELINES ON CLINICAL MANAGEMENT OF CRYPTOCOCCAL MENINGITIS.

OBSERVATION CHECK LIST (ADHERENCE TO WHO GUIDELINES ON CM MANAGEMENT) **No….....Gender……Job title……** **ACTIVITY DONE**	**YES**	**NO**
Methods of diagnosis of cryptococcal meningitis *(Confirm and tick if the health care provider performed the following)* • History taking • Physical examination **Diagnostic tests;** *(Confirm and tick which diagnostic test the health provider carried out)* • Lumber puncture and measuring of CSF fluid opening pressure • Lumber puncture with rapid CSF CrAg assay • Lumber puncture with CSF India ink test • Rapid serum/whole blood CrAg assay • Lumber puncture with CSF culture		
Induction phase of treatment *Confirm and tick the regimen used by the health care provider; in the first two weeks;*		

• Amphotericin B deoxycholate 1.0 mg/kg/day+Flucytosine 100mg/kg/day for 1 week then one week Fluconazole 1200mg/day. • Two weeks Fluconazole 1200mg/day+Flucytosine 100mg/kg/day. • Two weeks amphotericin B 1mg/kg/day+ Fluconazole 1200mg/day.		
Management of amphotericin B toxicity *(Confirm and tick if any of the following was done by the health care provider)* **Serum potassium**: • Baseline • 2–3 times every week in the second week of amphotericin B therapy. **Hypokalaemia** • Monitor potassium daily • 20 mEq of potassium chloride infused in 1 litre of normal saline over two hours before each infusion of amphotericin B • One to two 8-mEq KCl tablets orally twice daily. • An additional 8-mEq KCl tablet twice daily during the second week. • Two of 250-mg tablets of magnesium trisilicate twice daily, or magnesium chloride 4 mEq twice daily to supplement magnesium. **Serum creatinine**		

• Measured at baseline • Measured 2–3 times every week in the second week of amphotericin B drug regimen. **Timing of ART (In HIV positive patients)** • Withheld for 4–6 weeks following the initiation of antifungal therapy.		
Monitoring for raised intracranial pressure • Have an initial lumbar puncture • Measurement of CSF opening pressure • Perform subsequent lumbar puncture with measurement of CSF opening pressure to monitor patient progress in regard to raised ICP. **Management of raised intracranial pressure:** • Therapeutic lumbar puncture **Persistent raised intracranial pressure** • Perform lumbar puncture every day with measurement of CSF opening pressure if to treat raised ICP.		
Monitoring treatment response • Done every day during the induction phase of therapy**.**		
Management of Amphotericin B deoxycholate associated anemia • Blood transfusion		

APPENDIX III: STUDY QUESTIONNAIRE

Questionnaire Serial Number _____ Questionnaire Status _____ (1=complete; 2= partially complete)

Interviewer ID _____ Date of Interview ____/____/___

Your honest answers on the questionnaire that follows will be of great help in the clinical management of cryptococcal meningitis in adults.

SECTION A

Demographics

(Tick/indicate the correct response)

1. Indicate your gender?

Male [ ]

Female [ ]

2. What is your age in years?

……
……

3. What is your current job title?

Medical consultant [ ] Medical officer [ ]

Nursing officer [ ] Clinical officer [ ]

4. What number of years of experience do you have at work?

……
……..

5. Which work unit are you currently operating in?

Male medical ward [ ] Female medical ward [ ]

Patient support center [ ] Outpatient clinics [

SECTION B

Clinical management strategies of cryptococcal meningitis

(Tick/indicate the correct response)

1. Which method do you commonly use to diagnose cryptococcal meningitis? (*Choose one*)

Lumber puncture with rapid CrAg assay [ ]

Lumber puncture with rapid CSF India ink test [ ]

Lumber puncture with CSF culture [ ]

Others
(specify)……
……

……
……

2. Which antifungal drugs do you commonly use in the management of cryptococcal meningitis during the induction phase? (*Choose one*)

Amphotericin B deoxycholate + Flucytosine+Fluconazole [ ]

Fluconazole+Flucytosine [ ]

Amphotericin B deoxycholate+Fluconazole [ ]

Others
(specify)……
……

……
……..

