COMPARATIVE EFFECTIVENESS AND COST ANALYSIS OF AN ANTICOAGULATION CLINIC VERSUS LABORATORY BASED PRACTICE IN KENYAN TERTIARY REFERRAL HOSPITALS

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A thesis submitted in partial fulfillment of the requirements for the award of the degree of Master of Pharmacy in Pharmacoepidemiology and Pharmacovigilance.

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DEDICATION

I would like to dedicate this thesis to my dear family for their continued support. May God continue to bless them abundantly.

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ABSTRACT

Background: The laboratory based practice for monitoring oral anticoagulation therapy is laboratory testing of blood to measure the International Normalized Ratio. This is the current practice at Kenyatta National Hospital. Studies that have been carried out at Kenyatta National Hospital have shown that majority of patients on oral anticoagulation therapy spend most of their time with their International Normalized Ratios out of therapeutic range. Point of care testing devices offer an alternative to laboratory testing. At Moi Teaching and Referral Hospital, patients are monitored using point-of care devices and the warfarin dose adjusted according to protocols. This is done in a specialised anticoagulation clinic that specifically manages anticoagulation therapy.

Objectives: The objective of this study was to carry out a comparative effectiveness and cost analysis of specialized anticoagulant clinic at Moi Teaching and Referral Hospital versus current practice at Kenyatta National Hospital for monitoring of coagulation status.

Methodology: The study was divided into two sections: comparison of International Normalised Ratio values as a measure of effectiveness and the cost analysis of specialized anticoagulation clinic versus laboratory based practice. A comparative retrospective longitudinal study was carried out to compare the quality of anticoagulation therapy for the two modes of service delivery. The study was conducted at the hemato-oncology and cardiothoracic clinics of Kenyatta National Hospital and the anticoagulant clinic of Moi Teaching and Referral Hospital. The study population was all patients on oral anticoagulation therapy seen at the clinics from January 2015 to April 2017. The patients were included in the study if they; were above 18 years, required an oral anticoagulant for more than one month and had at least two International Normalised Ratio values. Universal sampling was carried out and the calculated sample size was 120 patient files. Data was collected with the aid of a predesigned structured data collection form designed by Karuri (2016).

For the cost analysis, a micro ingredient costing approach was used to examine all resources incurred in provision of the service. Health care provider perspective was considered. Key informant interviews were conducted to obtain costs. The key informants were selected by purposeful sampling and the inclusion criteria was: worked at the clinics for a period of at least 6 months, had managerial positions and provided informed consent. Data analysis was performed using STATA version 13 and R version 3.3.2 software. Socio demographic and clinical characteristics were summarized into percentages for categorical data and continuous data into means and standard deviation. Costs were summarised as cost per month and estimates of the

financial consequences of adopting a pharmacist led anticoagulation clinic was determined. Sensitivity analysis was carried out to determine the variables which greatly affected each intervention.

Results: Above 75% of the patients from both institutions were females. The most prevalent indication for anticoagulation use at both institutions was deep venous thrombosis. The most prevalent comorbidity in both instituitions was HIV. According to survival curves obtained from survival analysis, coagulation therapy in Kenyatta National Hospital was suboptimal compared to Moi Teaching and Referral Hospital and therefore there was better International Normalised Ratio control at the specialised anticoagulation clinic. According to the findings, there was a higher probability of patients being at hypercoagulability state in KNH compared to those in MTRH. Therapeutic INR was attained at a faster rate in MTRH compared to KNH and more patients in KNH were at a greater bleeding risk than those at MTRH.Total cost per month for monitoring International Normalised Ratio at Kenyatta National Hospital was Ksh1343762. Total cost per month for monitoring International Normalised Ratio at Moi Teaching and Referral Hospital was Ksh 1177696. The cost at Moi Teaching and Referral Hospital was slightly lower than the cost at Kenyatta National Hospital. The most sensitive variable that greatly affected the cost ratio was the fraction of time the healthcare workers spent in the Kenyatta National Hospital clinics. Approximately Ksh 5.8 million was required to start an anticoagulation clinic.

Conclusion: From the findings, the total cost per month at the anticoagulation clinic of Moi Teaching and Referral Hospital was lower and more effective than the laboratory based practice at Kenyatta National Hospital. The anticoagulation clinic had various advantages compared to the laboratory based practice. It is therefore recommended that Kenyatta National Hospital to consider implementing an anticoagulation clinic in order to improve monitoring of anticoagulation therapy.

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ABBREVIATIONS AND ACRONYMS

ACC	Anticoagulation Clinic
CAP	College of American Pathologists
CADTH	Canadian Agency for Drugs and Technology in Health
INR	International Normalized Ratio
KNH	Kenyatta National Hospital
LMWH	Low Molecular Weight Heparin
MTRH	Moi Teaching and Referral Hospital
OAT	Oral Anticoagulation Therapy
POCT	Point of Care Testing
PT	Prothrombin Time
TTR	Time in Therapeutic Range
VKA	Vitamin K antagonist
UFH	Unfractionated Heparin
HIV	Human Immunodeficiency Virus
DVT	Deep Venous Thrombosis
APTT	Activated Partial Thromboplastin Time

OPERATIONAL DEFINITIONS

Anticoagulation clinic	Services specialized in monitoring and managing medication that prevent blood clots. Physically, it is a specified location within a hospital or a medical office that is staffed by specially trained pharmacists, nurses or nurse practitioners.
Anticoagulant	An agent that is used to prevent the formation of blood clots.
Blood clot	A blood clot is a thickened mass in the blood formed by tiny substances called platelets. Clots form to stop bleeding, such as at the site of cut.
Comparative effectiveness	The direct comparison of existing health care interventions to determine which work best for which patients and which pose the greatest benefits and harms.
Cost analysis	It is the procedure of estimating all costs involved and possible profits to be derived from a given intervention.
Effectiveness	The degree to which objectives are achieved and the extent to which targeted problems are solved.
Monitoring	Observation and checking the progress of a patient over a period of time
Point of care testing	Testing at or near where a patient is located
Standard care	The level at which the average, health care provider in a given Facility would practice
Tertiary Referral Hospital	Specialized consultative care, usually on referral from primary or secondary medical care personnel, by specialists working in a center that has personnel and facilities for special investigation and treatment.

CHAPTER ONE: INTRODUCTION

1.1 Background

Patients take oral anticoagulation therapy (OAT) to prevent blood clots. Warfarin is a drug that is commonly used in OAT. Warfarin has a narrow therapeutic window and therefore requires frequent monitoring. When taking warfarin, patients need to be observed to make sure that they are getting the adequate amount of medicine and are not at risk of either bleeding or clotting. The degree of anticoagulation achieved by warfarin is monitored by the common coagulation test known as the prothrombin time (PT). PT is then used to compute International Normalized Ratio (INR). The normal INR is typically between 0.9 to about 1.1. On warfarin therapy, the INR elevates to between 2 and 3.5 and most hospital pharmacies and clinical hematology services will have specific INR goals documented in their treatment protocols (Harris, The International Normalized Ratio: How well do we understand this measurement?, 2012). The various modes of International Normalized Ratio (INR) testing include: clinical laboratory testing; patient self-testing and point of care testing (Nq, et al., 2009).

The clinical laboratory testing which is the current gold standard method for monitoring warfarin is testing of blood obtained by venepuncture to measure INR in a laboratory. The advantages of laboratory based INR monitoring are better accurate results therefore used as a reference standard, can analyse more than one sample at a time and analyse other tests such as APTT. The disadvantages are slow turnaround times therefore long waiting time and reduced patient compliance. Patients may find this testing to be time consuming and inconvenient. (Cepoiu, et al., 2010). At Kenyatta National Hospital INR monitoring is carried out in the laboratory. Patients are referred from the hematology and cardiothoracic clinic to the lab for INR measuring. The patients are then reviewed at the clinics by physicians and the doses adjusted according to protocols.

Point of care testing (POCT), as stated by the College of American Pathologists (CAP), is testing that is done near or at the site of a patient (Frigaard et al, 2016). POC INR involves obtaining a small sample of blood by pricking the fingertip and the blood is deposited onto a test strip which is then inserted into a coagulometer. The blood is then analysed and the INR result displayed (CADTH, 2015). In specialized anticoagulation clinics and patient self testing, POCT devices are normally used to monitor INR. The advantages of POCT devices compared to the laboratory based practice include: better patient convenience, compliance and

satisfaction; improved monitoring and fewer clotting and bleeding complications. The device's disadvantages are: the likelihood to underestimate high INR values or overestimate low INR values; poor thromboplastin sensitivity; inability to calculate a mean normal prothrombin time; and possible errors when determining INR in patients with antiphospholipid antibodies (Ontario Health Quality, 2009). Recent changes in diagnostics and healthcare service provision has resulted in an increase in the demand of POCT in the primary and community care environments (Chadwick et al, 2009). At Moi Teaching and Referral Hospital, there is an established anticoagulation clinic. Point of care testing devices are utilized at the clinic to measure INR. At every clinic visit, the patient's INR is checked using the Coaguchek XS® point-of-care device and the warfarin dose adjusted according to protocols developed by the American College of Chest Physicians (ACCP) guidelines (Manji et al, 2011).

The main aim of POCT is to bring testing nearer to the patient, get results in a more convenient and fast manner to the provider so as to hasten diagnosis, and to allow for monitoring and subsequent therapy. POCT allows for quicker clinical decisions in the health care setting, and at home (Futrell, 2015). The main aim of this study is to assess and compare the effectiveness of INR monitoring and cost of setting up an anticoagulation clinic that will improve efficiency when monitoring INR in patients who are on long term oral anticoagulation therapy.

1.2 Problem statement

The current care for patients on long term oral anticoagulation therapy at Kenyatta National Hospital is laboratory based INR testing with ambulatory clinics. Several studies have shown that ambulatory anticoagulation control is poor at the hospital (Nyamu D, 2017). The problems associated with monitoring patients on oral anticoagulation therapy at the hospital include: delays in obtaining laboratory results; lack of effective laboratory monitoring services and increased work load for staff (Kibiru, 2012 and Ogendo, 2001).

A recent study carried out at Kenyatta National Hospital showed that majority of patients on warfarin therapy spent most of their time with their INRs out of therapeutic range (Kibiru, 2012). Another study carried out at the same hospital came to the conclusion that the occurrence of anticoagulant-related bleeding was relatively common (Ogendo, 2001). Ndwiga (2009) found that the intensity of anticoagulation therapy in Kenyatta National Hospital was adequate but its monitoring was not up to par. According to Ouko (2012), a performance audit report by the Auditor-General on specialized healthcare delivery at Kenyatta National Hospital came to the conclusion that patients who sought specialized health care at the Kenyatta

National Hospital endured long waiting times before they could get any treatment. These delays prevented the hospital from achieving its unique mandate in an effective manner and put the lives of many patients at risk.

A study carried out to assess the impact of the anticoagulation management service at Moi Teaching and Referral Hospital found that patients who spent a minimum of 4 months in the anticoagulation clinic had lower time in the therapeutic range compared to those who had been followed longer. The mean time in therapeutic range of 64.6% showed that the clinic could provide high quality services and therefore was non-inferior to the laboratory based practice (Manji et al, 2011).

From these studies, it shows that evidence is required on the comparative effectiveness of a specialized anticoagulation clinic compared to laboratory INR monitoring so as to convince policy makers to establish one in tertiary health care facilities.

1.3 Research Questions

1. What is the cost of setting up an anticoagulation clinic at Kenyatta National Hospital?
2. Are International Normalised Ratio levels of patients followed up in Moi Teaching and Referral Hospital more likely to be in the therapeutic ranges compared to patients seen at Kenyatta National Hospital?
3. What is the comparative cost of International Normalised Ratio monitoring at Kenyatta National Hospital versus the specialized anticoagulation clinic of Moi Teaching and Referral Hospital?

1.4 Hypotheses

1. **Null hypotheses**: The costs of INR monitoring at Moi Teaching and Referral Hospital and Kenyatta National Hospital are not significantly different.
   Alternate hypotheses: The costs of INR monitoring at Moi Teaching and Referral Hospital and Kenyatta National Hospital are significantly different.
2. **Null hypotheses**: The INR levels of patients followed up in the ambulatory clinics of Kenyatta National Hospital and specialised clinic of Moi Teaching and Referral Hospital are not significantly different.

Alternate hypotheses: The INR levels of patients followed up in the ambulatory clinics of Kenyatta National Hospital and specialised clinic of Moi Teaching and Referral Hospital are significantly different.

1.5 Objectives

1.5.1 Main objective

To carry out an effectiveness comparison and cost analysis of specialized anticoagulant clinic of Moi Teaching and Referral Hospital versus standard care in monitoring of coagulation status at Kenyatta National Hospital.

1.5.2 Specific objectives

The specific objectives of this study were to:

1. Estimate the cost of setting up an anticoagulation clinic at Kenyatta National Hospital.
2. Compare the International Normalised Ratio levels of patients followed up in Moi Teaching and Referral Hospital versus patients seen at Kenyatta National Hospital.
3. Compare the cost of International Normalised Ratio monitoring using standard laboratory based practice at Kenyatta National Hospital versus the point of care testing based model at the specialized anticoagulation clinic of Moi Teaching and Referral Hospital.

1.6 Justification and significance of the study

Point of Care-INR testing (POCT) devices are an alternative to laboratory-based testing. Independent analysis has shown that POCT devices have a satisfactory level of precision. They allow INR results to be determined promptly, resulting to rapid dose adjustments. POCT devices are used in a variety of settings including: anticoagulation clinics; physician offices; pharmacies; long-term care facilities; or by patients through self-testing (PST). There is increasing evidence that better outcomes are obtained when anticoagulation therapy is managed by anticoagulation clinics rather than normal laboratory procedure. This is because specialized anticoagulation clinics improve efficiency when carrying out tests necessary for pharmacological monitoring by using POCT INR devices. Managers and policy makers at the Kenyatta National Hospital may not appreciate the need to establish a specialized anticoagulant clinic because there is lack of evidence of the benefits such a clinic may offer. Policy makers

require information on the benefits of setting up an anticoagulation clinic in order to enable them to allocate necessary funds . The purpose of this study was to compare the cost and the effectiveness of an anticoagulation clinic to the laboratory based practice. The findings of this study will be useful to provide estimates for the budget needed to establish an anticoagulation clinic at the Kenyatta National Hospital which will eventually improve health outcomes. The findings may be used to convince policy makers of the benefit of a specialist anticoagulation service.

CHAPTER TWO: LITERATURE REVIEW

2.1 Anticoagulant use in the ambulatory setting

Anticoagulants are widely used for the prevention and treatment of various thromboembolisms such as; deep venous thrombosis, pulmonary embolism, atrial fibrillation and mechanical heart valves venous thrombosis. (Kneeland & Fang, 2010). The most commonly used anticoagulants are unfractionated heparin (UFH), low molecular weight heparin (LMWH) vitamin K antagonists such as warfarin and antiplatelets such as warfarin. Other new oral anticoagulation drugs are the oral direct thrombin inhibitors for example dabigatran and oral direct factor Xa inhibitors for example rivaroxaban. These new oral anticoagulation therapy do not require INR monitoring (D.M.Adcock & R.Gosselin, 2015). LMWH, UFH and warfarin are known to be high risk drugs with a narrow therapeutic index and therefore should be carefully monitored.

