CLINICIAN'S ADHERENCE TO WORLD HEALTH ORGANISATION GUIDELINES AND SHORT-TERM OUTCOME OF MANAGEMENT OF NEONATAL SEIZURES AT MOI TEACHING AND REFERRAL HOSPITAL, ELDORET, KENYA.

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A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF REQUIREMENTS OF MASTER OF MEDICINE (CHILD HEALTH AND PAEDIATRICS) OF SCHOOL OF MEDICINE, MOI UNIVERSITY

DECLARATION

STUDENT'S DECLARATION

I declare that this research thesis is my original work and that it has not been presented for a degree in any other university. No part of this thesis may be reproduced without the prior written permission of the author and /or Moi University

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DEDICATION

I dedicate this work to my dear mother, Rosalind and my Husband for the prayers, moral support and for always standing with me throughout my studies/life.

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ABBREVIATIONS AND ACRONYMS

AEDS	Anti Epileptic Drugs
ANC	Antenatal Clinic
CNS	Central Nervous System
CSF	Cerebral Spinal fluid
EEG	Electroencephalography
HIE	Hypoxic Ischemic Encephalopathy
ILAE	International League Against Epilepsy
IMCI	Integrated Management of Childhood Illnesses
IMNCI	Integrated Management of Neonatal and Childhood Illnesses
IREC	Institutional Research and Ethics Committee
MTRH	Moi Teaching and Referral Hospital
NBU	Newborn Unit
WHO	World Health Organization

OPERATIONAL DEFINITIONS

Seizure	abnormal extremity movements, abnormal posturing, mouthing, body twitching as observed by a clinician or nurse. ILAE defines Epileptic seizures as a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain." (Fisher et al., 2014)
Neonatal seizures	seizures occurring within the first 28 days of life
Hypoglycemia	random blood sugar <3mmol/l
Low birth weight	weight at birth between 1500g and 2449g
Very low birth weight	weight at birth between 1000g and 1499g
Extremely low birth weight	weight at birth less than 1000g
Neonatal mortality	death occurring within the first 28 days of life
Short term outcomes	short term will be defined as the time from admission to the time of discharge from the unit or death.
Length of stay	time taken from admission to discharge or death
Characteristics	will involve seizure type and other associated factors e.g. sex, weight, apgar score, mode of delivery
Seizure control	48hours seizure free period

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ABSTRACT

CLINICIAN'S ADHERENCE TO WORLD HEALTH ORGANIZATION'S GUIDELINES AND SHORT-TERM OUTCOME OF MANAGEMENT OF NEONATAL SEIZURES AT MOI TEACHING AND REFERRAL HOSPITAL, ELDORET, KENYA.

Background: Neonatal seizures are the most common manifestation of neurological disease in New Born Units and have been associated with increased mortality and morbidity among survivors which underlies the need for early initiation of treatment. However, it continues to offer both diagnostic and therapeutic challenges to clinicians. Although it is clear that diagnosis requires prolonged electroencephalography monitoring accompanied by observation, many newborn units lack the technology and therefore rely on direct observation for diagnosis. Therapeutic challenges have been occasioned by lack of standardized protocols which was the basis of development of the World Health Organisation guidelines that has the potential of improving outcome. The local approach to diagnosis and the extent to which clinicians follow the guidelines is unknown.

Objective: To determine the clinical characteristics, adherence to World Health Organization (WHO) guidelines by clinicians and short-term outcomes in the management of neonates with clinical neonatal seizures in Moi Teaching and Referral Hospital newborn unit.

Methods: A prospective descriptive study of newborns admitted to newborn unit from January 2014 to July 2014. Nurses and doctors working in the unit were trained on recognition of neonatal seizures by direct observation. They were asked to record the observed behavior or motor movement in the patient's file and inform the researcher or research assistant of the same. The researcher or research assistant used a data collection tool to collect the required data from the newborns who met the inclusion criteria. The neonates were then followed up every 48 hours until death or discharge from the unit. Data was analyzed using STATA version 13 at 95% confidence interval. Categorical variables were summarized as frequencies and the corresponding percentages while continuous variables were summarized as mean, median and standard deviation.

Results: A total of 158 neonates were included in the study, and 31.6% had clinical neonatal seizures. The median age at admission was 4 (IQR: 1-48) hours. The male to female ratio was 1.5:1. Most of the neonates were born at term (82%). In univariate analysis, birth weight and gestation age were significantly associated with neonatal seizures (P = 0.001). The most frequent seizure type observed was tonic focal at 36%. Overall, Adherence to WHO guidelines was found to be inadequate. Compared to the WHO guidelines, only 12% and 16% of the neonates who had suspected sepsis and meningitis had blood cultures and lumbar punctures done respectively. None of the neonates had calcium levels checked while 64% had random blood sugar levels. The first line anticonvulsant was Phenobarbital. The median time taken to control seizures was 24 hours (IQR 0.17-48). Of the 50 participants, 44% died. A longer time taken to control seizures was associated with a higher mortality (p=0.006).

Conclusion: About a third of admitted neonates had seizures and almost half of them died. There was inadequate adherence to the WHO guidelines in the management of neonatal seizures.

Recommendations: There is need to reduce the prevalence of neonatal seizures through vigorous study of its aetiology and subsequent prevention. A future study should look at the reason for none adherence to WHO recommended guidelines in care of neonatal seizures at MTRH.

CHAPTER ONE: INTRODUCTION

1.1 Definition

Seizures can generally be described as a paroxysmal alteration in neurologic function either in the motor, behavior and/or autonomic function (Stafstrom and Carmant, 2015). All neonatal seizures or convulsions are epileptic fits usually occurring from birth to the end of the neonatal period. This period neonatal and is seen as the time of most exposures wind for developing seizures, this is observed predominantly in the first 1–2 days to the first week from birth (Tharp, 2002, Abend and Wushoff 2012). Seizures are not only predominant in the first 48 hours after birth they are also the most frequent manifestation of neonatal neurological diseases. It has been observed that the early postnatal development time increases susceptibility to seizures in relation to other ages. This however, may be due to some combined factors specific to assisting the brain development that enhance excitation and diminish inhibition (Strafstrom and Carmant, 2015).

1.2 Background Information

Seizures are the most common neurological emergency in newborns, and they are associated with high mortality and morbidity (Glass et al, 2009). Seizure incidence is highest during this period than in any other period of life and has an incidence of 2.6 per 1000 live births (Painter et al, 1999). However, the incidence is thought to vary from one place to another, for instance in Kenya one study reported an incidence of 39.5 per 1000 live births (Mwaniki et al, 2010). The incidence also varies with gestation, body weight and aetiology of the seizures (Volpe, 2008). Some of the known etiologies include hypoxic ischaemic encephalopathy, intracranial infections and neonatal sepsis.

The vulnerability to seizures during the neonatal period has been attributed to the relative imbalance of excitatory and inhibitory neurotransmission due to the immaturity of inhibitory pathways and early maturation of excitatory pathways excitatory pathways (Jensen, 2009). The immature brain has incomplete dendritic arborization, and this may explain the observation that newborns are unlikely to present with generalized seizures as observed in adults. Also, epileptic discharges may fail to be transmitted to the cerebral surface and lead to normal electroencephalographic findings. Therefore, diagnosis and classification continue to be a challenge (Mizrahi and Kellaway, 1998). Due to the challenges of the diagnosis of neonatal seizures, three classes of seizures have been described (Mizrahi and Kellaway, 1998). Clinical seizures refer to a diagnosis based on observation of paroxysmal stereotypic behavior with or without electrographic epileptiform activity. In contrast, electrographic epileptic seizures are diagnosed by consistent epileptiform electrographic activity. The third group is the clinical-electrographic seizures where the clinical seizures must be associated with the consistent electrographic activity. A diagnosis of clinical seizures was first suggested by Volpe, and it gained popularity because it does not require access to electroencephalography (Volpe, 1989). One shortcoming of the classification of clinical seizures is that it includes some behaviors that may not be epileptic (Mizrahi and Kellaway, 1998).