3. Which other management do you provide for the patient suffering from cryptococcal meningitis in your unit of work?

(i) Monitoring, management and Prevention of amphotericin B deoxycholate toxicity

Yes [ ] No [ ]

(ii) Monitoring for and management of raised intracranial pressure

Yes [ ] No [ ]

(iii) Timing of ART initiation in HIV infected patients

Yes [ ] No [ ]

(iv) Use of adjunctive corticosteroids in the management of cryptococcal meningitis in HIV infected patients

Yes [ ] No [ ]

(v) Monitoring of treatment response

Yes [ ] No [ ]

(vi) Monitoring and management of immune inflammatory reconstitution syndrome

Yes [ ] No [ ]

(Vii) Management of relapse for cryptococcal meningitis

Yes [ ] No [ ]

SECTION C

Factors influencing clinical management of Cryptococcal meningitis

(Tick/indicate the correct response)

The following factors influence my adherence to WHO endorsed standards on management of cryptococcal meningitis in adults

1. Iam aware of the WHO guidelines on management of Cryptococcal meningitis

Yes [ ] No [ ]

2. I have been trained on WHO guidelines on clinical management of cryptococcal meningitis?

Yes [ ] No [ ]

3. Adherence to WHO guidelines leads to better patient outcomes

Yes [ ] No [ ]

4. WHO guidelines are a useful source of information to me

Yes [ ] No [ ]

5. The WHO guidelines are based on sound evidence

Yes [ ] No [ ]

6. The adherence of WHO guidelines is part of my annual performance appraisal objective

Yes [ ] No [ ]

7. WHO guidelines are not available in my unit of work

Yes [ ] No [ ]

8. The WHO guidelines have information overload hence very complex to use

Yes [ ] No [ ]

9. The WHO guidelines have multiple rules and are not easy to comply

Yes [ ] No [ ]

10. The WHO guideline is outdated and unrealistic

Yes [ ] No [ ]

11. There is increased workload hence no enough time to comply with the WHO guidelines

Yes [ ] No [ ]

12. The WHO guidelines conflict with other clinical practice guidelines

Yes [ ] No [ ]

13. There are no adequate supplies and resources to facilitate adherence to the WHO guidelines

Yes [ ] No [ ]

APPENDIX IV: APPROVAL LETTER FROM SGS

MASINDE MULIRO UNIVERSITY OF SCIENCE AND TECHNOLOGY (MMUST)

Tel: 056-30870
Fax: 056-30153
E-mail: directordps@mmust.ac.ke
Website: www.mmust.ac.ke

P.O Box 190
Kakamega – 50100
Kenya

Directorate of Postgraduate Studies

Ref: MMU/COR: 509099

15th April, 2019

Robina Ogendo,
HNR/G/01-55716/2016,
P.O. Box 190-50100,
KAKAMEGA.

Dear Ms. Ogendo,

RE: APPROVAL OF PROPOSAL

I am pleased to inform you that the Directorate of Postgraduate Studies has considered and approved your Masters Proposal entitled: "***Clinical Management of Cryptococcal Meningitis among Health Care Providers in two Hospitals, Kisumu, Kenya*** " and appointed the following as supervisors:

1. Prof. Lt. Col (Rtd) John M. Okoth - SONMAPS, MMUST
2. Ms. Lilian Isiaho - SONMAPS, MMUST

You are required to submit through your supervisor(s) progress reports every three months to the Director of Postgraduate Studies. Such reports should be copied to the following: Chairman, School of Nursing & Midwifery Graduate Studies Committee and Chairman, Department of Clinical Nursing and Health Informatics and Graduate Studies Committee. Kindly adhere to research ethics consideration in conducting research.