LMWHs are produced by the enzymatic depolymerization of heparin thus obtaining mixtures of smaller polymers. The low-molecular-weight fractions are frequently pentasaccharide sequences while the higher weight fractions are more common in the longer sequences. LMWHs have fewer serious side effects such as heparin-induced osteopenia and thrombocytopenia (HIT) when compared with unfractionated heparin (Geno & James, 2010).

UFH is heterogeneous in respect to molecular size, anticoagulant activity, and pharmacokinetic properties. The molecular weights of these molecules range from 5,000 to 30,000 Da, with a mean molecular weight of 15,000 Da. About one third of an administered dose of UFH binds to a cofactor called Antithrombin III, and this fraction is responsible for most of its anticoagulant activity. UFH produces its major anticoagulant effect by inactivating thrombin and activated factor X (factor Xa) through an antithrombin-dependent mechanism. The most common methods for monitoring UFH are the activated partial thromboplastin time (aPTT) in a laboratory (Guervil et al., 2011).

Warfarin is an oral anticoagulant used for the prophylaxis and therapy of venous thrombosis and other thromboembolic complications.Warfarin is also used in reduction of the risk of recurrent myocardial infarction and to prevent recurrent transient ischemic attacks. The main aim of warfarin therapy is to maintain the targeted INR using the lowest effective dose. Warfarin prevents the synthesis of anticoagulant proteins C and S together with the clotting factors II, VII, IX, and X. The safety and effectiveness of warfarin therapy are dependent on maintaining INR within the targeted range for the indication (Walter A et al., 2012).

2.2 Prevalence of oral anticoagulation therapy

According to Sonak et al. (2010), the number of patients on oral anticoagulation is increasingly growing. In their study on need assessment analysis of vitamin K anticoagulation therapy, they found that 20 of the 554 patients (3.6%) who were admitted to the wards were candidates for vitamin K antagonist therapy. Out of 168 outpatient in the cardiology clinic, 72 patients (42.8%) needed Vitamin K antagonist therapy. In America, studies established that 20% to 80% of the patients with indication benefit from OAT. (Adelina-Mihaela S et al., 2018).

A study by Vats, et al. (2007) indicated that out of 3,778 patients in 38 hospitals in the U.S., about half of all patients who underwent total hip or knee replacement were given warfarin and 45% received LMWHs. A study of 15,000 acutely ill, hospitalized medical patients from 12 countries worldwide which was obtained from a report prepared by the International Medical Prevention Registry on Venous Thromboembolism (IMPROVE), observed that majority of prescribed anticoagulants were LMWHs. About 34% of patients used LMWH while 11% used UFH. (Tapson et al., 2007).

2.3 Monitoring of anticoagulation therapy

The main aim of oral anticoagulation treatment is not to prevent blood clotting completely but to reduce its clotting tendency. Thus, the bloods capability to clot must be monitored carefully. According to the results of regular blood tests, the dose should be adjusted to ensure the clotting time is within the targeted range. These tests can be carried out in the laboratory or through a POCT device at home. The tests carried out when monitoring anticoagulation therapy are prothrombin time and International Normalized Ratio.

High PT and INR values indicate a longer time is needed for blood to clot. Normally the desired targeted INR range is between 2 and 3, although in special circumstances other ranges may be used. The INR is approximately 1 for a person who is not on warfarin. There is a higher risk of bleeding if the INR is above the targeted range or a higher risk of clotting if the INR is below the targeted range (Russell & Garcia, 2016).

The dose of oral anticoagulation therapy is altered in order to achieve the PT/INR of the blood within the desired range. There is increased PT/INR monitoring when there is dose adjustment,

starting or stopping another treatment, or a change in the medical condition of a patient. There is reduced monitoring when the dose stabilises (Russell & Garcia, 2016).

2.4 How to measure and compute INR

Prothrombin time (PT) is a laboratory test used to measure the time taken in seconds for a clot to form. It is specifically sensitive to the clotting factors that are affected by warfarin. INR which is a measure used to adjust warfarin dose can be computed using PT. INR is a way of expressing the PT in a standardized way by comparing it to a reference value. This allows different laboratories in different facilities to compare their results more reliably. It is presented as a figure with no units (Russell & Garcia, 2016).

The first step of INR calculation is to normalize the PT by comparing it to the mean normal prothrombin time which is the geometric mean of the prothrombin time of a healthy adult population. In the second step, this ratio is raised to a power designated as ISI (international sensitivity index). The ISI is determined by the manufacturer of thromboplastin reagent. The usual range is between 0.9 to 1.7. The following equation is used to compute INR (Harris, 2012).

Formula: $INR = (PT\ patient/PT\ normal)^{ISI}$

2.5 Treatment guidelines and protocols for anticoagulation therapy

When warfarin therapy is initiated, it should be given the first day, along with a heparin product. The heparin product should be continued for at least 5 days and until the patient's international normalized ratio is at least 2.0 for two consecutive days. The INR goal and duration of treatment with warfarin vary depending on indication and risk (Wigle P, 2013). When initiating warfarin an initial INR should be done on the third day. In the absence of any bleeding, the warfarin dose should be adjusted accordingly. An INR should then be done every 3-4 days, until the INR is therapeutic and stable. The INR should be checked within 1-2 weeks for any change in dose. Any INR that falls below the therapeutic range should be checked within 1-2 weeks whether or not the dose is adjusted. For very stable patients who are within the therapeutic range for 6 months, INRs may be checked every 12 weeks (Blostein and kernzer, 2012). These guidelines were adopted from the american college of chest physicians

(ACCP). These guidelines are used at the specialised anticoagulation clinic of moi teaching and referral hospital (Manji et al., 2011).

2.6 Challenges with anticoagulation therapy

Warfarin therapy management can be challenging due to its complicated pharmacokinetic characteristics, narrow therapeutic index and dose response variability. There are a number of factors that may influence the activity of warfarin such as diet, drug–drug interactions, genetic variation and concurrent conditions. It is suggested that for optimum management, an anticoagulation management service should provides monitoring of INR, patient education and good patient– health worker communication and relationship. (Daniel et al, 2016). Unfractionated heparin poses a significant risk of heparin-induced thrombocytopenia (HIT) because it's highly antigenic. The presence of antibodies associated to heparin may also lead to adverse clinical outcomes and therefore justify the replacement of UFH (Francis & Groce, 2004).

The risk of bleeding is one of the challenges faced when administering oral anticoagulants. The bleeding risk is high during the start of warfarin and or during the time of illness. Generally, the risk of internal bleeding is approximately 1 to 3 percent per year. Patients who have tolerated Warfarin well for a minimum six months and are on a stable dose and usually have a risk closer to 1 percent per year for major internal bleeding. A rare adverse effect called skin necrosis can also be caused by warfarin. This condition is common in patients who have protein C deficiency, which is a rare inherited clotting disorder. It is likely observed during the first few days of warfarin treatment when it occurs (Russell & Garcia, 2016)

According to Ogendo (2011), the occurrence of anticoagulant related bleeding was relatively common at Kenyatta National Hospital. Most episodes of bleeding occurred within one year of hospital discharge or the previous bleeding episode. The risk of a second bleeding episode increased up to 50%. The risk factors for the occurrence of bleeding in this study were the number of valves implanted, their position and the time of occurrence of the bleed.

The other challenge of anticoagulation therapy is sub therapeutic anticoagulation which may lead to thromboembolism. A study by Pollack (2015) showed that many patients on warfarin who were seen at the emergency department for anticoagulation-related or other issues had either a sub therapeutic or a supratherapeutic INR.

2.7 Benefits of laboratory based INR monitoring

The clinical laboratory testing carried out at hematology laboratories is the current gold standard method for monitoring warfarin. There are various advantages laboratory based INR monitoring have over the point of care testing devices. laboratory based INR monitoring produce better accurate and reliable results therefore used as a reference standard. They can analyse more than one sample at a time hence good turn around time. Other tests apart from INR can be analysed for example APTT (Cepoiu, et al., 2010).

2.8 Specialized anticoagulation clinics

Anticoagulation clinics provide specialized services in management of patients on anticoagulant therapy. According to Testa, et al. (2012), studies showed that anticoagulation management was critical to ensure the quality of treatment and that anticoagulation clinics represent the best management model when compared to other types of management. There has been a trend of setting up practice based anticoagulation clinics over the last few years. Since the introduction of Primary Care Groups and Trusts, this trend has accelerated and most have supported and encouraged the practice of setting-up and running anticoagulation clinics (NPSA, 2006)

2.9 Purpose of setting up a specialized anticoagulation clinic

Oral anticoagulation management in primary care using point of care testing has been shown to lead to effective treatment management. Primary care services that are locally based allow more choice and flexibility for patients. There are substantial financial benefits for practices opting to offer a point of care testing anticoagulation service. Shifting some of the burden of anticoagulation monitoring to specialized care will permit Haematology Departments to concentrate on new and problematic cases. The possibility to improve the skill of health care workers when managing patients can also be provided in a specialised anticoagulation clinic. The collaborative approach between the healthcare professional and the patient is also improved. This encourages patients to become more aware and involved in their treatment (National Centre for Anticoagulation Training, 2006)

2.10 Benefits of specialized anticoagulation clinic and patient self-monitoring

The benefits of specialized anticoagulation clinics include: better anticoagulation control; decreased INR tests needed in maintaining good control; better safety of the patient; decreased dosing errors; better convenience for the patient; better use of health provider's time; increased efficiency in the use of resources; better contribution to practice, financial income among others (NPSA, 2006). Point-of-care INR testing (POCT) is now accessible in many areas of clinical medicine such as: self-monitoring; specialized anticoagulation clinics and the emergency department. The ability to move testing closer to the patient has resulted in benefits when monitoring INR. A systematic review that was carried out at Ontario came to the conclusion that for a group of patients who have been well trained and motivated, Patient self-monitoring led to few thromboembolic events compared to laboratory-based INR testing (Ontario Health Quality, 2009). Other studies concluded that patient self-monitoring improved anticoagulation control and reduced risk of clotting compared to clinic-based care (Pluddemann et al., 2012)

2.11 International guidelines of setting up an anticoagulation clinic

There are internationally set guidelines for setting up an anticoagulation clinic. The National Centre for anticoagulation training established in Europe has developed steps for setting up an anticoagulation clinic. The first step is planning which involves: setting up a governing group; identifying patients who are eligible; selecting an appropriate mode of service; assessing the impact on staffing and workload; agreeing on the referral systems; agreeing on time and location of service; assessing financial implications and developing a business proposal; and presenting the business proposal to the relevant commissioning body. The second step is setting up the service which involves: designation of a clinical lead; developing protocols and Standard Operating Procedures; organizing training of staff; selecting and purchasing POCT monitoring device; selecting and purchasing decision support software and informing patients of the service. Finally beginning the service which involves: continuous external & internal quality assurance; ongoing staff training and assessment; reviewing the service continuously; providing the patients with proper and consistent quality of care (National Centre for Anticoagulation Training, 2006). In Kenya there are no set guidelines on how to set up an anticoagulation clinic but there has been implementation of a pharmacist managed anticoagulation clinic in Eldoret, Kenya. According to the research carried out on the clinic, several setting specific problems were observed including the possibility of warfarin

interacting with other drugs due to concurrent treatments of diseases such as Human Immunodeficiency Virus (HIV) and tuberculosis (TB). The researchers concluded that there is need for more infrastructure due to the growing burden of diseases requiring anticoagulation treatment in sub-Saharan Africa (Pastakia, 2010)

2.12 The cost of setting up an anticoagulation clinic

According to the National Patient Safety Agency (NPSA) the costs considered when setting up an anticoagulation clinic include: costs of purchasing a coagulometer system (point of care testing device), Clinical Decision Support System (CDSS) software, training and administration time. Recurrent cost mainly consists staff time, reagents and clinic accommodation cost. Costs of quality control may differ depending on the number of control samples taken to the laboratory and if a National Quality Control Scheme is utilised (NPSA, 2006).

2.13 Cost effectiveness of a specialized anticoagulation clinic versus usual care

Research has consistently shown increased efficiency and effectiveness of an anticoagulation clinic. A study by Sullivan, et al. (2006) on the cost effectiveness of anticoagulation management services for patients with atrial fibrillation showed that effectiveness improved by 0.057 Quality Adjusted Life Years (QALYs) in an anticoagulation management service and reduced costs compared with the usual care. Another study on the cost effectiveness of an anticoagulation clinic versus the usual care showed that the anticoagulation management service appeared to cost much less and provide better effectiveness than the usual care (Thanimalai et al., 2014). A systematic review where 16 randomized and 8 non randomized trials were selected, found that patient self-monitoring of oral anticoagulation treatment was more effective than poor quality normal care provided by family doctors and was as effective as good quality specialized anticoagulation clinics in maintaining the quality of anticoagulation treatment (Connock et al., 2007). However another study suggested that an anticoagulation clinic is not as cost effective and found that there was no major difference when compared to the usual care (Sue et al., 2006)

CHAPTER THREE: METHODS

This study was divided into two sections:

Comparison of the effectiveness of INR control at Kenyatta National Hospital and Moi Teaching and Referral Hospital.

Comparative cost analysis of specialized anticoagulation clinic versus laboratory based practice in Kenyatta National Hospital clinics.

The methods for each of these studies will be discussed separately.

3.1 Study sites

The study was conducted at the hemato-oncology and cardiothoracic clinic of Kenyatta National Hospital and the specialized anticoagulation clinic of Moi Teaching and Referral Hospital. These sites were chosen because most patients on oral anticoagulation therapy attend and are followed up in these clinics. Kenyatta National Hospital was chosen because it is the largest referral hospital in Kenya with an inpatient bed capacity of 1800. The monthly average number of patient visits in the hemato-oncology clinics of Kenyatta National Hospital is 685 (Nyamu, 2016). At KNH, the patients who were on oral anticoagulation clinic attended either the hemato-oncolgy clinic which was run on Monday or cardiothoracic clinic which was run on Tuesday. At every patient visit to the clinic, the nurse performed a basic triage and the patient's information was taken by the records clerk. The patient then proceeded to see the consultant or registrar. After seeing the consultant or registra, the patient was then sent to the hematology laboratory for INR testing and then referred back to the clinic for review by the physician. According to Nyamu 2016, treatment protocols were unavailable to over 75% of precribers at KNH.

Moi Teaching and Referral Hospital was chosen because it had an existing anticoagulation clinic. MTRH is the primary referral hospital in western Kenya and the second largest referral hospital in Kenya. The hospital has an inpatient bed capacity of 550 and outpatient specialty clinics which are; diabetic, cardiology, mental health, obstetrics/gynaecology, surgery and oncology (Manji, 2011). At every clinic visit in MTRH, the patient's INR was checked using the Coaguchek XS® point of care device and the warfarin dose adjusted according to protocols

developed by the American College of Chest Physicians (ACCP) guidelines (Manji et al, 2011).