Neonatal seizures are associated with increased neonatal deaths and predispose the survivors to neurological disability (Glass et al, 2009). Control of the seizures has been associated with improved neurological outcome (Van Rooij et al, 2013). However, control of neonatal seizures is hampered by diagnostic challenges and limited information on effective anti-epileptic drugs. To improve both diagnosis and treatment, WHO has developed standardized guidelines and recommended that they

should be used by all healthcare staff that takes care of neonates with seizure (WHO, 2011). Studies have shown an improvement in treatment outcomes when clinical guidelines are used (Harris et al, 2016). However, to date, it is not known how far newborn units have implemented the WHO guidelines on management of neonatal seizures. In a study done in Kenya, adherence to pneumonia clinical guidelines in children was found to be inadequate (Mutinda et al, 2014) This study aims at the description of neonatal seizures, their treatment, and outcome as well as an audit of how far the WHO guidelines are used. The results of the study may be useful in guiding planning for the care of neonatal seizures and implementation of interventions to improve their outcome.

1.3 Problem Statement

Neonatal seizures are a common neurological presentation in newborns and have been associated with high mortality and long-term neurological complications (Glass et al, 2009). In a hospital-based study in Kilifi, the mortality associated with neonatal seizures was found to be 19% (Mwaniki et al, 2010). A higher mortality rate was reported in Nigeria (Adebami, 2015, Asindi, 1995). The global campaign against epilepsy, WHO, and the ILAE has come up with evidence-based guidelines on the management of neonatal seizures which include the basic investigations and treatment (WHO, 2011).These guidelines are aimed at improving diagnosis of neonatal seizures as well as guiding the decision on when to start treatment to benefit those who need medication and save those who do not require medicine from harmful side effects (Maitre et al, 2013, WHO, 2011). These guidelines are developed in such a way that they can be applied in limited resource centers (WHO, 2011). The use of standardized guidelines to improve the care of neonates has been shown in many other areas

(Lapillonell et al, 2013). However, the benefits can only be realized following adherence to the guidelines to a critical level (Harris et al, 2016).

Although the burden of Neonatal seizures is known to be high (Glass et al, 2009), neither its incidence and prevalence nor its outcome is uniform. The incidence has been shown to be higher in developing countries (Mwaniki et al, 2010, Asindi et al, 1995) as compared to the developed world (Glass et al, 2009). The management of neonatal seizures also varies from one region to another (Carmo and Barr, 2005) In our hospital the measures of neonatal seizures occurrence are unknown. Also, it is not clear whether there is adherence to the WHO guidelines on management.

1.4 Justification

The leading causes of neonatal seizures are hypoxic Ischaemic Encephalopathy, brain malformation and brain infections like meningitis which are common in developing countries (Mwaniki et al, 2010). MTRH is a regional referral centre and has a unit that cares for newborns with a wide spectrum of disorders. Birth asphyxia and neonatal sepsis and prematurity, which are the leading causes of admission, are also associated with increased likelihood of occurrence of neonatal seizures. The burden of neonatal seizures has been shown to be high both worldwide and regionally (Mwaniki et al, 2010). The outcome of neonatal seizures in MTRH is also largely unknown. The major types of neonatal seizures in MTRH are also unknown. Though unknown, the hospital is likely to have a high burden of neonatal seizures. This study described the current practice about WHO guidelines on the management of neonatal seizures and the results will be used to determine whether the practice needs reinforcement or improvement. Also, practice in MTRH has either positive or negative ripple effect on the country wide because it is a teaching hospital for all cadres of clinical staff.

Therefore, if that inappropriate care is not identified and remedied, many neonates will be exposed to danger.

1:5 Research Question

1. What is the prevalence of neonatal seizures in MTRH?
2. What is the adherence to WHO guidelines in the management of neonatal seizures?
3. What are the short-term outcomes of neonates with neonatal seizures in MTRH newborn unit?

1:6 Study Objectives

1.6.1 Broad Objective

To establish the level of adherence to WHO guidelines by clinicians and short-term outcomes of clinical neonatal seizures at MTRH.

1.6.2: Specific objectives

1) To determine the prevalence of clinical neonatal seizures in MTRH.
2) To determine the classification of clinical neonatal seizures at MTRH.
3) To describe adherence to WHO guidelines in the care given to neonates with clinical seizures.
4) Determine the outcome of clinical neonatal seizures at MTRH.

CHAPTER TWO: LITERATURE REVIEW

2.1 Etiology and Diagnosis

The neonatal brain is prone to seizures which have been ascribed to relative imbalance between inhibition and excitation (Sankar, 2016). Neonatal brain is characterized by delayed maturation of inhibitory circuits and early maturation of excitatory circuits that predisposes it to hypersynchronous per excitability (Bromfield, 2006). The neonatal brain is vulnerable to a wide range of traumatic, toxic and metabolic insults which may lead to seizures. The frequency of this insults vary from one study to another but review of literature shows their frequency as follows, hypoxic-ischemic encephalopathy (30–53%), intracranial haemorrhage (7–17%), cerebral infarction (6–17%) cerebral malformations (3–17%), meningitis/septicaemia (2–14%) metabolic hypoglycemia (0.1–5%), hypocalcaemia, hypomagnesaemia (4–22%) hypo-/hypernatremia, inborn errors of metabolism (3–4%) kernicterus (1%), maternal drug withdrawal (4%) and idiopathic (2%) (Volpe, 2008).

Diagnosis of clinical seizures was first suggested by Volpe, and it gained popularity because it does not require access to electroencephalography (Volpe,1989). The only shortcoming challenges of classifying seizures is that they it includes some behavior's that may not be epileptic (Jensen, 2009). These guidelines were not quite clear prompting the WHO to strategize on guidelines in the management of seizure in neonates (WHO, 2011).

2.2 Recap to the Development of the WHO Neonatal Seizure management guidelines

The WHO 2011 guidelines were developed in such a way that they can be applied in limited resource centers (Mizrahi and Kellaway, 1998). Though the use of standardized guidelines to improve the care of neonates has been shown in many other areas (WHO, 2011). However, the benefits can only be realized following critical adherence to the guidelines (Lapillonne et al, 2013). According to the WHO even though diagnosis and management of seizures are often considered within the context of tertiary care health centres, they found that seizures seemed to be a common manifestation in newborns presenting to the full range of health-care facilities (Mizrahi and Kellaway,1998). Therefore, they suggested a need for evidence-based guidelines that could be used by different health-care facilities with varying resources and adapted by health-care providers of all levels of expertise. Since neonatal seizures were found to be one of the most common neurological events in newborn infants, revealing a variety of pre-, peri- or postnatal disorders of the central nervous system (Harris et al, 2016), there was a need for a more comprehensive mode of management. This was because of clinical manifestations arising from the illness ranging from benign, self-limited illnesses to severe, prolonged or life-threatening disorders. Metabolic abnormalities or infections were also observed as other common manifestations (Harris, 2016). Enhanced diagnostic tools, such as electroencephalography (EEG), video-EEG monitoring, and early neuroimaging has now supplemented clinical observations and made diagnosis easier and more accurate (Harris, 2016). This era might have even changed the known incidence index of neonatal seizures. Some studies suggest that the incidence and prevalence rates of neonatal seizures may differ between developed and developing

countries with the later experiencing higher rates (Yamamoto et al, 2011, Garcia et al, 2004, Okun et al, 1995, Leveno et al, 1989).