It is the policy and regulations of the University that you observe a deadline of two years from the date of registration to complete your master's thesis. Do not hesitate to consult this office in case of any problem encountered in the course of your work.

We wish you the best in your research and hope the study will make original contribution to knowledge.

Yours Sincerely,

DEAN
SCHOOL OF GRADUATE STUDIES
MASINDE MULIRO UNIVERSITY
OF SCIENCE & TECHNOLOGY
Date:.....Sign:.....

Dr. Consolata Ngala
ASSOCIATE DEAN, DIRECTORATE OF POSTGRADUATE STUDIES

APPENDIX V: APPROVAL LETTER FROM INSTITUTIONAL ETHICS REVIEW COMMITTEE

MASINDE MULIRO UNIVERSITY OF SCIENCE AND TECHNOLOGY
Tel: 056-31375 P. O. Box 190-50100
Fax: 056-30153 Kakamega, Kenya
E-mail: ierc@mmust.ac.ke
Website: www.mmust.ac.ke

Institutional Ethics Review Committee (IERC)

Ref: MMU/COR: 403012 vol2 (21) **Date: 6th** June, 2019

Robina Ogendo
Masinde Muliro University of Science and Technology
P.O. Box 190-50100
KAKAMEGA

Dear Ms. Ogendo

RE: Clinical management of cryptococcal meningitis among health care providers in two hospitals Kisumu, Kenya - MMUST/IERC/33/19

Thank you for submitting your proposal entitled as above for initial review. This is to inform you, that the committee conducted the initial review and approved (with minor changes) the above Referenced application for one year.

This approval is valid from **6th June, 2019 through to 6th June, 2020**. Please note that authorization to conduct this study will automatically expire on **6th June, 2020**. If you plan to continue with data collection or analysis beyond this date please submit an application for continuing approval to the MMUST IERC by **6th May, 2020.**

Approval for continuation of the study will be subject to submission and review of an annual report that must reach the MMUST IERC secretariat by **6th May, 2020**. You are required to submit any amendments to this protocol and any other information pertinent to human participation in this study to MMUST IERC prior to implementation.

Please note that any unanticipated problems or adverse effects/events resulting from the conduct of this study must be reported to **MMUST IERC**. Also note that you are required to seek for research permit from **NACOSTI** prior to the initiation of the study.

Yours faithfully,

Dr. Gordon Nguka (PhD)
Chairman, Institutional Ethics Review Committee

Copy to:
- The Secretary, National Bio-Ethics Committee
- Vice Chancellor
- DVC (PR&I)
- DVC (A & F)

APPENDIX VI: APPROVAL LETTER TO CONDUCT RESEARCH FROM COUNTY GOVERNMENT OF KISUMU

COUNTY GOVERNMENT OF KISUMU

Telegrams: "PRO.(MED)"
Tel: 254-057-2020105
Fax: 254-057-2023176
E-mail: kisumucdh@gmail.com

County Director of Health,
Kisumu.
P. O. Box 721-40100,
KISUMU.

DEPARTMENT OF HEALTH

REF: GN.133.VOL. III/625

Date: 27/06/2019

Received 1.7.19.
Allowed to conduct Research

Robina Ogendo

RE: **APPROVAL TO CONDUCT RESEARCH ON EVALUATION OF CLINICAL MANAGEMENT OF CRYPTOCOCCAL MENINGITIS AMONG HEALTH CARE PROVIDERS IN TWO HOSPITALS" –MMUST/IERC/33/19**

We are in receipt of the request for research approval.

The County Department of Health has reviewed the proposal to conduct the above study and support it's implementation.

This office has no objection on the same and grants you permission to continue with research for a period of one year at JOOTRH and KCRH then share your findings with this office in both hard & soft copy after the study.