3.2 COMPARISON OF INTERNATIONAL NORMALISED RATIO VALUES AS A MEASURE OF EFFECTIVENESS

The quality of anticoagulation therapy was assessed by comparing the proportion of patients with International Normalised Ratio values within therapeutic range in the two facilities.

3.2.1 Study design

A comparative retrospective longitudinal study was carried out to compare the quality of anticoagulation therapy. Quality was measured using the proportion of patients within and out of therapeutic INR range. The first study arm was the specialist anticoagulation clinic of MTRH and the second was the lab based practice in KNH clinics.

3.2.2 Study population

The study population was ambulatory patients on oral anticoagulation therapy seen at the hemato-oncology and cardiothoracic clinics of Kenyatta National Hospital.The secondary data obtained by Karuri was collected during January 2014 to April 2016 (Salome, 2016). For the specialist anticoagulant clinic of MTRH data was collected from January 2015 to April 2017. The target population was all patients on anticoagulation therapy in Kenyan tertiary hospitals.

3.2.3 Inclusion and exclusion criteria

Patients were included in the study if they; were above 18 years, required an oral anticoagulant for more than one month, had at least two INR values and were seen between the period of January 2015 to April 2017. Patients who did not meet the inclusion criteria were excluded.

3.2.4 Sample size consideration

The formula in equation 1 was used to compute the sample size, (Charan, 2013)

Equation 1: Formula for sample size estimation for comparative studies

$$n = \frac{2SD^2(z_{\frac{\alpha}{2}} + z\text{ß})^2}{d^2}$$

Where,

$z_{\alpha/2}$ is the standard normal variate for the desired confidence level (1.96 for 95% confidence). d is the effect size which was the difference in the proportion of patients in the therapeutic range in the two sites. SD is the standard deviation of the outcome of interest. zß is the value corresponding to 0.842 from the Z tables at statitistical power of 80% and n is the sample size.

The standard deviation was estimated at 26.7, whis was derived from a study that was conducted at KNH (Karuri, 2016). d was taken as 10 (Charan, 2013).

Using equation 1, the calculated sample size was 120 patients files.

For the KNH site a total of 369 patient files were retrieved (Salome, 2016).

3.2.5 Sampling method

For the data at KNH site, Universal sampling method was used. Patient records were obtained from either KNH Medical records department, or KNH outpatient cardiothoracic and hemato-oncology clinic during the period between January 2014 and April 2016 (Karuri, 2016). Universal sampling was also carried out at MTRH. All patients files from January 2015 to April 2017 were perused to check for eligibility. Those which met the inclusion criteria were included in the study. Data was extracted from the patient files.

3.2.6 Data collection

Data on demographic characteristics, indication for anticoagulation, duration of oral anticoagulant therapy, date of INR test and the corresponding INR was collected with the aid of a predesigned structured data collection form (Appendix A). This form was adopted from Karuri (2016). The form was used for retrospective data collection at MTRH. For the KNH site secondary data analysis was done on data collected by Karuri in 2016. Concomitant drugs prescribed with the oral anticoagulant that may affect INR and any patient comorbidities was also recorded.

3.2.7 Variables

The primary outcome variable was INR reading at different time points. This continuous variable was converted into an ordinal variable with three levels. The first level was when the INR was less than 2 (below therapeutic range), the second when INR was between 2 to 3 (therapeutic range), and the last was INR above 3 (increased risk of bleeding). This cut-off values were guided by findings of a study by Nelson et al. (2015).

3.2.8 Data Management

Data cleaning was done on the KNH dataset to eliminate duplicated observations. Data cleaning was done using STATA version 13 and Excel software. The number of observations reduced from 405 t0 369 after the duplicated entries were removed. The number of files which were examined and met the inclusion criteria from MTRH were 120. The dataset obtained from MTRH was entered into Epi Info 7 software and STATA version 13 was used to analyse the data.

3.2.9 Data analysis

Socio demographic and clinical characteristics were summarized as percentages for categorical data and continuous data into means and standard deviation. The duration on anticoagulation was computed as the difference between the date a patient started anticoagulation and date ended anticoagulation. Patients who were lost to follow up were not included in the study.

Multistate modelling was done using R version 3.3.2 the *msm* package (Christopher, 2016). This package was selected because it allowed computation of transition states and evaluation of the effects of covariates. Parameter estimation was done using BOBYQA estimation and this was implemented using the *minqa* package. The likelihood ratio and Wald tests were used for covariate selection. The time independent covariates were sex, age at the time of the study, indications for anticoagulation therapy, chronic therapy, alcohol consumption and selected co-morbidities such as hypertension, diabetes and HIV infection.The *minqa* package was used to generate survival curves that compared proportions of patients at subtherapeutic, therapeutic and increased bleeding risk.

3.3 COMPARATIVE COST ANALYSIS STUDY FOR OUTPATIENT COST OF MONITORING COAGULATION STATUS IN KENYATTA NATIONAL AND MOI TEACHING AND REFERRAL HOSPITALS

3.3.1 Study design for the cost comparative study

Data on costs was collected using both qualitative and quantitative approaches. Hence this was a mixed method study. A quantitative cross sectional survey was done to obtain the market prices for various resources. Key informant interviews were done to obtain cost for selected variables whose market prices could not be obtained. The data was collected between March to April 2017.

3.3.2 Comparator interventions

The interventions that were compared were: INR monitoring in a specialized pharmacist led anticoagulation clinic that uses point of care devices against a medical consultant clinic that uses laboratory testing for monitoring coagulation status. MTRH has a specialised anticoagulation clinic while KNH has medical consultant led clinic.

3.3.3 Study perspective

Health care provider perspective was considered because the cost of the health care personnel and service provision was critical when setting up an anticoagulation clinic.

3.3.4 Study population

The study population for the key informant interview was healthcare workers working at the laboratory, anticoagulant and outpatient clinics who were in managerial positions or could provide information on costs.

3.3.5 Inclusion and exclusion criteria

The personnel included in the study were those who met the following criteria:

1. Worked at the laboratory or outpatient clinics of KNH and MTRH
2. Had worked at their current station for at least 6 months
3. Provided informed consent to participate in the study

The personnel were excluded in the study if they did not meet the the inclusion criteria

3.3.6 Sample size determination

The principle of sample size calculation for qualitative studies was used to determine the number of health care providers to be interviewed (Mason, 2010). A minimum of 4 participants working in the: Laboratory, outpatient clinics and any other relevant departments of KNH and MTRH were interviewed. This sample size was adequate for a key informant interview. The maximum sample size was determined by the principle of saturation in qualitative studies whereby participant recruitment should be stopped when no extra emerging information can be obtained by interviewing more people (Mason, 2010).

3.3.7 Sampling and Participant Recruitment

Purposeful sampling, which entails a selection of individuals who have a vast knowledge and experience in a specific area, was conducted. Participants in KNH and MTRH who met the inclusion criteria were approached by a visit to the office and a request to be interviewed was made. Before the onset of the interview the details of the study were explained to the participant and they were requested to sign an informed consent form.

3.3.8 Procedure for determining the cost

A micro ingredient costing approach was used. In this approach, examination of all resources and unit prices incurred when setting up and providing the service were considered. Costs and prices were obtained using key informant interviews and market surveys to obtain information on resource consumptions and prices.This study considered capital, personnel and recurrent costs.

3.3.8.1 Capital cost of devices for measuring INR levels

To obtain the capital cost, the current market prices for point of care testing devices and laboratory INR testing machine were sought. This information was obtained by a market survey that entailed getting prices from suppliers of laboratory equipment. A questionnaire appended in appendix B was used to collect information on capital costs. The equivalent monthly cost was then computed for the capital cost obtained. Equation 2 was used to compute the annuitization factor.

Equation 2: Formula for computation of Annuitization factor

The annuitization factor was used to compute equivalent monthly value as presented in

equation 3

$$Annuitization\ factor = (1\ -\ (1\ /\ (1\ +\ r)\ \hat{}\ t))\ /\ r$$

t = life expectancy in months and r = discount factor

The discount factor was 0.00833, this was derived from the rate of returns on government of Kenya bonds which was 10%. The rate of return was divided by 12 in order to obtain the discount factor in months (Bernard, 2018).

Equation 3: Formula for computation of the equivalent monthly cost of a capital asset

$$EMV = \frac{Net\ present\ value\ of\ the\ asset}{Annuitization\ factor}$$

3.3.8.2 Personnel cost

A key informant interview was done to obtain information on the number and type of personnel required to run a specialized anticoagulation clinic. Information was also obtained on the staffing levels of the hematology laboratory and the cardiothoracic and hematoncolgy clinic, of Kenyatta National Hospital. The government approved salaries for pharmaceutical personnel and any other staff were used to compute the personnel cost.

The staffing level at MTRH anticoagulation clinic included one consultant who sees about 40% of the patients who attend the clinic, one pharmacist, four clinical officers, one pharmaceutical technologist, one records clerk and one support staff. The healthcare workers cost of MTRH was obtained by multiplying the total number of healthcare workers in each cadre by their monthly salary as shown in equation 4. Since the consultant was seeing about 40% of the patients, the salary of the consultant was multiplied by 40%. The total healthcare worker cost obtained in running the anticoagulation clinic at MTRH was then computed.

Equation 2: Formula MTRH healthcareworker cost

$$MTRH healthcare\ worker\ cost = Total\ Number\ of\ healthcare\ workers\ in\ each\ cadre * one\ month\ salary$$

Since the clinics and the hematology laboratory were running independently at KNH, the healthcare worker cost at the clinic and the healthcare worker cost at the laboratory were determined separately. The total cost of the healthcare personnel working at the KNH clinics was obtained by the sum of product of total number of healthcare workers in each cadre by

their one month salary. The total cost of health care personnel working at the clinic obtained was then adjusted by multiplying the fraction which represents the proportion of time in a week spent running the clinic as shown in equation 5. This fraction was set at 40% because the clinic opertates for two days in a week. The clinic is run by 4 consultants, 4 registrars, 6 nurses, 2 record clerks and 2 support staff.

Equation 5: Formula of KNH clinic healthcareworkers cost of an INR test

$$KNH\ clinic\ healthcareworker\ cost = Total\ Number\ of clinic\ healthcare\ workers\ in\ each\ cadre * one\ month\ salary * fraction\ of\ number\ of\ days\ worked\ in\ the\ clinic$$

Where

The fraction of number of days worked in the clinic= number of days worked in the clinic in a week divided by total number of working days in a week

Similarly, In the hemtaology laboratory, the lab healthcare worker cost spent on INR testing was computed by the sum of product of healthcare personnel in each cadre working in the laboratory by the one month salary. The computed laboratory healthcare personnel cost was then adjusted by multiplying the fraction which represents the proportion of INR tests done in a month as shown in equation 6. The fraction was obtained by, total INR tests in a month divided by total number of tests done in a month in the lab. The estimated fraction was 0.135. The hematology lab is run by 4 lab technologists(degree holder), 8 lab technologist(diploma holder), 1 lab technician, 1 records clerk and 1 support staff.

Equation 6: Formula lab healthcareworker cost of an INR test

$$KNH\ lab\ healthcare\ worker\ cost\ of\ an\ INR\ test = Total\ Number\ of\ lab\ healthcare\ workers * one\ month\ salary * fraction\ of\ INR\ tests\ in\ a\ month$$

Where

The Fraction of INR test= Total INR tests in a month divided by total number of tests done in a month in the lab.

The total personnel cost at KNH was obtained by summing up the total healthcare personnel cost at the clinic with the total healthcare personnel cost of the laboratory.

3.3.8.9 Recurrent consumable costs

A key informant interview was carried out at Moi Teaching and Referral hospital to collect information on the recurrent consumable costs that are incurred when setting up and running a specialized anticoagulation clinic. To determine the recurrent consumable cost of the practice at Kenyatta National Hospital , a key informant interview was also conducted with the laboratory and clinic staff of Kenyatta National Hospital. The total cost of the recurrent consumables was then computed using equation 7

Equation 7: Formula of obtaining recurrent consumable costs

$$Total\ cost\ of\ consumbles\ in\ a\ month\ = Total\ Number\ of\ consumables\ per\ day * total\ number\ of\ patients\ seen\ per\ day * total\ working\ days\ in\ a\ month$$

The total cost of INR monitoring was computed as a sum of cost of consumables, equivalent monthly cost and personnel cost as presented in equation 8.

Equation 8 :Total cost per patient

$$\text{Total cost of INR} = \text{Total Equivalent monthly cost} + \text{Cost of consumables per patient in a month} + \text{Healthcare personnel cost per month}$$

Patient charges for carrying out the INR test in Kenyatta National Hospital were obtained.

Likewise the charges for carrying out the INR test in the specialized anticoagulation clinic at Moi Teaching and Referral hospital was also obtained.

3.3.9 Procedure for carrying out the key informant interview

The interview was conducted by two research assistants; one research assistant conducted the oral interview and the second researcher recorded all the proceedings. In addition to recording the responses, the second researcher also recorded all non-verbal communication such as facial expressions and voice intonation. An interview guide appended in appendix C was used.

The interview began with an explanation of the purpose of the interview, the intended uses of the information and assurance of confidentiality. The questions were as simple as possible in order to make it easy for the respondents to understand and give appropriate response.

The questions were sequential whereby factual questions were asked first followed by opinions and judgments. The informants were encouraged to give details of the basis of their conclusions and recommendations by giving examples. A neutral attitude was maintained when conducting the interview to minimize bias.

3.3.10 Costs that were not considered in the study

Since the study only focussed on health care perspective, patient related costs such as travel costs, care giver cost and cost of food were not considered in the study. Overhead costs were also ignored because the clinic was assumed to consume a small fraction of management and utility costs of the facilities.

3.3.11 Data management and analysis

For the key informant interview, an interview summary sheet was prepared at the end of each interview reducing the information into manageable issues, themes and recommendations. Each summary had information about the position of the key informant, the reason for inclusion into the list of informants, the main points that were made, implications of these observations, and any ideas or insights the interviewer had during the interview. Within 24hrs after the interview all the notes were transcribed into a Microsoft word document. The costing data was entered into excel spreadsheet. Any written material was archived and will be destroyed 5 years after the interview. The reliability and validity of the data was checked. This was done by checking the representativeness of the key informants their knowledgeability, credibility, impartiality, willingness to respond, and presence of outsiders who may have inhibited their responses.

3.3.12 Sensitivity analysis

One way sensitivity analysis was conducted by substituiting individual variables with the highest or lowest possible values. To obtain the point estimates, the cost ratio and the cost difference of the two facilities was computed by dividing the total cost in KNH by the total cost in MTRH. One way sensitivity analysis was done whereby the extreme variable used to compute the cost were used to calculate the cost ratio. This analysis was restricted to 25 variables. Using the output of one way sensitivity analysis, a tornado diagram was generated to show the variable to which the cost ratio was more sensitive. The tornado diagram was generated using excel software.