The observations that had been seen in terms of treatment of neonatal seizures tend to have suggested minimal change over the last 50 years. Newborns with seizures were to have an early diagnostic work up to determine the cause, depending upon the facilities available. Antiepileptic (AEDs) were the drugs of choice for neonates presenting with seizures, this being at the backdrop of few investigations carried addressing the issues related to the administration of the regime such as first-line and second-line drugs, their pharmacokinetics, the duration of treatment, and the methods of discontinuing treatment after achieving adequate control of seizures (Mizrahi and Kellaway, 1998). The WHO investigators found that there were no randomized controlled trials to validate a treatment algorithm of neonatal seizures. At that moment they found that the AEDs which were in use were older generation drugs associated with the more side effects (Brown et al, 2003). Besides, clinical control of neonatal seizures using common AEDs, phenobarbital and phenytoin, benefited only 50 to 80% of cases, with even less effect in the control of most neonatal electrical seizures (Co JPT et al, 2007, Boylan et al, 2004, Rennie and Boylan, 2003, Boylan, 2002). They further found that the management of neonatal seizures had even become more difficult in resource limited settings because of few facilities available for diagnosis, treatment and monitoring (Boylan, 2002).

Data extracted from clinics and other experiments suggested that the longer duration a seizure takes the lesser the chances of achieving control (Painter 1999). To make things worse, seizures can have immediate and long-term adverse consequences on the immature and developing brain (Painter, 1999). Though there has been a dedicated attempt on suppressing neonatal seizures using AED’s, there could be a subsequent or

ripple effects of having neuro-developmental deficits and or early mortality. Newborn babies have been observed to be at risk of death, whereas the survivors may be at risk of having neurological impairment, developmental delay, later epilepsy and cognitive impairment (Painter, 1999). It has been observed that newborn babies may be at risk of death, whereas those who may have survived may be at risk of getting neurological impairment, developmental delay, later epilepsy and cognitive impairment (Shany et al, 2007). This prompted the WHO to suggest investigators to conduct systematic reviews of evidence to determine the optimal care of neonatal seizures (WHO 2011)

2.3. Literature review on adherence to WHO guidelines

Treatment guidelines are important in making care more efficient and consistent and close the gaps between what clinicians do and what scientific evidence supports. Studies on adherence to WHO guidelines in the management of neonatal seizures are lacking. However, studies looking at adherence to guidelines in the management of other conditions have shown an improvement in the overall outcome. In Indianapolis, outcome of neonatal seizures was improved after introducing a standardized treatment protocol (Harris et al, 2016). In a study in a Ugandan hospital in the management of severe anaemia, there was lower inpatient mortality in patients managed according to the guidelines (Opoka et al, 2019). In a prospective study done at the Kenyatta National Hospital, only 41% of clinicians were found to have adhered to the WHO guidelines in the management of pneumonia in children (Mutinda et al, 2014).

2.4 Literature Review on the prevalence of neonatal seizures

Seizures have been shown to occur in the neonatal period more than any other time during childhood. Information about the prevalence of neonatal seizures is scarce. The reported prevalence varies from one region to another. It has been shown to range

from 1.5 to 5.5 per 1000 live births in term neonates (Lanska et al, 1995, Ronen, 1999, Saliba et al ,1999). The incidence has been shown to be higher in premature infants (Scher et al, 1993). In a study done in Kilifi, Kenya the incidence was found to be high at 39.5 per 1000 live births (Mwaniki et al, 2010). In Ethiopia, a hospital-based study found an incidence of 13.6 per 1000 live births (Gebremariam et al, 2006). In a study done in a tertiary hospital in India, the prevalence of neonatal seizures was found to be 19.2% (Digra,2007). In Europe the prevalence has been shown to be lower than in Africa. In a study done in Stockholm, clinical seizures were reported in 1.5 per 1000 live births in term neonates (Eriksson andZetterstrom, 1979). This was shown in a more recent study in Italy where the incidence was 1.1 per 1000 live births in term neonates (Francesco et al, 2018).

2.5 Literature review on outcomes of neonatal seizures

The outcome of neonatal seizures is mainly determined by the etiology and the seizure burden (Clancy, 2000). The incidence of mortality has been shown to be 15 to 20% in the developed world (Glass et al, 2016). The mortality rate is higher in premature neonates ranging from 25 to 35% (Lloyd et al, 2017, Glass et al, 2017). In the developing world, the mortality has been shown to be higher. In a study done in a hospital in Kilifi, Kenya, the mortality was found to be 19.1% (Mwaniki et al, 2010). In Nigeria, the mortality rate was found to be as high as 50% (Asindi et al, 1995). In a more recent study in Nigeria the mortality rate was still found to be higher compared to studies in the developed countries at 45.8% (Adabemi, 2010). For the neonates who survive, neurologic impairement, developmental delay and post-neonatal epilepsy is common (Tekgul et al, 2006, Ortibus et al, 1996, Blume et al, 2001).

CHAPTER THREE: METHODOLOGY

3.1: Study Design

This Research is a prospective descriptive study. The objectives are descriptive and where association is required the measurement of exposure and outcome is done in the same period. Further, the research participants are not chosen in record to time of outcome or exposure. Therefore, a cross-sectional design is most suitable.

3.2: Study Site

The study was conducted at the New Born Unit, MTRH which is located in Eldoret town, about 300km from Nairobi, in Uasin Gishu County, Kenya. Eldoret is a mainly agricultural region with both large-scale and small-scale farming.

The hospital is an 800-bed capacity tertiary hospital that also serves institutions around Eldoret. It also serves as a referral hospital for the western part of Kenya, with a catchment population of about 20 million people - 33% of Kenyan population. The hospital provides various services ranging from primary to specialized care and serves urban, peri-urban and rural populations from near and far districts.

The hospital also serves patients from neighboring countries; Uganda, Sudan, South Sudan and Rwanda.

The hospital's new born unit is located in the Riley Mother and Baby wing, a new extension of the hospital that was opened in 2009. The NBU has a capacity of seventy of which fourteen are incubators, and fifty-six are baby cots and can provide basic neonatal services and incubator nursing with a nurse to patient ratio of around 1:20. The NBU is also able to carry out tests like random blood sugar, calcium, electrolytes, complete blood count, CSF studies and blood cultures. Cranial ultrasound and EEG are however not routinely done.

The staffs allocated to the unit include six pediatricians, twenty-nine nurses, a nutritionist, an average of six pediatric resident doctors, one medical officer intern and clinical officer, interns.

Neonates admitted in the NBU are either born in the hospital, referred from neighboring health facilities or come directly from home**.** They are managed using the basic Pediatric protocol in Kenya which has been adopted from the WHO guidelines. However, this also depends on the experience of the various doctors in the unit and availability of supplies.

3.3: Study Population

All neonates admitted to the MTRH new born unit during the study period who met the inclusion criteria were recruited. The population included all neonates born in MTRH labor ward, those referred from other health facilities and those born at home and whose mothers/guardians gave consent. All babies with congenital malformations not compatible with life for example anencephaly were excluded from the study.

Sample Size was calculated by use of Epi Info calculator. The population of new admissions in NBU in six months was estimated at 450 neonates based on baseline record survey for the preceding twelve months. The expected frequency of seizures was 19.2% based on a study by Digra (2007). This study was done in Jammu hospital, India and it was chosen because the set-up of the hospital and newborn unit admissions were similar to our study. The sample was calculated at 95% confidence level. The expected sample size was 156 neonates as shown in figure 1 below.

Population survey or descriptive study
For simple random sampling, leave design effect and clusters equal to 1.