By a copy of this letter kindly accord her your necessary cooperation.

Dr. Ngong'a A
For: County Director of Health
Kisumu County

COUNTY DIRECTOR OF HEALTH KISUMU

MINISTRY OF HEALTH
02 JUL 2019
P. O BOX 1818 KISUMU - 40100

From the County Director of Health office

APPENDIX VI: APPROVAL LETTER FROM NACOSTI

NATIONAL COMMISSION FOR SCIENCE, TECHNOLOGY AND INNOVATION

Telephone:+254-20-2213471,
2241349,3310571,2219420
Fax:+254-20-318245,318249
Email: dg@nacosti.go.ke
Website : www.nacosti.go.ke
When replying please quote

NACOSTI, Upper Kabete
Off Waiyaki Way
P.O. Box 30623-00100
NAIROBI-KENYA

Ref: No. **NACOSTI/P/19/80613/31301**

Date: **2nd August, 2019**

Robina Ogendo Ogendo
Masinde Muliro University of Science
And Technology
P.O. Box 190-50100
KAKAMEGA.

RE: RESEARCH AUTHORIZATION

Following your application for authority to carry out research on ***"Evaluation of clinical management of cryptococcal meningitis among health care providers in two hospitals Kisumu Kenya."*** I am pleased to inform you that you have been authorized to undertake research in **Kisumu County** for the period ending **2nd August, 2019.**

You are advised to report to **the County Commissioner, the County Director of Health Services, and the County Director of Education, Kisumu County** before embarking on the research project.

Kindly note that, as an applicant who has been licensed under the Science, Technology and Innovation Act, 2013 to conduct research in Kenya, you shall deposit **a copy** of the final research report to the Commission within **one year** of completion. The soft copy of the same should be submitted through the Online Research Information System.

DR. MOSES RUGUTT, PhD, ODW.
DIRECTOR-GENERAL/CEO

Copy to:

The County Commissioner
Kisumu County.

The County Director of Education

THIS IS TO CERTIFY THAT:
MISS. ROBINA OGENDO
of MASINDE MULIRO UNIVERSITY OF SCIENCE AND TECHNOLOGY, 0-40100 KISUMU,has been permitted to conduct research in *Kisumu County*

on the topic: *EVALUATION OF CLINICAL MANAGEMENT OF CRYPTOCOCCAL MENINGITIS AMONG HEALTH CARE PROVIDERS IN TWO HOSPITALS KISUMU KENYA*

for the period ending:
2nd August,2020

Permit No : NACOSTI/P/19/80613/31301
Date Of Issue : 2nd August,2019
Fee Recieved :Ksh 1000

.....
Applicant's Signature

Director General
National Commission for Science, Technology & Innovation

THE SCIENCE, TECHNOLOGY AND INNOVATION ACT, 2013

The Grant of Research Licenses is guided by the Science, Technology and Innovation (Research Licensing) Regulations, 2014.

CONDITIONS

1. The License is valid for the proposed research, location and specified period.
2. The License and any rights thereunder are non-transferable.
3. The Licensee shall inform the County Governor before commencement of the research.
4. Excavation, filming and collection of specimens are subject to further necessary clearance from relevant Government Agencies.
5. The License does not give authority to transfer research materials.
6. NACOSTI may monitor and evaluate the licensed research project.
7. The Licensee shall submit one hard copy and upload a soft copy of their final report within one year of completion of the research.
8. NACOSTI reserves the right to modify the conditions of the License including cancellation without prior notice.

National Commission for Science, Technology and innovation
P.O. Box 30623 - 00100, Nairobi, Kenya
TEL: 020 400 7000, 0713 788787, 0735 404245
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REPUBLIC OF KENYA

NACOSTI

National Commission for Science, Technology and Innovation

RESEARCH LICENSE

Serial No.A 26313

CONDITIONS: see back page

APPENDIX VII: STUDY AREA MAP