3.3.13 Estimated costs of setting up a pharmacist led anticoagulation clinic in KNH

To determine estimates of the financial consequences of adopting a new intervention. The cost of setting up an anticoagulation clinic at KNH was estimated from MTRH model. Capital cost, healthcare personnel cost and recurrent cost were used to determine the cost required to start an anticoagulation clinic.

The anticoagulation clinic at MTRH was run by pharmacists, clinical officers, records clerk and pharmaceutical technician. These information was used to provide the healthcare personnel cost. The capital and recurrent costs at MTRH were used to determine the cost needed to start an anticoagulation clinic at KNH.

3.4 Ethical Considerations

Ethical approval was sought from Kenyatta National Hospital and University of Nairobi Research and Ethics committee and the Ethics Committee of Moi Teaching and Referral Hospital/Moi University and the date of approval from each instituition was obtained on the 11th January 2017 and 29th June 2017 respectively.

Information obtained from patient files was held in confidence and only relevant details were extracted from each file. Health care providers who were willing to participate were provided with the details of the study and they were requested to sign the consent form. Confidentiality of the participants was maintained. The filled data collection forms were filed and locked securely where only the researcher had access. Informed consent was presented in appendix D

3.5 Dissemination plan

After completion of the study, results were communicated to the relevant participants for informed decision making. A paper will be written and published in an open access journal.

CHAPTER FOUR: RESULTS

4.1 Participant recruitment and reasons for exclusion

Secondary dataset from Kenyatta National Hospital was obtained from a study conducted on the quality of oral anticoagulation management among patients on follow up at Kenyatta National Hospital (Salome, 2016). At Moi Teaching Referral Hospital, 205 patient files were retrieved and screened for eligibility. Of these, 120 patient files met the inclusion criteria and were reviewed. About 46% of the patients at KNH had used warfarin for less than 3 months whereas about 95% of the patients at MTRH had used warfarin for less than 2months. Figure 1 gives reasons for exclusion of 85 files from the study at Moi Teaching and Referral Hospital.

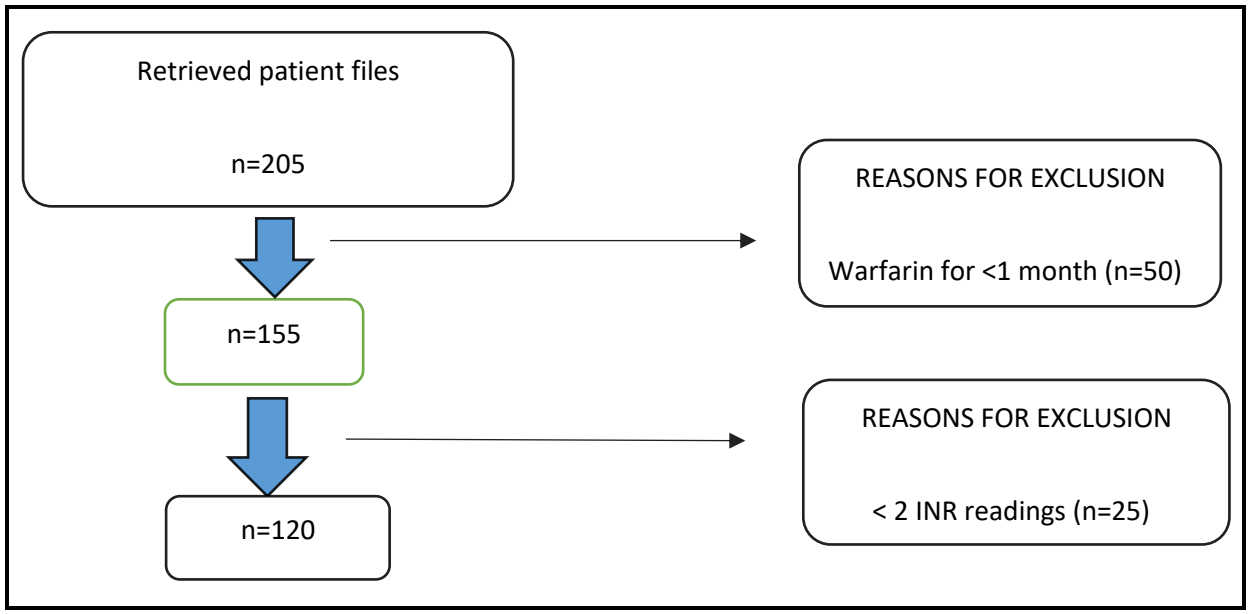

Figure 1: Consort diagram for participants inclusion at MTRH

4.2 Socio Demographic characteristics of study participants

Majority of the patients from both institutions were females; KNH had 289 (74.7%) and MTRH had 95 (79.2%) female participants. There was no statistical significance in the difference in proportions of females in KNH and MTRH (p=0.262). The mean age of patients in KNH and MTRH was 42.6 and 51.8 years respectively. The difference in age was statistically significant with a p value of less than 0.001. This was statistical significant meaning the patients at MTRH tended to be older. Majority of patients from both institutions did not take alcohol; KNH (88.3%) and MTRH (93.1%). There was no statistical significance in the difference in alcohol

consumption amongst participants in KNH and MTRH (0.145). The baseline characteristics of the participants are summarized in Table 4.1.

Table 4.1: Comparison of the social demographic characteristics of study participants on warfarin in KNH and MTRH

	KNH n (%)	MTRH n (%)	Total	P value
Gender				
Male	105 (25.8%)	25 (20.8%)	130	0.262
Female	301 (74.1%)	95 (79.2%)	396	
Age (years)				
19-35	119 (30.7%)	33 (27%)	152	<0.001
36-65	210 (54.2%)	58 (48%)	268	
>65	37 (9.5%)	29 (25%)	66	
Takes alcohol				
Yes	45 (11.6%)	8 (6.5%)	53	0.145
No	342 (88.3%)	108 (93.1%)	450	
Marital status				
Married	220 (56.8%)	-	-	-
Single	104 (26.8%)	-	-	-
Divorced	5 (1.3%)	-	-	-
Separated	16 (4.1%)	-	-	-
Widowed	42 (10.9%)	-	-	-
Employment				
Employed	86 (22.2%)	-	-	-
Self-employed	173 (44.7%)	-	-	-
Unemployed	96 (24.8%)	-	-	-
Student	32 (8.3%)	-	-	-
Education				
Informal	37 (9.6%)	-	-	-
Primary	164 (42.4%)	-	-	-
Secondary	128 (33.1%)	-	-	-
College and Above	58 (15.0%)	-	-	-

Data on marital status, employment, level of education was not available in the patient files of MTRH. Consequently for these variables, no comparison across facilities could be done.

4.3 Clinical characteristics of study participants on warfarin therapy at KNH and MTRH

4.3.1 Indication for anticoagulant use

The most prevalent indication for anticoagulation use at KNH and MTRH was Deep Venous Thrombosis (DVT) with a prevalence of 72.1 and 36.1 respectively. There was a statistical significant difference in the percentage participants who had DVT in KNH and MTRH ($p<0.001$). More patients in KNH had DVT compared to MTRH. There was a statistical significant difference in the percentage participants who had atrial fibrillation in KNH and MTRH ($p<0.001$). More participants in MTRH had atrial fibrillation compared to KNH. There was no statistical significant differences in the prevalence of pulmonary embolism, congestive heart failure and prosthetic valve disease in the two facilities. Indication for anticoagulation use are presented in Table 4.2

Table 4.2: Indication for anticoagulation use in KNH and MTRH

Condition	KNH n(%)	MTRH n(%)	P-value
Deep Venous Thrombosis	279 (72.1%)	44 (36.1%)	<0.001
Pulmonary Embolism	36 (9.3%)	8 (6.6%)	0.347
Valvular heart disease	26 (6.7%)	1 (6.3%)	0.159
Atrial flutter/fibrillation	27 (7%)	36 (29.5%)	<0.001
Prosthetic Valve Disease	30 (7.7%)	12 (9.84%)	0.466
Stroke	3 (0.8%)	2 (12.5%)	0.133
Jugular Vein Thrombosis	1 (0.3%)	1 (6.3%)	0.386
AV Fistula Thrombosis	1 (0.3%)	-	-
MI STEMI	1 (0.3%)	-	-
Recurrent MI Thrombosis	-	1 (6.3%)	-
IVC thrombosis	-	2 (12.5%)	-
Rheumatic Heart Disease	-	16 (13.1%)	-
Protein C deficiency	-	1 (6.3%)	-
Sinus thrombosis	-	2 (12.5%)	-

4.3.2 Prevalence of comorbidities that may have influenced coagulation management

Thirty nine percent of patients had comorbidities that may have influenced anticoagulation control in KNH. The most prevalent comorbidity in KNH was HIV (15%) followed by hypertension (14%). Sixteen percent of patients had comorbidities that may have influenced anticoagulation control in MTRH. The most prevalent comorbidity was HIV (4.1%) followed by cancer (3.3%). These are summarized in Figure 2

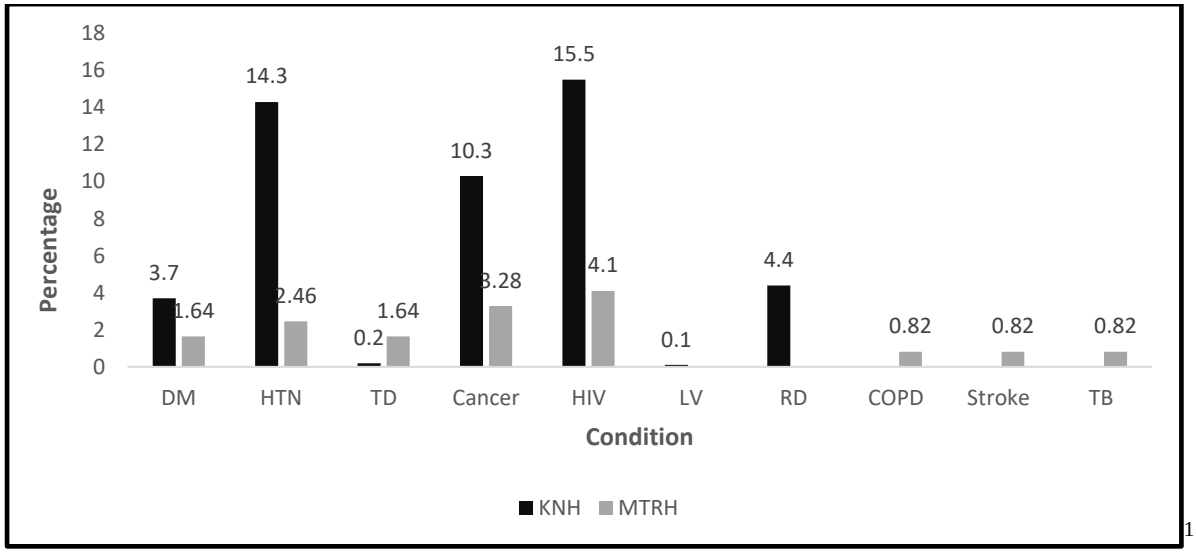

Figure 2: Prevalence of comorbidities that may influence anticoagulation control in KNH and MTRH

More patients in KNH seemed to have comorbidities that could have compromised management of the coagulation status.

4.3.3 Use of drugs that interact with warfarin

The most widely used drugs that may have interacted with warfarin at KNH were antithrombotics such as asprin followed by antibacterials. Whereas at MTRH the most widely used drugs were antihypertensives followed by analgesics and antibiotics. These are summarised in Table 4.3. In KNH the prevalence use of antibacterials, opioids and corticosteroids was far greater than use of these drugs in MTRH.

DM – Diabetes Mellitus, HTN – Hypertension, TD – Thyroid Function, LV – Liver Failure, RD – Renal Dysfunction, TB – Tuberculosis

Table 4.3: Use of co-medication that may interact with warfarin

Group	KNH	MTRH	P-Value
Opioids	110 (28.4%)	1 (0.83%)	<0.001
Antibacterial	154 (39.8%)	2 (1.67%)	<0.001
Paracetamol	2 (0.52%)	2 (1.67%)	Not significant
Corticosteroids	17 (4.4%)	1 (0.83%)	<0.001
NSAIDS	46 (11.8%)	-	-
Antifungal	8 (2.1%)	-	-
Antiviral	48 (12.4%)	-	-
Antiarrhythmic	69 (17.8%)	-	-
Statins	20 (5.2%)	-	-
Anticonvulsants	11 (2.8%)	-	-
Antidepressants	1 (0.26%)	-	-
Anticoagulants	307 (79.3%)	-	-
Antiplatelet	14 (3.6%)	-	-
PPI	103 (26.6%)	-	-
Lactulose	-	1(0.83%)	-
Antihypertensive	-	6 (5%)	-

The data from MTRH was scanty with regards to medication use.

4.3.4 Differences in the prevalence of levels of coagulation in KNH and MTRH

A transition was defined as a change from one therapeutic level to another. The three therapeutic states were; subtherapeutic where INR was less than 2, therapeutic where INR was between 2-3 and increased bleeding risk where INR was greater than 3. The transitions that were considered favourable were; moving from subtherapeutic to therapeutic, remaining within therapeutic range and moving from increased bleeding risk to therapeutic range. Transitions that were not considered favourable were those deteriorating from therapeutic to subtherapeutic and moving from therapeutic to increased bleeding risk. Patients at KNH and MTRH made a total of 2373 and 1095 transitions respectively during the course of therapy. The prevalence of each of the transition is presented in Table 4.4. The most prevalent transition state was remaining at subtherapeutic state for both instituitions.

Table 4.4: Prevalence of transitions between different coagulation states for KNH and MTRH

Transition states	KNH n= 2373	MTRH n= 1095
Favourable transitions		
Improvement from subtherapeutic to therapeutic range	11.5%	14%
Remained in therapeutic range	8.5%	15.2%
Move from increased bleeding risk to therapeutic range	5.6%	7.8%
No change in coagulation status		
Remained at subtherapeutic state	33.1%	22.8%
Remained at increased bleeding risk	9%	6.8%
Worsening transitions		
Deterioration from Therapeutic to subtherapeutic	8.1%	11.6%
From therapeutic to increased bleeding risk	5.4%	8.1%

According to Table 4.4, there was a higher prevalence of favourable transitions at MTRH. However MTRH had a greater prevalence of worsening transition compared to KNH. At KNH there was greater prevalence in no change in coagulation status.

4.3.5 Proportion of patients at different coagulant states at different time

Survival analysis was done to explore how patients coagulation status changed over the course of treatment. The survival curves are subsequently presented in Figures 3 to 5.