Population size:	450	
Expected frequency:	19.2 %	
Acceptable Margin of Error:	5 %	
Design effect:	1.0	
Clusters:	1	

Confidence Level	Cluster Size	Total Sample
80%	**83**	**83**
90%	**122**	**122**
95%	**156**	**156**
97%	**177**	**177**
99%	**215**	**215**
99.9%	**270**	**270**
99.99%	**304**	**304**

3.4 Eligibility Criteria

3.4.1 Inclusion criteria:

- Neonates admitted to the newborn
- Neonates whose mothers/guardians accepted to give consent.

3.4.2 Exclusion criteria:

- Neonate with congenital abnormality that was incompatible with life.
- Neonates brought to NBU for reasons other than illness like accommodation or awaiting adoption.

3.5 Sampling Technique

We sampled all neonates who were admitted with seizures during the study period.

3.6 Outcome Measures

Mortality was the outcome of interest.

3.7 Data Collection

Data was collected using a pre-tested standard questionnaire and follow up data collection form the mothers/guardians were taken through the consent form to make them understand the purpose of the study and for those who accepted they were given the consent form to sign. The demographic data, neonatal and maternal characteristics were entered in the data collection form on admission. For completeness, any missing data were obtained through maternal interview and by checking the ANC attendance booklet.

3.8 Study Execution

The principal investigator arranged for a meeting with the clinicians and nurses in the NBU to introduce the study and provide detailed information on recruitment of participants and data collection. A research assistant who was a nurse with training in newborn medicine and care was appointed and trained on the study. The PI and research assistant reviewed consecutive neonates admitted in NBU daily. For those who satisfied the inclusion criteria, consent was sought from the mother at admission and data collection sheet was used to extract data from the patient's notes and mother's antenatal book. Missing data was collected by interviewing the mother. The patients' symptoms and signs of current illness were recorded. For participants who did not have seizures demographic, perinatal and clinical features were recorded and follow-up was done every 48 hours up until discharge to see whether they developed seizures while in the unit. For those admitted with seizures or developed seizures while in the unit, a description of the seizure was recorded from the clinicians' notes. Where the description in the notes was not complete, the PI interviewed the clinician, nurse or mother who had observed the seizure. The principal investigator followed up the neonates to determine their outcome. Diagnostic investigations, primary diagnosis,

comorbidities, and treatment information was extracted from the patient charts as recorded by the primary care clinicians. The nine items of WHO guidelines on neonatal seizures were used to extract data on diagnosis and treatment. The PI updated data on each baby daily until discharge, death or day of care. The outcome of the neonate was determined at discharge from the unit or at death.

3.9 Data Management, Analysis, and Presentation

Data were coded to maintain confidentiality and then entered into a Microsoft Access data base. It was then checked for consistency by providing validation checks in Microsoft Access. Data were then exported to STATA version 13.0 and analyzed at 95% level of confidence.

3.9.1Data Analysis

Data analysis was done using STATA version 13 special edition. Categorical variables were summarized as frequencies and the corresponding percentages. The continuous variables were assessed for Gaussian assumptions using Shapiro-Wilk test. Those that were normally distributed were summarized as mean and the corresponding standard deviation while those that violated the Gaussian assumptions were summarized as median and the appropriate interquartile range (IQR). The test for association between categorical variables was conducted using the Pearson's Chi-Square test. A p-value less than 0.05 was considered statistically significant. The magnitude of association was assessed using a logistic regression model that gave the magnitude and direction of the effect. We reported the odds ratio (OR) and the corresponding 95% confidence limits.

3.10 Ethical Considerations

The study was conducted after seeking approval from IREC and the management of MTRH. Patients' data were handled confidentially by use of computer password known by the principal investigator only. All patients received the necessary standard treatment regardless of their willingness or unwillingness to participate in the study. No incentives or inducements were used to convince mothers to allow their babies to participate in this study. Study findings and recommendations will be shared with the hospital and used to improve care of neonates admitted with seizures and also help in developing a hospital protocol for management of neonatal seizures.

CHAPTER FOUR: RESULTS

4.1: Burden of neonatal seizures

A total of 158 neonates were included in the study, and 31.6% had clinical neonatal seizures. The median age at admission was 4 (IQR: 1-48) hours. The male to female ratio was 1.5:1). As shown in the figure below, majority of the babies (56%) were born in peripheral health facilities and referred to MTRH. In contrast to the 50 neonates with seizures, the ratio of those born in MTRH to those born outside was 1.

4.2 Clinical features of all neonates

The median gestational age was 38 (IQR: 33-40) days. Most of the babies (77.9%) were delivered by spontaneous vaginal delivery. The median duration of labor was 9 (IQR: 6-12) hours with a minimum of 1 and a maximum of 48 hours. The median birth weight was 2.7 (IQR: 1.8-3.2) kilograms with a minimum of 700 kilograms and a maximum of 4400 kilograms. The median age at the time of admission was 4 (IQR: 1-48) hours with a minimum of zero and a maximum of 672 hours. The mean APGAR-Score at 5 minutes was 8 with arrange of 3 to 10. The median gestational age was 38(IQR: 33-40) weeks. 12% were delivered through EMCs method. The rest of the participants were delivered via other methods of delivery (table 1).

Table 1: Characteristics of all neonates

Characteristic	Sample size	Mode	Frequency (%)
Gender	158	male	93(58.9%)
		female	65(41.1%)
Mode of delivery	158	SVD	123(77.9%)
		SBD	3(1.9%)
		AVD	2(1.3%)
		EMCs	19(12.0%)
		ELCs	11(7.0%)
Gestational age (weeks)	158	Term (37 completed weeks)	97(61.4%)
		Preterm	61(38.6%)
Duration of active labour (hours)	158	Normal	93(59%)
		Prolonged	65(41%)
Birth weight (kilograms)	158	2.5 and above	91(57.5%)
		Below 2.5	67(42.5)
Age at admission (hours)	158	Within 24 hours	46(29.1%)
		More than 24 hours	112(70.9%)
APGAR Score at 5 minutes	158	7 to 10	119(75%)
		4 to 6	35(22.1%)
		0 to 3	4(2.9%)
Place of delivery	158	MTRH	70(44%)
		Other health Facility	75(47.7%)
		Home	13(8.3%)

Table 2: Clinical signs and symptoms among neonates with seizures

Clinical Feature	Frequency	Proportion (%)
Difficulty in breathing	33	66
Inability to breastfeed	26	52
Irritability	18	36
Fever	17	34
Cyanosis	15	30
Hypothermia	12	24
Apnoea	8	16
Pallor	4	8
Jaundice	4	8
Anaemia	3	6

Difficulty in breathing (66%) and inability to breastfeed were the leading presenting clinical features while the less frequent clinical features were anaemia and jaundice (table 2).

4.3 Clinical Characteristics of neonates with neonatal seizures

The number of term babies was 41 (82%), and 44 (88%) had a birth weight equal to or above 2500 grams. Majority of them 30 (60%) suffered from prolonged labour. However, majority 32 (64%) had 5-minute Apgar score of 7 – 10. In 27(54%) neonates it took more than 24 hours from onset to control of the seizures (table 3).

Table 3: Clinical characteristics of neonates with seizures

features	**Sample size**	**mode**	**Frequency (%)**
Gestational age	50	**Term**	**41(82%)**
		preterm	9(18%)
Duration of labour	50	normal	20(40%)
		prolonged	30(60%)
Birth weight	50	< 2.5	6(12%)
		>2.5	**44(88%)**
Apgar score at 5 minutes	50	**7-10**	**32(64%)**
		4-6	13(26%)
		0-3	5(10%)
Time from onset to control of seizure	50	Within 24hrs	23(46%)
		More than 24hrs	27(54%)

Most of the seizures were focal with 36.7% being focal tonic and 22.5% being focal clonic (table 4).