4.3.5.1 Proportion of patients in hypercoagulability state

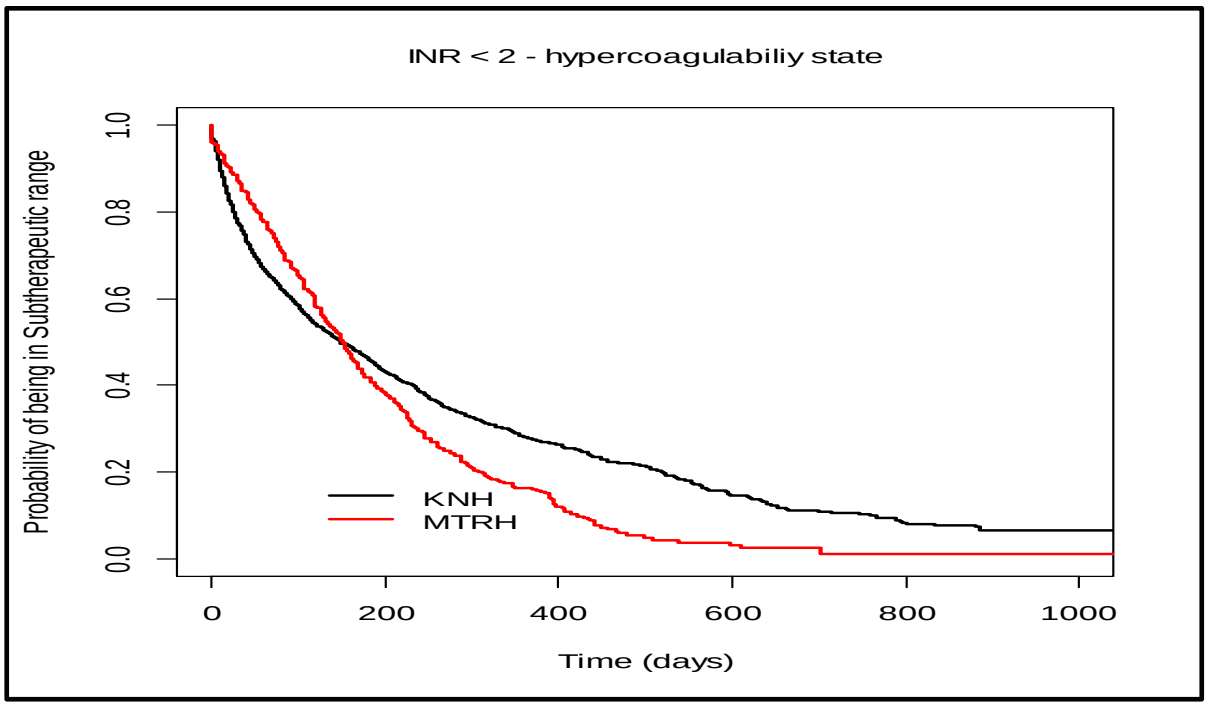

Figure 3: Survival curve depicting the probability of being in hypercoagulability state

At the start, all patients were at hypercoagulability state but with time this declined as shown in Figure 3. Initially the rate of decline of patients in this state was higher for patients in KNH compared to MTRH. But after about 180 days, there was a higher probability of being in hypercoagulability state for patients in KNH compared to those in MTRH. This indicates that coagulation therapy in KNH seemed to be suboptimal compared to MTRH and higher doses of warfarin may be required in KNH.

4.3.5.2 Proportion of patients with a therapeutic INR value

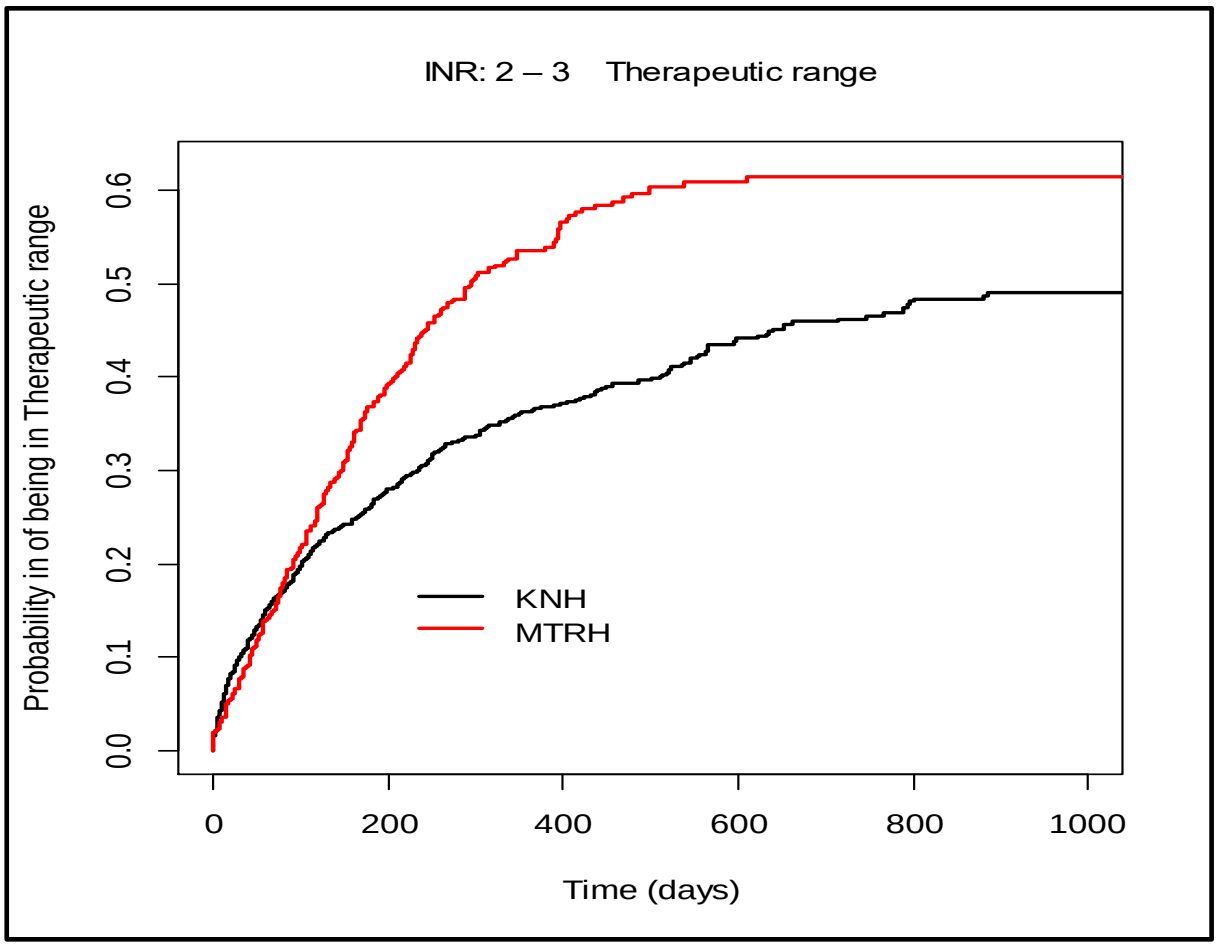

Figure 4: Survival curve depicting the probability of being in therapeutic range

In the first 120 days of therapy, there was no difference in the proportion of patients in therapeutic range between KNH and MTRH. This could be explained by the fact that in the first month the patients were on therapy with heparin or heparinoids. Initially the probability of being in therapeutic range was low for patients in both KNH and MTRH. But with time there was a gradual increase in patients with therapeutic INR as shown in Figure 4. The rate of increase of patients in therapeutic INR was attained at a faster rate in MTRH compared to KNH. The probability of being in therapeutic INR was much higher for patients in MTRH compared to KNH. This means that anticoagulation therapy in MTRH seemed to be more effective compared to KNH.

4.3.5.3: Proportion of patients at increased risk of bleeding

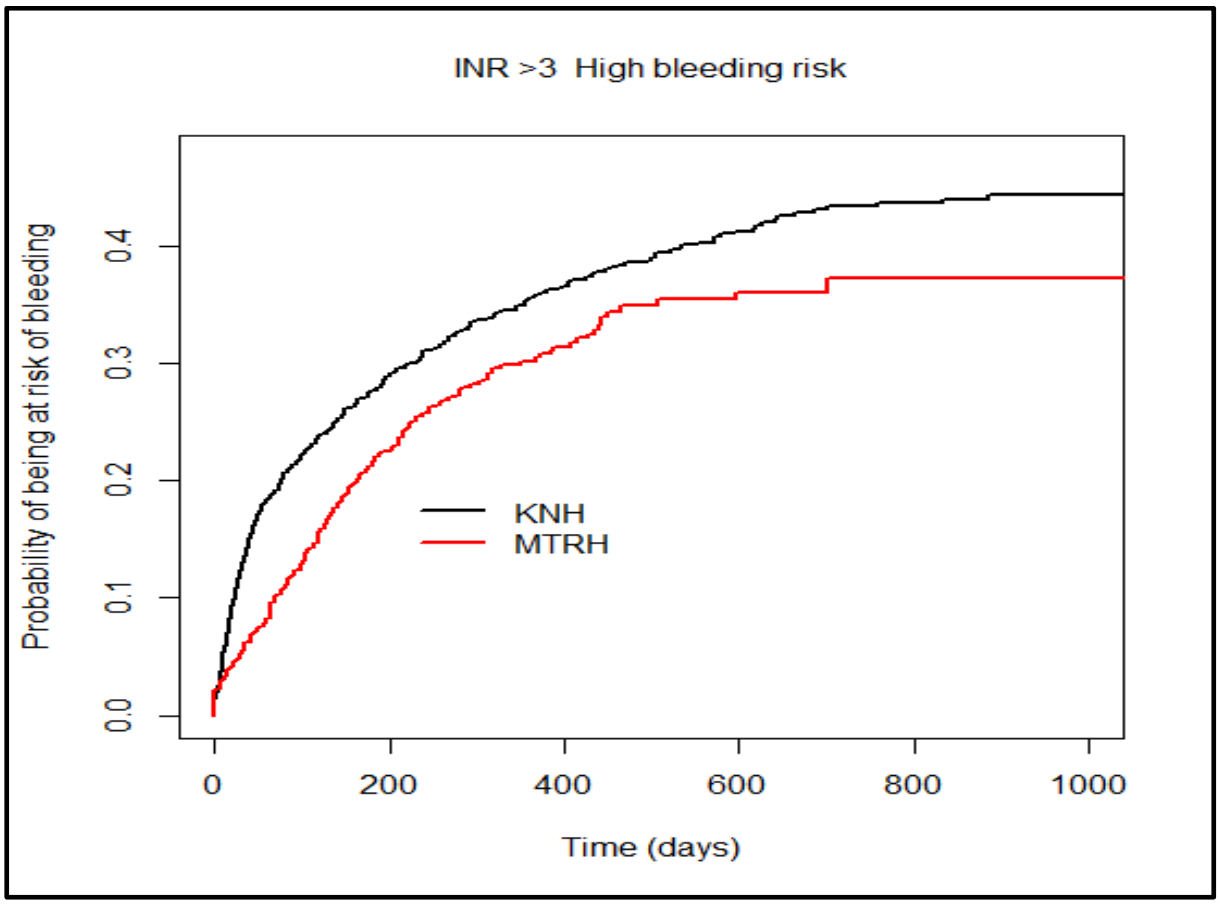

Figure 5: Survival curve depicting the probability of being at a hypocoagulability state

At the start, all patients at KNH and MTRH had a low bleeding risk but with time there was a gradual increase in the risk of bleeding as shown in figure 5. The rate of increase in patients in this state was faster in KNH compared to MTRH. This means that more patients in KNH were at a greater bleeding risk than those at MTRH. At about 500 days the rate of increase in the risk of bleeding reduced and remained at a steady state for both participants in KNH and MTRH.

4.3.6 Regression analysis to identify variables that affected coagulation status

Multistate survival data analysis using R MSM package was used to carry out the regression analysis to identify variables that affected the rate of transition between different states. Only bivariable analysis was done. The following conditions had an effect on the rate of transition between different states; the facility, diabetes, HIV Infection, thyroid dysfunction, and carbamazepine. Variables like age and gender did not have an effect on the risk of improving from a subtherapeutic INR to the targeted therapeutic level.

Table 4.5 and 4.6 presents the hazard ratio for the association between the variables that had an effect on the coagulation state.

Table 4.5: Hazard ratios that had a favourable effect on the coagulation status

Variables	Improvement from subtherapeutic to therapeutic	Improvement fom increased bleeding risk to therapeutic
KNH vs MTRH	Not significant	Not significant
Diabetes	3324.3 (1492, 7410)	Not significant
HIV infection	Not significant	0.404 (0.168, 0.966)
Thyroid dysfunction	0.462 (0.252,0.845)	Not significant
Carbamazepine	0.084 (0.0242,0.291)	Not significant

Table 4.5 represents the Hazard ratio with the transitions that were considered favourable. The first was an improvement from subtherapeutic state to desired therapeutic range. There was no statistical significant difference in improvement of hypercoagulability state to desired therapeutic range for patients in KNH and MTRH. Therefore there was no difference between the institutions. Patients with thyroid dysfunction 0.462 (0.252,0.845) and those who were on carbamazepine 0.084 (0.0242,0.291) were less likely to show improvements from hypercoagulability state to the desired therapeutic INR. HIV patients 0.404 (0.168, 0.966) were least likely to move from increased risk of bleeding to therapeutic state.

There was no statistical significant difference in the risk of deterioration from therapeutic INR to subtherapeutic level in patients in KNH and MTRH, hazard ratio (0.556, 0.2716, 1.141). No other variable was found to be a significant predictor of deterioration to hypercoagulative state. Although the risk of developing a high INR that was associated with increased bleeding risk was not significantly different when the two facilities were compared, the magnitude of the hazard ratio was very large indicating that the risks of developing increased bleeding in KNH was almost 3000 fold that of MTRH. This finding was supported by the survival curves that showed that the probability of being in a hypercoagulability state was much higher for patients in KNH as illustrated in figure 5. There was no significant predictors of being in hypercoagulability state.

4.3.7 Interval of INR readings

A minimum of 10 INR readings per patient was obtained for both sites. The intervals between the INR readings per patient was obtained and presented in table 4.6

Table 4.6: Interval of INR readings

Interval	KNH			MTRH			Total			P value
between INR readings	Total no. of patients	Median	IQ range	Total no. of patients	median	IQ range	Total no. of patients	median	IQ range	
1st and 2nd	387	6	[3,14]	122	14	[7,28]	509	7	[4,20]	0.00001
2nd and 3rd	382	8	[4,25]	122	14	[7,27]	504	9.5	[4,25.5]	0.001
3rd and 4th	313	13	[4,35]	122	21	[10,28]	435	14	[6,34]	0.0386
4th and 5th	247	16	[6,41]	122	21	[14,29]	369	20	[7,36]	0.2582
5th and 6th	197	19	[6,42]	122	21	[13,29]	319	21	[7,37]	0.4007
6th and 7th	161	21	[7,44]	122	25.5	[13,35]	283	21	[8,41]	0.8775
7th and 8th	136	28.5	[10.5,56]	122	27.5	[14,35]	258	28	[13,42]	0.2223
8th and 9th	105	28	[9,57]	122	23.5	[14,35]	227	25	[14,42]	0.2387
9th and 10th	86	35	[14,63]	122	21	[11,29]	208	24.5	[12.5,39.5]	0.0027
10th and 11th	65	32	[12,59]	-	-	-	-	-	-	-
11th and 12th	56	35	[14,62.5]	-	-	-	-	-	-	-
12th and 13th	45	32	[15,53]	-	-	-	-	-	-	-
13th and 14th	34	35	[14,63]	-	-	-	-	-	-	-
14th and 15th	25	32	[14,61]	-	-	-	-	-	-	-
15th and 16th	1	10	[10,10]	-	-	-	-	-	-	-
16th and 17th	1	7	[7,7]	-	-	-	-	-	-	-

At MTRH, the initial stage of INR testing for follow up was once every 14 days. With time the gap of follow up increased to 21 days hence INR testing was being done once in every three weeks. The gap for follow up further increased to once in 28 days. At KNH, the initial stage for INR testing for follow up was once a week. Thereafter the follow up of patients increased to once every two weeks. It further increased to once every three weeks and then one month apart. The Interval between visits started to increase thereafter. Follow up at MTRH was further apart and relatively constant compared to KNH. These findings were consistent with the survival curve shown in figure 3 where the rate of decline in patients at hypercoagulability state was faster for patients in KNH compared to MTRH. This could be due to the intense initial

follow up of patients at KNH. But with time the rate of decline was faster in MTRH maybe because there was consistent follow up of patients at MTRH.

4.4 Results for estimated costs of INR monitoring

4.4.1 Recurrent cost of INR monitoring at KNH

The equipment used in the haematology lab for INR measurement at Kenyatta National Hospital is ACL Elite Pro™. The machine was able to measure other biochemical parametres such as APTT, full haemogram and bone marrow cytology. Daily maintenance of the machine is done at no cost. The machine is serviced twice a year by the biomedical department. The machine came with a service contract at the time of procurement. The cleaning cycle is already installed in the machine therefore there is no extra cost for cleaning. The machine uses electricity and when there is a blackout a water bath is used as a backup which is not reliable. The patient charges at the clinic are divided into cost of consultation and INR test. The patient is charged Ksh 600 for INR test and Ksh 600 for consultation. Therefore the total patient charges is ksh1200. Table 4.6 presents the consumables and their costs used to perform the INR test at KNH.

Table 4.7: Recurrent cost of consumables used at KNH for INR testing

Consumables	Amount of material used per day	Total cost of each item per day	Total cost per month	% Contribution to the total recurrent cost
PT Fibrinogen per vial	0.75	2620	20960	21.5
Rotor per piece	10	5025	40200	41.2
Sample cups per cup	60	480	3840	3.9
Vacutainer per piece	60	540	4320	4.4
Normal control per vial	1	2192.4	17536	17.9
Yellow/blue tips	60	28.8	230.4	0.2
PT test tube	60	840	6720	6.9
Needle with syringe	60	480	3840	3.9
Total recurrent cost per month			97670.4	100

From Table 4.7 the largest contributer to the recurrent cost was the rotor which accounted for slightly above 40% of the recurrent cost. The other two major contributers of the recurrent cost was PT fibrinogen and the normal controls which collectively accounted for about 40% of the recurrent cost of INR monitoring at KNH. The recurrent expenditure could be reduced by sourcing this items at a lower price. From table 4.7, the total consumable cost of INR monitoring at KNH per month is about Ksh 97670.4.

4.4.2 Recurrent cost of INR monitoring at MTRH

The equipment used in the anticoagulation clinic of MTRH are point of care INR testing devices. The two brands of the machine used at the clinic are Abbot I Start™ machine and Coaguchek™. The machines can both generate INR and prothrombin time test results. There are no maintenance costs of the machines though data bundles are required to update the software. The machine uses a rechargeable battery therefore there are no costs of replacing the battery. The patient charges in the clinic covers both consultation and INR testing. The patient charge is 300 ksh. The pharmacist in charge mentioned that this cost was highly subsidized. Table 4.8 presents the consumables used for running the equipment. The Abbot I Start™ machine uses cartridges while the Coaguchek™ uses strips. The cartridges are more expensive compared to the test strips. Since both machines were used at the clinic concurrently, the total cost per month of each consumable was adjusted on the basis that there was a 50% chance of using either machine. Hence the fraction of using any device at any time was 0.5. It was multiplied by the total cost of each consumable to obtain the adjusted cost per month for each consumable.The total adjusted recurrent cost for INR monitoring per month at MTRH was 329000. The recurrent costs could be reduced substantially if cheaper brands that use strips instead of cartridges were used.

Table 4.8: Recurrent cost of consumables used with the point of care testing device per day at MTRH

Consumables	Unit consumed per patient	Cost per unit	Cost of lancet per patient	Total cost of consumables per person per day (Ksh)	Total cost per month	Adjusted total cost per month
Strips	1	430	5	435	304500	152250
Cartridges	1	500	5	505	353500	176750

Total cost of consumable						329000

4.4.3 Personnel cost for INR monitoring for MTRH and KNH

Though personnel cost are often classified under recurrent expenditure, in this study they were assessed separately because they often account over 60% of healthcare expenditure in healthcare systems. Secondly by task shifting from medical doctors to lesser qualified technologies there is a large potential for cost containment.

To compute the personnel cost per month, the number of personnel working in the MTRH and KNH was obtained as well as their monthly salaries. The salary of the consultants at MTRH was adjusted using the fraction 0.4. The fraction was obtained by estimating the proportion of patients seen by the consultants in every clinic visit. The fraction was computed by dividing the number of patients seen by the consultants per day over the total number of patients visiting the clinic per day. The fraction obtained was 0.4. The salaries of the rest of the healthworkers were not adjusted bescause they work at the clinic full time. Hence the total healthcare personnel cost at MTRH was the sum of adjusted consultant cost and the total healthcare personnel cost working at the clinic.

The total clinic health care workers cost in the KNH hematoncolgy and cardiothoracic clinic was computed by multiplying the product of total number of healthworkers in each cadre and the their salaries with the fraction of time in month the healthworkers spent in the clinic. This fraction was obtained by total number of clinic days in a week divided by the total number of working days in a week. As mentioned in the methodology the clinics were run only on Monday and Tuesday therefore the health workers worked a total number of 2 days in a week. The number of working days in a week is 5 hence the fraction 2 divided by 5 to obtain 0.4.

The total lab healthcare workers costs in the KNH hematology lab was computed by multiplying the product of total number of healthworkers in each cadre and their salaries with the fraction obtained by total INR test done in a month divided by the total number of tests carried out in the hematology lab. The fraction obtained was 0.135. The sum of the total clinic health care workers cost and the total lab healthcare workers costs was then computed to obtain the total healthcare personnel cost of KNH.

The estimated personnel cost per month for MTRH and KNH was Ksh 1224844 and Ksh 781580 respectively as presented in Table 4.9.

Table 4.9: Healthcare personnel cost at MTRH and KNH

Health Care Workers	Number of personnel in each cadre	Unit Salary per month (Ksh)	Adjusted salary	Total salary per month (Ksh)
	Moi Teaching and Referral Hospital			
Pharmacist	1	228000	-	228000
Consultants*	1	300000	120000	120000
Clinical officer	4	71200	-	284800
Pharmaceutical Technician	1	69200	-	69200
Records clerk	1	69200	-	69200
Support staff	1	10380	-	10380
Total Cost per month				**781580**
	Kenyatta National Hospital			
Consultants in clinic	4	300000	120000	480000[a]
Registars in clinic	4	228000	91200	364800
Nurses in clinic	6	71200	28480	170880
Records clerk in clinic	2	69200	27680	55360
Support staff in clinic	2	10380	4152	8304
Lab Technologist(degree) in lab	4	94000	12690	50760
Lab Technologist(diploma) in lab	8	70200	9477	75816
Lab Technician(certificate) in lab	1	60600	8181	8181
Records clerk in lab	1	69200	9342	9342
Support staff in lab	1	10,380	1401	1401

Total monthly cost per month	29			1224844

4.4.4 Capital expenditure of INR testing

4.4.4.1 Capital costs for KNH

The laboratory in charge who was interviewed did not know the cost of the ACL Elite Pro™. According to a market survey the ACL Elite Pro™ costs Ksh 1 million. The lab receives around 60 blood samples a day from the clinic. Hence the estimated number of patients visiting the clinic who require INR testing are about 60. It takes about one hour to deliver the blood samples from the clinic. The machine takes about 1 hour to process the samples and give a print out of INR results. It takes another 30 minutes to 1 hour for the results to reach the patient. It therefore takes an average of 2.5 to 3 hours for the patient to obtain INR test results. After obtaining the results the patient goes back to the clinic for consultation which takes another 5-10 minutes.

4.4.4.2 Capital costs for MTRH

The clinic has a total of 4 Abbot I start machine™ and 2 Coaguchek™ machines. All the machines were donated to the anticoagulation clinic therefore the clinic did not procure any of the machines. According to the interview with the pharmacist in charge of the clinic, the cost of 1 Abbot I Start machine™ at the time of donation was Ksh 1 million and for the Coaguchek,™ Ksh 250000. A market search showed that the Abbot I Start machine™ costs Ksh 975000 and the Coaguchek™ Ksh 130000. An average of 35 patients visit the clinic every day. INR testing and consultation is done at the clinic. INR test results are determined within 2-3 minutes and consultation takes another 5 minutes. Therefore the patient spends an average of 10 minutes in the clinic.

The equivalent monthly cost of the machine used in KNH and MTRH was calculated. For computing the equivalent monthly cost, the life span of laboratory based equipment was assumed to be 60 months while the lifespan of the point of care devices was assumed to be 36 months. These values were obtained from the manufactures. Since the machines at MTRH were used concurrently, the total capital cost of MTRH was adjusted by the fraction 0.5. The adjustment was on the basis that there was a 50% chance of using either machine at any given time. The capital costs of MTRH and KNH were presented in table 4.10.

Table 4.10: Capital costs for KNH and MTRH

Facility	Equipment	Capital cost per unit	Number of units	Total cost Ksh	Equivalent monthly cost Ksh
KNH	ACL Elite Pro™	1,000,000	1	1,000,000	21247.03
MTRH	Abbot I Stat™	975,000	4	3,900,000	67115.71
	Coaguchek™	130,000	2	260,000	

4.4.5 Comparison of the total cost of INR monitoring at MTRH and KNH

In KNH the key cost driver was the personnel cost which accounted for 90% of the total INR cost. In MTRH the key cost driver was also the personnel cost which accounted for 66% of the total INR cost. The cost ratio which was determined as total cost of KNH divided by total cost of MTRH was 1.141009. The cost difference of both facilities was 166066. The total cost is different across both facilities with MTRH being slightly lower than KNH as shown in table 4.11

Table 4.11: Comparison of Total Cost of INR monitoring at MTRH and KNH

	MTRH		**KNH**	
	Cost per month (Ksh)	**% of total cost**	**Cost per month (Ksh)**	**% of total cost**
Recurrent cost of consumables	329000	27.9	97670.4	7.2
Personnel costs	781580	66.4	1224844	91.1
Capital costs	67115.71	5.7	21247.03	1.7
Total	1177696	100	1343762	100

4.4.6 Cost sensitivity analysis

One way sensitivity analysis was conducted by substituiting individual variables with the highest or lowest possible values to determine the most sensitive variables. The results of the sensitivity analysis are presented in table 4.12. The most sensitive variables were extracted to produce a tornado diagram as presented in figure 6.

Table 4.12: Table showing the most sensitive variables

Variables	Low	High
fraction of Healthworkers at KNH	0.2245213	2.515741
number of consultants knh	0.7334337	1.752373
fraction of lab healthworkers	1.017463	1.932623
registras number knh	0.8312518	1.605645
pharmacist number mtrh	1.414939	0.6430418
clinical officer number mtrh	1.504948	0.8372891
number of consultants mtrh	1.270462	0.8106203
Numberofdayspermonthmtrh	1.370772	1.001167

nurse number knh	0.9959124	1.358655
Numberofdayspermonth	1.099543	1.369076
salary of consultant knh	1.086666	1.276868
Cartidgecostpermonthmtrh	1.213114	1.047608
Numberofpatientsperdayknh	1.071898	1.223943
number of lab technologist diploma knh	1.076633	1.205386

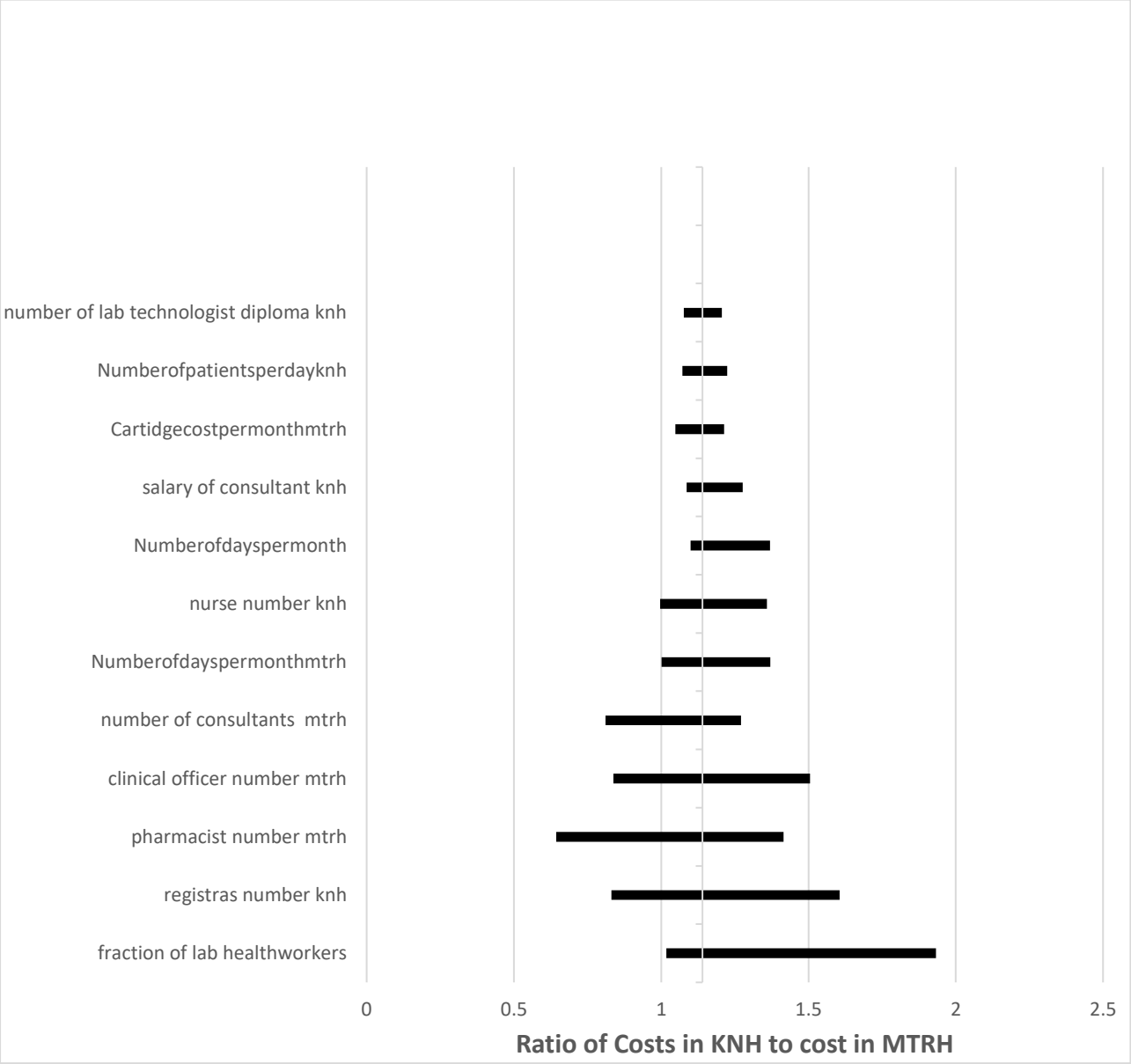

Figure 6: Tornado diagram showing the most sensitive variables

From the tornado diagram the variable to which the cost ratio was more sensitive to was the fraction of time the healthcare worker spent in the hemtaoncology and cardiothoracic clinic per week. To determine the point estimate, it was assumed that the fraction was 0.4 which was