Table 4: Types of seizures

Seizure Type		Frequency	Percentage (%)
Subtle		3	6.1
Clonic	Focal	11	22.5
	Multifocal	0	0
Tonic	Focal	18	36.7
	Generalised	14	28.6
Myoclonic	Focal	0	0
	Multifocal	0	0
	Generalised	3	6.1

4.4 Management of neonatal seizures

Fourty eight neonates (96%) were started on antiepileptic medication and the median time from onset of seizures to medication was 21 hours with interquartile range of 5 to 60 hours. As shown in the table 5 below the drugs used were phenobarbitone and phenytoin with phenobarbitone being the most common. The median time to control of seizures was 24 hours with interquartile range of 0.17 to 48 hours.

Table 5: Treatment of seizures

characteristics		**Sample size**	**n(%) or median (IQR)**
Drugs given	**Phenobarbitone**	48	**36 (75%)**
	Phenytoin		12 (25%)

4.5 Assessment of adherence to WHO Guidelines

All the diagnosis of neonatal seizures was clinical, and 48 (96%) of the diagnosis led to initiation of treatment. There was no indication in the clinical notes whether duration of seizures was considered before decision was made to commence treatment. Random blood sugar, serum calcium, and lumbar punctures were not done as recommended. The choice of phenobarbitone as the first line AED was recorded in 75% while in 25% of cases it was phenytoin. (Table 5) There was no documentation of use of second-line AEDs. There was no attempt to confirm clinical seizures by doing EEG. There was no use of neurological imaging to establish neonatal seizures which were 100% adherence to the guidelines. Similarly, there was no brain imaging done to confirm the aetiology and for prognosis, as shown in table 6 below.

Investigations done on the neonates included random blood sugar (68%), Complete blood count (98%), Urea, electrolytes, and creatinine 98%, blood culture 12 % and Lumber puncture 16%. (Table 6).

Thirty patients (60%) were treated for suspected sepsis of whom 12% had blood drawn for culture while only one (3%) had a lumbar puncture to draw cerebrospinal fluid for analysis. There was no neurological imaging done on neonates with seizures during the study period. There were no electroencephalographic studies done on any of the newborns.

Table 6: Adherence to WHO guidelines by clinicians

ITEM	WHO Recommendation	Adherence to the study
1) The decision to treat:	if clinical NS last > 3 minutes or brief episodes that occur series	96% started on treatment. No evidence in files that duration of seizures was used as criteria to decide treatment
2) Diagnosis	i) Random blood sugar 100% ii) Testing for hypocalcaemia and treatment as indicated 100% iii Lumbar puncture in suspected sepsis 100% iv) Empirical treatment for meningitis where LP is not done 100% v) in all other etiologies consider pyridoxine before AEDs administration - open	i) 68% ii) 0% iii) 0.3% iv) 17.2% v) No consideration
3) First line AED	Phenobarbitone 100%	75% (36)
4) Second line AED	Phenytoin, lidocaine or benzodiazepine	No second line drug consideration made
5) When to Consider stopping AED	baby is seizure free for >72 hours, and the EEG or Neurological exam is normal	Not assessed in this study
6) How to stop AED	Abrupt without tapering is seizure is controlled by one drug	Not assessed in this study
7) Use of Prophylactic AED in HIE	Not recommended in the absence of seizures	Not assessed in this study
8) Confirmation of clinical seizures with EEG	Where feasible 100%	0%
9) Radiological investigation	i) Should not be done to confirm diagnosis or control of seizures 100% ii) May be done to confirm aetiology or for prognostication	i) 100% ii) 0%

4.6 Factors associated with neonatal seizures

In bivariate analysis, birth weight and gestation age were significantly associated with neonatal seizures (P = 0.001). However, none of the other infant characteristics were associated with a diagnosis of neonatal seizures (table 7). On multivariate analysis, none of the characteristics was found to be an independent predictor of neonatal seizures.

Table 7: Bivariate analysis of association between neonatal seizures and infant characteristics (n=50).

Characteristic	Frequency	X^2/Fisher Exact test	Significance
Place of delivery (MTRH)	20	0.186	0.461
Place of delivery (outside MTRH)	30	4.32	0.123
Duration of Labor(prolonged)	30	2.455	0.117
Birth weight(>2.5kgs)	44	19.078	0.001
Apgar score at 5mins (7-10)	32	1.46	0.227
Mode of delivery (SVD)	38	0.327	0.567
Gestation(term)	41	22.935	0.001

4.7 Outcome of neonates with Seizures

Twenty-two, (44%) of the patients with neonatal seizures died. Nine patients had an abnormal neurological exam on discharge. The average length of stay was seven days.

In bivariate analysis, none of the clinical signs and symptoms was a risk factor for death among children with neonatal sepsis (Table 8). Similarly, among clinical features of perinatal history, all features except duration to seizure control above 24 hours were not significantly associated with mortality (table 9).

Table 8: Association of clinical features and death among newborns with convulsions(n=50).

Clinical Features (presence of)	**Frequency**		**X^2**	**Significance**
	Yes	**No**		
Fever	17	33	0.14	1
Hypothermia	12	48	0.046	0.829
Jaundice	4	46	0.279	0.626
A cough	5	45	1.271	0.519
Difficulty in breathing	33	17	0.088	0.766
Apnoea	8	42	2.39	0.23
Cyanosis	15	35	0.823	0.546
Pallor	4	46	0.320	0.711
Diarrhea	6	44	1.684	0.378
Vomiting	2	48	1.684	0.378
Abdominal distension	3	47	5.13	0.051
Irritability	18	32	0.032	0.660
Dehydration	7	43	1.198	0.545
Inability to breastfeed	26	24	0.799	0.537

Table 9: association of Perinatal features and death among newborns with seizures (n=50)

characteristics	**Frequency**	**X2/fisher exact test**	**significance**
Gestation(preterm)	9	0.015	0.629
Birth weight (>2.5kgs)	44	00	1
Apgar score at 5 mins (7-10)	32	2.678	0.102
Duration of labour(prolonged)	30	1.161	0.281
Mode of delivery (SVD)		2.56	0.132
Place of delivery 1 (outside MTRH)	30	1.841	0.175
Place of delivery 2 (MTRH)	20	0.594	0.641
Gender	50	1.093	0.237
Time to control of seizures (>24hrs)	**27**	**15.633**	**0.000**

CHAPTER FIVE: DISCUSSION

The purpose of this study was to find the burden of neonatal seizures in the newborn unit at MTRH. Also, we studied the adherence of clinicians to WHO guidelines in the management of clinical neonatal seizures and the short-term outcomes of these neonates.

5.1 The Burden of Neonatal Seizures

Neonatal Seizures are the commonest neurological presentation among sick newborn (Glass et al, 2009, Digra et al, 2007). In this study, we found a prevalence of a third which is higher than that reported in comparable studies. In a study of clinical neonatal seizures in Kenya Mwaniki et al (2010) reported a lower prevalence than the one reported in our study. In a similar hospital-based study among 31 neonates, the prevalence of neonatal seizures was 19.2% (Digra et al, 2007). The high prevalence reported in our study may be due to the status of the hospital as a referral centre and therefore receives complicated cases from other facilities. Also, there may be other factors, like birth asphyxia, related to etiology of neonatal seizures in different areas that could explain the high prevalence.

There was a male preponderance of neonatal seizures which is similar to findings in other studies. Similar results have been replicated in elsewhere (Kumar et al, 2007, Adebami, 2010, Moayedi and Zakeri, 2007). There is no plausible explanation for the consistent gender disparity.