obtained by dividing the number of clinic days divided by the total working days in a week. From the analysis, as this fraction increased, the cost ratio reduced. This fraction affected all cadres of healthcare workers working in the clinic. The second variable to which the cost ratio was sensitive to was the number of consultants providing services in KNH. Similarly the cost ratio was very sensitive to the number of registrars serving at the clinic in KNH. As the number of consultants and registrars increased the cost ratio became smaller in favour of MTRH. This finding implies that to reduce the cost of INR monitoring , the optimal number of consultants and registrars needs to be determined. This cost can be minimised by labor substituition as the practice in MTRH where services are primarily provided by pharmacists, clinical officers and pharmaceutical technologist. With regards to MTRH, the one way sensitivity analysis showed that the number of consultants and clinical officers serving at the clinic of MTRH also affected the cost ratio. Similar to the scenario of the number of operating days per month in the KNH clinic the cost ratio was significantly affected by the number of operating days at the anticoagulation clinic. Apart from healthcare workers cost, the cost of the cartridge and number of days patients are seen daily also affected the cost ratio. However their effects were not profound.

4.4.7 Sunk costs for setting up an anticoagulation clinic

The cost of setting up an anticoagulation clinic at KNH was estimated using the MTRH model. The cost of procuring the point of care INR testing device (POCT) was considered as the capital cost and was estimated at Ksh 2,000,000. This was arrived by determining the value of 12 coagucheck™ POCT devices that will be needed at KNH. The anticoagulation clinic at MTRH was run by pharmacists, clinical officers, pharmaceutical technician and records clerk. These information was used to estimate the healthcare personnel cost which was estimated at Ksh 3271180 per month. The costs required to run the anticoagulation clinic was considered as the recurrent costs which was estimated at Ksh 527,000 per month. The estimated sunk costs are presented in Table 4.13.

Table 4.13: Estimated sunk costs for establishment of an anticoagulation clinc at KNH

Item	Unit Cost (ksh)	Total cost per month (ksh)
Capital costs		
Coaguchek/ software (12)	165,000	**2,000,000**
Recurrent / healthcare personnel cost		
Pharmacists (10)	228000	2280000
Clinical officers (6)	71200	427200
Pharmaceutical technician (6)	69200	415200
Records clerk (2)	69200	138400
Support staff (1)	10,380	10,380
Total healthcare personnel cost		**3271180**
Recurrent consumable costs		
Test strips	430	516,000
Lancets	5	6,000
Stationery	-	5,000
Total consumable costs		**527,000**

The total estimated cost to establish an anticoagulation clinic in KNH was Ksh 5,798,180.

CHAPTER 5: DISCUSSION

5.1 Discussion

The mean age of patients in KNH was 42.6 years. A study done by Ndwiga 2009 at KNH found the mean age of patients at the medical outpatient clinic to be 48 years (Ndwiga 2009). The mean age of MTRH was 51.8 years meaning that MTRH had older patients compared to KNH. This may be possible because MTRH is located in a rural area where there is a high population of the elderly compared to urban area. MTRH having older patients could have affected the coagulation levels by having patient adherence problems. Also at KNH, the younger patients were more likely to have rheumatic heart disease.

Majority of the patients from both KNH and MTRH were females, KNH had 289 (74.7%) and MTRH 95 (79.1%). This can be supported by similar studies carried out at KNH and MTRH where the females were found to be a majority (Kibiru, 2011, Manji, 2011, Sonak et al, 2010). Several other studies also show that majority of patients attending the anticoagulation clinic are female (Anakwue, 2014, Teklay, 2014). However studies in the UK, USA have shown that majority of patients are male (Apostolakis, 2013, MacEdo, 2015). In Kenya, the greater propensity of females attending such clinic could be due to the increased use of contraceptives and pregnancy related DVT.

The most prevalent indication for anticoagulation use at KNH and MTRH was Deep Venous Thrombosis with a prevalence of 72.1% and 36.1% respectively. This is supported by similar studies that have been carried out in KNH and MTRH (Manji, 2011, Kizito, 2015). Studies in USA, Portugal and China show that the most prevalent indication is atrial fibrillation (MacEdo, 2015, Chan, 2006, Caldeira, 2014). This difference is expected because the disease burden varies in different populations and regions. The prevalence of DVT was much lower in MTRH because it s may be serving a rural-urban population that is more active and less likely to have DVT.

Some comorbidities may complicate anticoagulation control. Moreover patients with this comorbidities may also be taking drugs which may be interacting with the antcoagulants. It may therefore be difficult to maintain the INR of these patients within therapeutic range. About 39 and 16 percent of patients had comorbidities that may have influenced anticoagulation control in KNH and MTRH respectively. The difference in the coagulation status across the

two facilities could have been contributed by KNH having patients with more co-morbidities compared to MTRH. HIV was the most prevalent comorbidity in KNH (15%) and MTRH (4.1%). This is possible because Kenya has an average HIV prevalence rate of 6% and with about 1.6 million people living with HIV infection, it is one of the six HIV 'high burden' countries in Africa. In Ethiopia the most prevalent comorbidity in patients on warfarin was also HIV followed by TB (Teklay, 2014). High income countries such as the USA show that hypertension followed by diabetes are the most prevalent comorbiditiesin patients on warfarin.

Patient for both facilities were taking warfarin for prophylaxis. Warfarin can interact with more than 100 different medications from various classes thus affecting INR control (Allison, 2016). According to Allison 2016 the top 5 drugs that mainly interact with warfarin are; selective serotonin reuptake inhibitors, antiplatelets such as asprin, antibiotics, non steroidal antinflamatory drugs and herbals (Allison, 2016). The most widely used drugs that may have interacted with warfarin at KNH were antithrombotics such as asprin followed by antibiotics. Whereas at MTRH the most widely used drugs were antihypertensives followed by analgesics and antibiotics. In Ethiopia and Canada there is extensive use of drugs that interact with warfarin (Teklay, 2014, Verhovsek, 2008). Antibiotics are the most widely used in Ethiopia while analgesics are the most widely used in Canada. Carbamazepine was also found to have an effect on the coagulation state of patients. Carbamazepine induces metabolism of warfarin. From literature carbamazepine is known to induce metabolism of warfarin hence will decrease the level or effect of warfarin. Therefore carbamazepine reduced the probability of achieving coagulation control.

Patients in the facilities transitioned from sub therapeutic, therapeutic or supratherapeutic INR range. Patients at KNH and MTRH made a total of 2373 and 1095 transitions respectively. According to the findings, there was a higher probability of patients being at hypercoagulability state in KNH compared to those in MTRH. Therapeutic INR was attained at a faster rate in MTRH compared to KNH and more patients in KNH were at a greater bleeding risk than those at MTRH. This findings can be supported by studies that compare anticoagulation clinics to the standard laboratory when monitoring INR. A study carried out by Stephanie et al showed that the pharmacist-managed anticoagulation clinic achieved significantly better INR control compared to usual care by the physicians and that patients spent more time in therapeutic range at the clinic compared to usual care (Stephanie et al, 2011). Studies carried out in USA and Spain support this finding as well (Lafata, 2000, Sola-Morales,

2003). However a systematic review where eight RCTs were included in the study showed that the advantages of a pharmacist-managed anticoagulation clinic were unclear. A Meta-analysis showed that there was a significant difference between pharmacist-managed care and usual care but the pharmacist-managed group demonstrated no significant improvement on the percentage of time within the expanded therapeutic range (Zhou, 2016).

The following conditions had an effect on the rate of transition between different states; diabetes, HIV Infection and thyroid dysfunction. Patients with diabetes had an increased tendancy to move from hypercoagulability state to desired therapeutic range. There was no statistical significant difference in improvement of hypercoagulability state to desired therapeutic range for patients in KNH and MTRH (HR 0.978 (0.503, 1.889)). Patients with diabetes had a high HR of 3324.3 (1492, 7410) with a wide confidence interval. The confidence interval was wide probably due to small sample size. The high HR could be due to the drug interaction of antidiabetic medication and warfarin. According to literature, antidiabetic medication especially sulphonyl ureas tend to be highly plasma protein bound and therefore could have displaced warfarin from binding sites hence improving the efficiency of warfarin. Studies have also shown that diabetes may cause coagulation abnormalities, resulting to thrombophilia. These observations have been supported by epidemiological studies which show that these coagulation abnormalities observed in diabetic patients seem to be caused by hyperglycaemia, which is a distinguishing feature of the disease. (Ceriello, 1993, Michiel et al, 2006). Patients with thyroid dysfunction also showed no improvement from hypercogulability state to the desired therapeutic state. A systematic review indicated that the pathophysiological mechanism that affected coagulation was due to an excess or deficit of the thyroid hormone. Patients who had hypothyroidism and hyperthyroidism appeared to have an increased risk of bleeding and of thrombosis, respectively (Squizzato et al, 2007).

HIV patients were least likely to move from increased risk of bleeding to therapeutic state this could be due to the use of protease inhibitor (PI) drugs in treatment regimens for HIV infected patients. In a study done in MTRH, HIV infection increased the risk of DVT (Manji, 2011)

The capital costs of the equipments used at MTRH were more expensive compared to KNH. This is because a minimum of 6 point of care testing devices were required to run the anticoagulation clinic for efficiency to be realised. At KNH only one machine (ACL Elite Pro™) was used to analyse the blood samples. The capital cost per month at MTRH (Ksh 67115.71) was higher compared to KNH (ksh 21247). Recurrent cost are regular or ongoing

cost incurred repeatedly following a capital expenditure. Cost of consumables and healthcare provider salaries were considered as the recurrent costs. The cost per month of the consumables at MTRH(Ksh 329,000) was higher compared to KNH (Ksh 97670.4). The healthcare provider cost per month at KNH (Ksh 1224844) was higher compared to MTRH (Ksh 97670.4). The healthcare provider cost at KNH was higher because the number of staff at KNH were more compared to MTRH. Consultants and registrars were managing patients at the clinics of KNH. The total cost per month at MTRH (Ksh1177696) was lower than for KNH (Ksh 1343762). Considering that the clinics at KNH were being run 2 days in a week as opposed to the specialised anticoagulation clinic which was being run for 5 days in a week, the total cost at KNH was still higher compared to the total cost at MTRH. This indicates that the anticoagulation clinic is less costly than the laboratory based practise. A study done in China showed that pharmacist managed anticoagulation clinic was less costly compared to physician-managed service in achieving target anticoagulation control (Chan, 2006). Another study carried out in the USA found that anticoagulation clinic saved upto $162058 per 100 patients annually (Chiquette, 1998). Other studies also confirm that there is significant cost savings in anticoagulation clinics and in patient self monitoring. (Aziz et al., 2011, Ontario, 2009 lafata et al., 2000).

Estimates of the financial consequences of adopting the anticoagulation clinic was determined. The costs included were; capital costs, healthcare personnel costs and recurent costs. A paper written by National Patient Safety Agency (NPSA) which is a special health authority of the National Health Service in England indicates what is required when settting up an anticoagulation clinic.According to the NPSA, the following costs should be considered when setting up an anticoagulation clinic; the costs of purchasing a coagulometer system (along with an initial supply of reagents/test cards/control reagents.), CDSS software costs, training costs and administration time. It describes the recurrent costs as the cost of staff time, reagent costs and the cost of the clinic accommodation. The total estimated cost per 100 patients is approximately £10.50 (NPSA, 2001). This cost is comparable to the total cost per patient obtained for the anticoagulation clinic of MTRH**.**

5.2 Study Limitation

A full cost effectiveness study was not carried out because of time limitation therefore long term conditions associated with improper anticoagulation monitoring such as thrombosis and major bleeding disorder were not determined.

This study involved use of some estimated costs that may not have portrayed the actual cost implication.

Data on medication use from Mtrh was scanty hence the results on drug interactions with warfarin could have underestimated the drug drug interaction. Hence there could be an element of bias.

There could have been systematic differences in the machine readings of the results of the machines used in KNH and MTRH which was not accounted for.

Dietary factors could have been a potential confounder. Differences in the diet across the two populations could have contributed to the differences in INR.

CHAPTER 6: CONCLUSION AND RECOMMENDATION

6.1 Conclusion

Anticoagulation clinic is more cost effective compared to the standard laboratory practice when monitoring oral anticoagulation therapy. Anticoagulation control of patients at KNH was suboptimal compared to MTRH. The calculated cost per patients at MTRH was lower than KNH.

Based on the findings anticoagulation clinics have advantages compared to usual care. Anticoagulation clinics improve anticoagulation control and therefore should be highly considered by instituitions with high patient turnover such as KNH.

6.2 Recommendation

Based on the findings it is clear that Kenyatta National Hospital should consider implementing an anticoagulation clinic in order to improve monitoring of anticoagulation therapy.

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APPENDICES

APPENDIX A: Data Collection Form

CODE……..

1. DATE……..
2. ELIGIBILITY CHECKLIST

	YES	NO
• Age 18>	☐	☐
• On an oral anticoagulant for more than one month	☐	☐
• At least Two INR readings	☐	☐

3. PATIENT DEMOGRAPHY

- Age: ……
- Sex: …….
- Weight: ……..
- BMI …….

Tick appropriately

4. What is the highest level of education attained?

- Informal ☐
- Primary ☐
- Secondary ☐
- Tertiary ☐

6. Employment status

- Employed ☐
- Self-employed ☐

- Unemployed ☐
- Student ☐

7. Alcohol consumption; Yes ☐ No ☐

8. Patient's medical history:

…….....

……

……

9. Diagnosis

- Deep Venous Thrombosis ☐
- Atrial fibrillation/flutter ☐
- Rheumatic Heart Disease (RHD) ☐
- Mechanical heart valves venous thrombosis ☐
- Post-surgical procedures ☐
- Pulmonary embolism ☐
- Congestive Heart Failure ☐
- Stroke ☐
- Pregnant patient ☐
- Others …….