Contrary to our findings, Mwaniki et al (2010) and Adebami (2010) found that there was significantly higher occurrence of seizures among newborns with higher gestation and higher birth weight. Similarly, (Ronen et al, 1999) reported higher number of neonatal seizures among babies born 38-43 weeks compared to younger ones. The

risk ascribed to gestation could be due to a higher number of babies delivered after gestation of 42 weeks as well as babies admitted from home in the two studies. However, there was no explanation for the increase in risk with increasing birth weight.

Duration of labour and place of delivery were not associated with risk of neonatal seizures. Mwaniki et al (2010) found that being delivered in hospital or at home did not influence the risk of neonatal seizures. This study supports finding in other studies that clinical signs and symptoms cannot be used to predict the risk of neonatal seizures (Millichamp, 1991, Mwaniki et al, 2010). Also, there was no significant association between perinatal characteristics and neonatal seizures which implies that these features were not predictors of neonatal seizures.

5.2 Clinical Characteristics Neonates with Seizures

Tonic focal seizures were the most common seizure type in our study which was Contrary to reports from other studies. Gebremariam et al, (2006) found that two thirds of seizures were multifocal clonic. Similarly, Digra et al (2007) found that multifocal seizures were the most common type followed by subtle, tonic and focal clonic in that order. On the contrary, Sabzehei et al. (2014) reported that the commonest clinical seizures were subtle seizures. Arpino et al (2001) in Italy found that generalized tonic-clonic seizures were the most common seizure. Similarly, in a study which was done by Asindi et al (1995) in a Nigerian hospital there was an unusually high prevalence (two thirds) of the generalized seizures. The different findings on classification of seizures could be due to methodological challenges. Studies vary in method used to document seizures. The ideal way to observe for seizures would be by video monitoring rather than direct observation or reliance on

reports from parents and other health workers who may not give accurate description (Murray et al, 2008). In the current study, subtle seizures were probably under-reported while generalized seizures were over-reported. Similar methodological challenges could have led to over-reporting of generalized seizures. The short coming of studies based on clinical seizures should be interpreted in consideration of findings based on clinical-electrographic seizures. Clinical seizures that are consistently associated with electrographic activity are focal tonic, some myoclonic and focal clonic. It is doubtful whether most subtle seizures and generalized seizures are epileptic (Mizrahi and Kellaway, 1998).

There was limited investigation of neonates with neonatal seizures. Random blood sugar was tested in about two thirds of the neonates, and none was found to have hypoglycemia. Finding no case of hypoglycemia was contrary to expectation because hypoglycemia has been shown to be associated with 5 – 6.5% of neonatal seizures in the developed world (Arthur and Lombroso, 1970). Similarly, in a study done in Kenya among neonates with seizures, the prevalence of hypoglycemia was 22.3% (Mwaniki et al, 2010). The contrary results in the current study could be explained by the observation that blood sugar was not done on all neonates and that it was not documented whether blood sugar was done before or after an intervention that could potentially correct hypoglycemia.

It has been shown that hypocalcaemia occurs with a frequency of 2-3% among neonates with convulsions (Arthur et al, 1970). In Nigeria, adebami (2010) reported the frequency of hypocalcaemia of 3.4% in neonates with seizures. In this study serum, calcium was not documented in any of the neonates. It is likely that there was missed opportunity to diagnose and treat hypocalcaemia.

Seizures are an indication of neurological disease and where sepsis is suspected, there is a high probability of meningitis hence the recommendation that lumbar puncture should be performed. (WHO, 2011). In this study, two thirds of the neonates with seizures had suspected sepsis. However, only one patient had lumber puncture performed. Additionally, even though it is recommended that where lumbar puncture is not performed, such neonates should be treated for meningitis, only five (17.2%) out of the probable 29 were treated. There is a possibility that some neonates with meningitis were exposed to inappropriate treatment and left at risk of further brain damage.

None of the neonates underwent radiological investigations. There is strong evidence that radiological investigations are not useful in confirming diagnosis of seizures or monitoring control of seizures (WHO, 2011). Therefore, the finding that radiological investigations were not done is good clinical practice. However, radiological investigations are important in identification of the underlying aetiologies and prognostication, regarding which, the lack of investigations implies that these two were ignored by the clinicians.

Most of the neonates seen with seizures in this study were started on antiepileptic medication. There was no documentation of criteria if any used to decide who needed to be started on medication. Although antiepileptic drugs are useful in control of seizures, they may not be necessary and may even be harmful in some neonates (Maitre et al, 2013) which explains the basis of WHO guidelines on when to start AEDS (WHO, 2011). Phenobarbitone and phenytoin were the AEDs used in this study. Similar studies have shown that clinicians tend to use older AEDs in treatment of neonatal seizures (Glass et al 2009, Van Rooij et al, 2013). Painter et al (1999) showed that phenobarbitone and phenytoin are equally but incompletely effective in

treatment of neonatal seizures. Although WHO recommends phenobarbitone as the first line drug, the evidence for its preference is weak (Painter et al, 1999). Therefore, clinicians may not be at fault for having chosen phenytoin as the first line drug. In this study, none of the neonates was started on second line AEDs. Painter et al (1999) found out that using a combination of phenytoin and phenobarbitone, regardless of which one was the first line, was associated with increased effectiveness. There is a potential benefit of using combination therapy where first-line medication failed. However, this study could not estimate the benefit because data on seizures that failed to respond to first-line medication was not available.

5.3 Adherence to WHO guidelines

Adherence to the WHO Guidelines for those elements that could be assessed was all suboptimal except for the subsection on radiological investigation. We are not aware of any study that has evaluated the adherence of clinicians to WHO guidelines on management of neonatal seizures. The challenges that face the care of neonates with seizures are lack of appropriate diagnostic criteria (Mizrahi and Kellaway, 1998) and evidence-based guidelines on pharmacological treatment (Slaughter et al, 2013). The value of standardized treatment protocols in improving care of neonates cannot be overstated. Lapillonell et al (2013) showed that guidelines are important in improving quality of care offered to neonates. Harris demonstrated that adherence to standardized protocol in management of neonates with seizures improved outcome (Harris et al, 2016). The WHO guidelines offer an opportunity to standardize care based on available evidence. If well applied, the guidelines have the potential to improve outcome of neonatal seizures.

5.4 Outcome

The outcome of neonatal seizures may be short term or long term. The short-term outcome includes duration of stay in hospital and the death rate (Volpe, 2008). In this study, the death rate was 44% which is high but comparable to findings in Nigeria (45.8% and 43.6%) Adebami, 2010, Ogunlesi et al, 2007). Contrary to our findings, there are reports of lower mortality rates. Mwaniki et al (2010) and Gebremariam et al (2006) found mortality rates of 19.1 and 11% respectively in hospital-based studies, while Ronen et al (1999) found a rate of 9% in Newfoundland in a community-based study. The wide variation in outcome could be explained by methodological differences as well as management of seizures and the underlying aetiology. Death in patients with neonatal seizures is a reflection of the underlying aetiology (McInerny et al, 1969, Glass et al, 2009). However, there have been studies that suggest that neonatal seizures may be an independent determinant of mortality (Miller et al, 2002, Glass et al, 2009).

Neonates whose seizures were not controlled within 24 hours were more likely to die as compared to the controlled ones. None of the other possible predictors of outcome was significantly associated with mortality. Our study failed to show significance of birth weight contrary to findings in similar studies (Mwaniki et al, 2010). Other studies have shown that aetiology is a strong predictor of mortality (Millichamp et al, 1991) but, our data on aetiology was incomplete and therefore it was not included in the analysis.

5.5 Limitations

- This study did not use video EEG monitoring which could have led to non-identification of some seizures and incomplete description of the seizure semiology.

- Relying on recorded information. This was mitigated by comparing records from all cadres of staff.

CHAPTER SIX: CONCLUSIONS AND RECOMMENDATIONS

6.1 Conclusions

Neonatal seizures were found in about a third of the neonates and the factors significantly increased the risk of seizures were low birth weight and gestation age.

The most common type of seizures was focal tonic and phenobarbitone was the most common medicine used in treatment.

There is inadequate adherence to the WHO guidelines in management of neonatal seizures

The mortality among neonates with seizures was high (44%)

6.2 Recommendations

There is need to reduce the prevalence of neonatal seizures through vigorous study of its aetiology and subsequent prevention. Low birth weight and gestation age as found in this study are factors that ought to be addressed.

A future study should look at the reason for none adherence to WHO recommended guidelines in care of neonatal seizures at MTRH. This could be followed by an intervention to increase adherence to these evidence-based guidelines with a potential to improve outcome.

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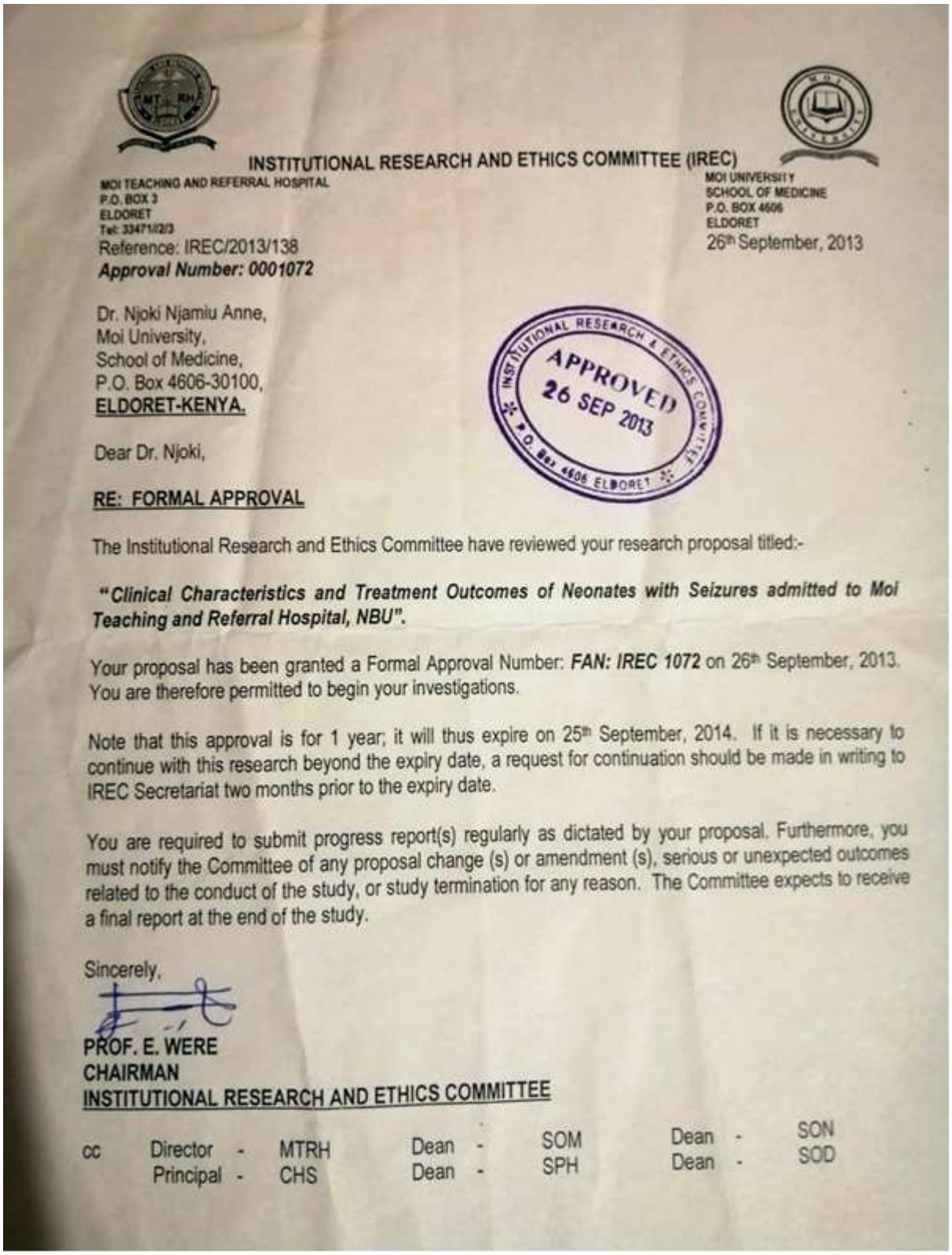
APPENDICES

Appendix I: Prevalence of various causes of neonatal seizures in different geographical regions of the world

Study population	Study period	Hypoxic-ischaemic encephalopathy	Hypoglycaemia	Hypocalcaemia	CNS infection
Only full term neonates	**Until 1990**	Eriksson & Zetterström - 48% Rose & Lombroso - 13% Gunn & Cable - 83% *Range: 13 to 83%* *Median: 48%*	Eriksson & Zetterström - 6.5% Rose & Lombroso - 5% Gunn & Cable - NA *Range: 5 to 6.5%* *Median: 5.5%*	Eriksson & Zetterström - 2.6% Rose & Lombroso - 20% Gunn & Cable - 9% *Range: 2.6 to 20%* *Median: 9%*	Eriksson & Zetterström - 12% Rose & Lombroso - 9.5% Gunn & Cable – NA *Range: 9.5 to 12%* *Median: 10.3%*
	Since 1990	Lien et al.- 38% *Range: NA* *Median: 38%*	Lien et al. - NA	Lien et al. - NA	Lien et al. - 7.5% *Range: NA* *Median: 7.5%*
Mixed (full term and preterm neonates) or not known	**Until 1990**	Craig - NA Schulte - 54% Keen & Lee - 12.5% (+ICH) Combes et al. - 77% (+ICH) Rossiter et al. - NA Dennis - 44% (including hypoglycaemia and hypocalcaemia) Andre et al. - 56% McInerny & Schubert - 33% Langevin - 57% Ellison et al. - 24% Holden et al. - NA Ment et al. - 32% Goldberg - 30 to 41% Bergman et al. - 59% Zalneraitis - 74% Tudehope et al. - 40% *Range: 12.5% to 77%* *Median: 42.5%*	Craig - NA Schulte - NA Keen & Lee - 4% Combes et al. - NA Rossiter et al. - 13% Dennis - 12% Andre et al. - 1.4% McInerny & Schubert - 7% Langevin - NA Ellison et al. - NA Holden et al. - NA Ment et al. - NA Goldberg - 1 to 11% Bergman et al. - 5% Zalneraitis - NA Tudehope et al. - NA *Range: 1% to 13%* *Median: 6%*	Craig 0.5% Schulte - NA Keen & Lee - 42% Combes et al. - 10% Rossiter et al. - NA Dennis - 14% (pure) Andre et al. - 2.8% McInerny & Schubert - 30% Langevin - 43% Ellison et al. - 2% Holden et al. - NA Ment et al. - NA Goldberg - 4 to 6% Bergman et al. - 1.5% Zalneraitis - NA Tudehope et al. - NA *Range: 0.5% to 43%* *Median: 6%*	Craig - 6% Schulte - 7% Keen & Lee - 0.7% Combes et al. - 7% Rossiter et al. - 13% Dennis - NA Andre et al. - 24% McInerny & Schubert - 10% Langevin - NA Ellison et al. - 3% Holden et al. - 17% Ment et al. - 11% Goldberg - 4 to 5% Bergman et al. - 12% Zalneraitis - 13% Tudehope et al. - 11% *Range: 0.7% to 24%* *Median: 10%*
	Since 1990	Toet et al. - 80% Legido et al. - 35% Lanska & Lanska - 40% Ortibus et al. - 37% Ronen et al. - 40% Brunquell et al. - 49% Garcias da Silva et al. - 34% Bye et al. - 42% Idro et al. - 12% *Range: 12% to 80%* *Median: 40%*	Toet et al. - NA Legido et al. - NA Lanska & Lanska - NA Ortibus et al. - NA Ronen et al. - 13% Brunquell et al. - NA Garcias da Silva et al. - NA Bye et al. - 4% Idro et al. - NA *Range: 4% to 13%* *Median: 8.5%*	Toet et al. - NA Legido et al. - NA Lanska & Lanska - NA Ortibus et al. - NA Ronen et al. - 5% Brunquell et al. - NA Garcias da Silva et al. - NA Bye et al. - NA Idro et al. - 5%	Toet et al. - NA Legido et al. - 12.5% Lanska & Lanska - Ortibus et al. - 9% Ronen et al. - 8% Brunquell et al. - 2% Garcias da Silva et al. - 13% Bye et al. - 6% Idro et al. - 6% *Range: 2% to 13%* *Median: 8%*
Preterm neonates or low birth weight	**Until 1990**	Seay & Bray - 87% (birthweight<2,5kg) Watkins et al. - 40% *Range: 40% to 87%* *Median: 63.5 %*	Seay & Bray - NA Watkins et al. - 3% *Range: NA* *Median: 3%*	Seay & Bray - 3% Watkins et al. - 1.5% *Range: 1.5% to 3%* *Median: 2.3%*	Seay & Bray - 6% Watkins et al. - 5% *Range: 5% to 6%* *Median: 5.5%*
	Since 1990	—	—	—	—

Note. GRADE could not be applied to epidemiological data *NA= not available*

Appendix 2: IREC Approval



INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE (IREC)

MOI TEACHING AND REFERRAL HOSPITAL
P.O. BOX 3
ELDORET
Tel: 33471/2/3

MOI UNIVERSITY
SCHOOL OF MEDICINE
P.O. BOX 4606
ELDORET

Reference: IREC/2013/138
Approval Number: 0001072

26th September, 2013

Dr. Njoki Njamiu Anne,
Moi University,
School of Medicine,
P.O. Box 4606-30100,
ELDORET-KENYA.

INSTITUTIONAL RESEARCH & ETHICS COMMITTEE
APPROVED
26 SEP 2013
P.O. Box 4606 ELDORET

Dear Dr. Njoki,

RE: FORMAL APPROVAL

The Institutional Research and Ethics Committee have reviewed your research proposal titled:-

"Clinical Characteristics and Treatment Outcomes of Neonates with Seizures admitted to Moi Teaching and Referral Hospital, NBU".

Your proposal has been granted a Formal Approval Number: ***FAN: IREC 1072*** on 26th September, 2013. You are therefore permitted to begin your investigations.

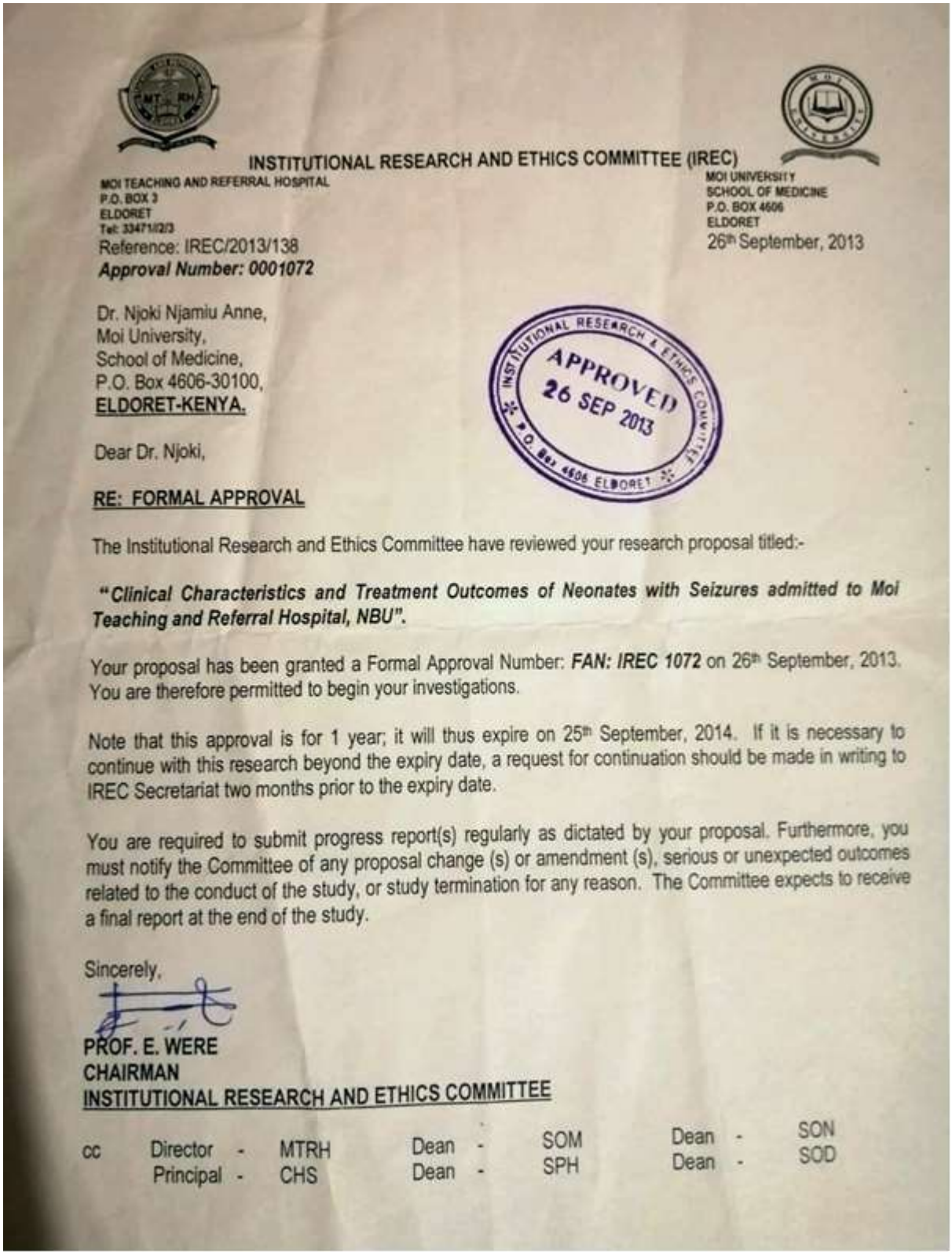
Note that this approval is for 1 year; it will thus expire on 25th September, 2014. If it is necessary to continue with this research beyond the expiry date, a request for continuation should be made in writing to IREC Secretariat two months prior to the expiry date.

You are required to submit progress report(s) regularly as dictated by your proposal. Furthermore, you must notify the Committee of any proposal change (s) or amendment (s), serious or unexpected outcomes related to the conduct of the study, or study termination for any reason. The Committee expects to receive a final report at the end of the study.

Sincerely,

PROF. E. WERE
CHAIRMAN
INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE

cc Director - MTRH
Principal - CHS
Dean - SOM
Dean - SPH
Dean - SON
Dean - SOD



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Sincerely,

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cc Director - MTRH Dean - SOM Dean - SON
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