10. Type of Anticoagulant

DRUG NAME	DOSE	FREQUENCY	DURATION	DATE STARTED ON ANTICOAGULATION

11. Drug-drug interactions: which drug the patient is taking together with the oral anticoagulant. (Check with Medscape interaction check)

Drug name	Dose	Duration	Nature of interaction

12. Any patient comorbidities that may influence INR

Disease	Yes/ No	Duration of illness
Diabetes mellitus		
Hypertension		
Thyroid function		
Liver failure		
Renal dysfunction		
Cancer		
HIV		
OTHER/SPECIFY		

13. Indicate the date the INR test was done and the value between the period January 2015 to the time of study in order to determine the duration of time spent in therapeutic INR and frequency of monitoring.

INR Reading	Date	INR value
Reading 1		
Reading 2		
Reading 3		
Reading 4		
Reading 5		
Reading 6		
Reading 7		
Reading 8		
Reading 9		
Reading 10		

APPENDIX B: Data collection form to collect costs

Item	Cost
Point of care testing device	
Laboratory INR testing Machine	
Support software	
Other consumables	

APPENDIX C: Interview Guides

1. Eligibility checklist

	YES	NO
• Works at the Laboratory	☐	☐
• Have managerial position	☐	☐
• Worked at their current station for at least 6 months	☐	☐
• Provide informed consent	☐	☐

2. Code number…….

3. Date……

4. Age…….

5. Sex…….

6. Cadre……..

Interview guide at the Kenyatta National Hospital

The interview will be used to collect the following information on the sunk cost, personnel cost, patient charges.

7. Staffing levels of the standard laboratory of Kenyatta National Hospital

- How many staff are employed who work in the laboratory on a single day?
- What are the levels of training of the staff?

8. Consumables used to carry out the INR test

- The types of materials used to carry out the test?
- The amount of materials used in a single day per patient?
- What are the costs of each item used?

The information will be collected in the table below.

Consumable	Amount of material used per day	Unit Cost of each item	Total cost
Needle			
Cotton wool			
Gloves			
Reagents			
Equipment for drawing blood			
Other consumable/specify			

9. Maintenance of the Laboratory equipment

- Which equipment need to be maintained?
- What is the cost of maintaining each equipment?

10. What are the patient charges in the clinic?

- How much are patients charged in the clinic for every visit?

Cost of the INR test……..

Cost of consultation ……

Interview guide at the Moi Teaching and Referral hospital anticoagulation clinic

The interview will be used to collect the following information on the sunk cost, personnel cost, patient charges and patient turnaround time of the specialized anticoagulation clinic

11. The human resource that will be required in the specialized anticoagulation clinic

- How many staff are needed to run the anticoagulation clinic?
- What are the levels of training of the staff needed to run the anticoagulation clinic?

12. What resources are needed in the anticoagulation clinic?

a. What is the Cost of POC-INR testing device?
b. The types of materials used to carry out the test for example gloves, test strips, lancets and any other?
c. The amount of materials used in a single day
d. What are the costs of each item used?

Consumable	Amount of material used per day	Unit Cost of each item	Total cost
POC-INR Testing device			
Lancets			
Cotton wool			
Gloves			
Reagents			
Test strips			
Other consumable/specify			

13. The time spent by the personnel and patient in the anticoagulation clinic

a. What is the time spent by each personnel at the clinic?

b. What is the approximate time spent by each patient when visiting the clinic, from the time the patient arrives at the clinic to the time the patient leaves the clinic?

14. What are the patient charges in the anticoagulation clinic?

How much are patients charged in the clinic for every visit?

Cost of the INR test……..

Cost of consultation ……

APPENDIX D: Informed Consent Form Health Workers

INFORMED CONSENT FORM

This Informed Consent Form is for Health Workers serving at the hematoncology and cardiothoracic clinics of Kenyatta National hospital and the specialized anticoagulation clinic of Moi Teaching and Referral Hospital whom I am inviting to participate in the research **"COST EFFECTIVENESS ANALYSIS OF ANTICOAGULATION CLINIC VERSUS STANDARD CARE IN MONITORING OF COAGULATION STATUS IN KENYAN TERTIARY REFERRAL HOSPITALS"**

Study Title: "COST EFFECTIVENESS ANALYSIS OF ANTICOAGULATION CLINIC VERSUS STANDARD CARE IN MONITORING OF COAGULATION STATUS IN KENYAN TERTIARY REFERRAL HOSPITALS"

Institution: Department of Pharmacology and Pharmacognosy, School of Pharmacy, University of Nairobi. P.O. Box 30197-00400, Nairobi.

Principle Investigator: Dr. Emmah Mongina Nyandigisi, Postgraduate student (Pharmacoepidemiology and Pharmacovigilance) P.O. Box 39905-00623, Nairobi. Mobile: 0715036350.

Supervisors:

Dr. Faith Okalebo, PhD. Department of Pharmacology and Pharmacognosy, School of Pharmacy, University of Nairobi.

Dr. David Nyamu, Clinical Pharmacist, Department of Pharmaceutics and Clinical Practice, School of Pharmacy, University of Nairobi.

Dr. Levi Mbugua, PhD. Department of Statistics, School of Mathematics and Actuarial Sciences, Technical University of Kenya.

Ethical Approval: Kenyatta National Hospital- University of Nairobi Ethical Research Committee, P.O.BOX 20723-00100, Nairobi. Tel 2726300 / 2716450 Ext 44102 and Moi University/Moi Teaching & Referral Hospital ethics and research committee P.O. Box 3-30100, Eldoret.

Part 1 Information sheet

I am Dr. Emmah Mongina Nyandigisi conducting the above mentioned study to partly fulfill the requirements for a Master Degree of Pharmacy in Pharmacoepidemiology and Pharmacovigilance at the University of Nairobi.

Introduction to the study

This study is to determine the cost and effectiveness of a specialized anticoagulation clinic versus standard care at Kenyan referral hospitals. It will involve the comparison of standard practice at Kenyatta National Hospital and the specialized anticoagulation clinic of Moi Teaching and Referral Hospital.

Purpose of the study

Currently patients attending the hematoncology and cardiothoracic clinics of Kenyatta National Hospital are experiencing delays in obtaining laboratory results, increased patient waiting time and lack of effective laboratory monitoring services. The purpose of this study is to provide evidence on the cost effectiveness of a specialized anticoagulation clinic so as to convince policy makers to consider establishing one at the Kenyatta National Hospital and any other hospital.

Participation

The research will require your participation in a key informant interview with the researcher in order to gather necessary information that will be useful for the study.

Participant selection

You are being invited to participate in this research based on your knowledge, training and experience in INR testing and anticoagulation management.

Voluntary participation

Your participation in this research is entirely voluntary. It is your choice whether to participate or not. You are free to withdraw your participation at any point in the study without any form of jeopardy and without necessarily giving a reason for withdrawal.

Benefits for participation

There will be no direct benefit to you, but your participation is likely to help us find out more on the cost effectiveness of the current practices and will help policy makers to make an informed decision when establishing an anticoagulation clinic.

Risks for participation

There are no risks or harm anticipated during the course of this study. All information obtained will be treated with confidence.

Confidentiality

We will not be sharing information about you to anyone outside of the research team. The information that we collect from this research project will be kept private. Any information about you will have a code rather than your name. The information collected will be kept under lock and key and will not be shared with or given to anyone.

Who to contact

If you have any questions, you can ask them now or later. If you wish to ask questions later, you may contact the principle investigator: Emmah Nyandigisi 0715036350, P O BOX 39905-00623 Nairobi, kmongina@gmail.com.

This proposal has been reviewed and approved by the ethical and research committee of Kenyatta National Hospital-University of Nairobi and Moi Teaching and Referral hospital-Moi University. This is a committee whose task is to make sure that the research participants are protected from harm.

If you wish to find out more on the research you can contact:

KNH-UoN Ethics and Research Committee Secretary: Prof. Mark Chindia Tel +254 207 726300 ext. 44355, E-mail uonknh.erc@uonbi.ac.ke

Moi University/Moi Teaching & Referral Hospital ethics and research committee secretary Dr. I. Marete P.O BOX 3-30100,Eldoret E-mail: eowere@gmail.com.

Part II: Certificate of Consent

I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it and any questions I have been asked have been answered to my satisfaction. I consent voluntarily to be a participant in this study

Name of Participant_____

Signature of Participant _____

Date _____

Day/month/year

Statement by the researcher/person taking consent

I confirm that I have explained the nature and effect of the study to this participant and encouraged them to ask questions which I took time to answer to their satisfaction. I am adequately convinced that the participant fully understands all aspects of the research as discussed.

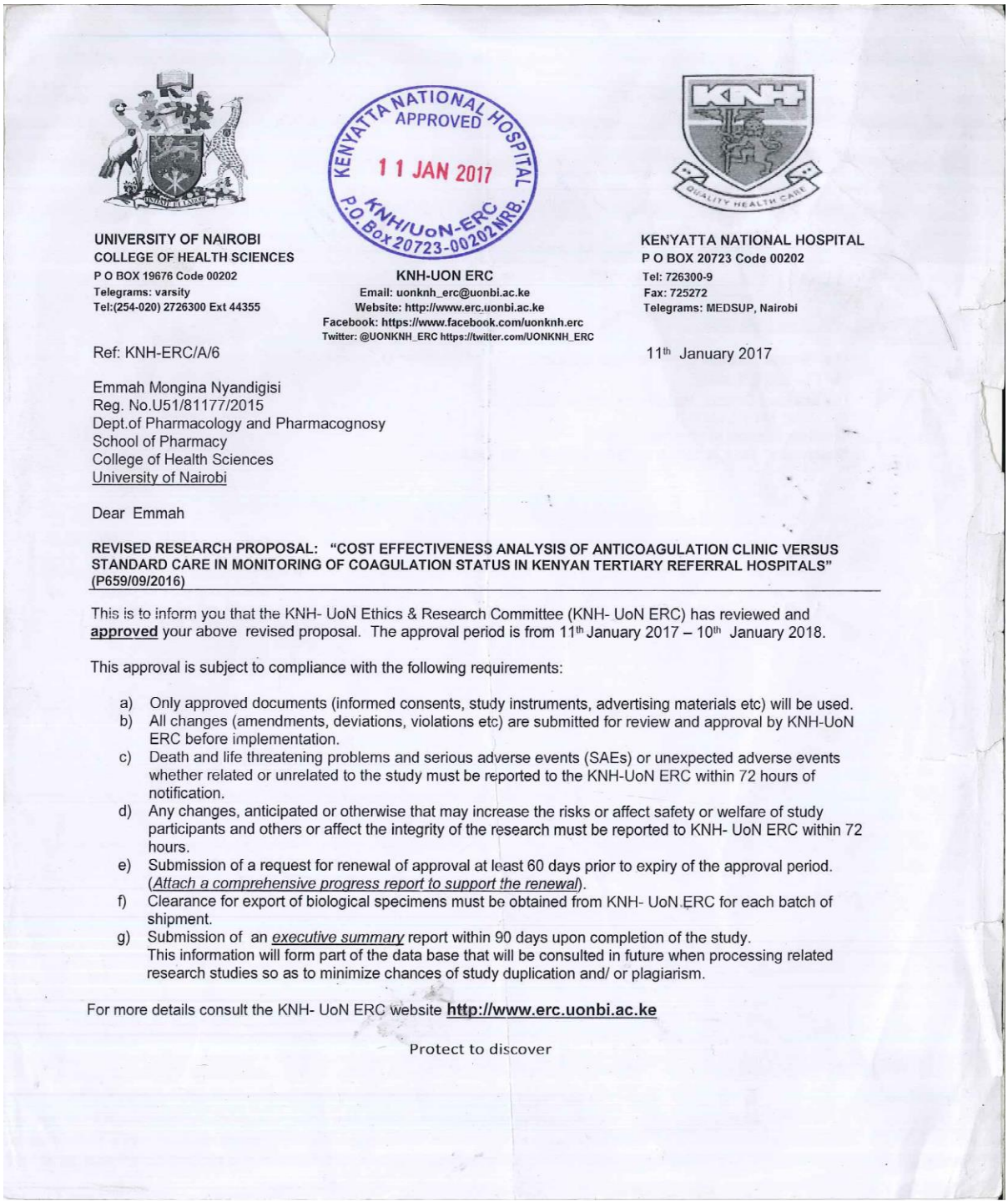
A copy of this ICF has been provided to the participant.

Name of Researcher/person taking the consent_____

Signature of Researcher/person taking the consent _____

Date _____

APPENDIX E: Ethical Approval Letters



KENYATTA NATIONAL HOSPITAL APPROVED 11 JAN 2017 KNH/UoN-ERC P.O.Box 20723-00202 NRB.

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Ref: KNH-ERC/A/6

11th January 2017

Emmah Mongina Nyandigisi
Reg. No.U51/81177/2015
Dept.of Pharmacology and Pharmacognosy
School of Pharmacy
College of Health Sciences
University of Nairobi

Dear Emmah

REVISED RESEARCH PROPOSAL: "COST EFFECTIVENESS ANALYSIS OF ANTICOAGULATION CLINIC VERSUS STANDARD CARE IN MONITORING OF COAGULATION STATUS IN KENYAN TERTIARY REFERRAL HOSPITALS" (P659/09/2016)

This is to inform you that the KNH- UoN Ethics & Research Committee (KNH- UoN ERC) has reviewed and **approved** your above revised proposal. The approval period is from 11th January 2017 – 10th January 2018.

This approval is subject to compliance with the following requirements:

a) Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
b) All changes (amendments, deviations, violations etc) are submitted for review and approval by KNH-UoN ERC before implementation.
c) Death and life threatening problems and serious adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH-UoN ERC within 72 hours of notification.
d) Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH- UoN ERC within 72 hours.
e) Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. (*Attach a comprehensive progress report to support the renewal*).
f) Clearance for export of biological specimens must be obtained from KNH- UoN ERC for each batch of shipment.
g) Submission of an *executive summary* report within 90 days upon completion of the study. This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/ or plagiarism.

For more details consult the KNH- UoN ERC website **http://www.erc.uonbi.ac.ke**

Protect to discover

Yours sincerely,

PROF M. L. CHINDIA
SECRETARY, KNH-UoN ERC

c.c. The Principal, College of Health Sciences, UoN
The Director, CS, KNH
The Assistant Director, Health Information, KNH
The Chair, KNH- UoN ERC
The Dean, School of Pharmacy, UoN
Supervisors: Dr. F.A. Okalebo, Dr. D.G. Nyamu, Dr. L. Mbugua

Protect to discover

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/2016/226
Approval Number: 0001896

29th June, 2017

Ms. Emmah Mongina Nyandigisi,
University of Nairobi,
School of Pharmacy,
P.O. Box 30197-00100,
NAIROBI-KENYA.

Dear Ms. Mongina,

RE: FORMAL APPROVAL

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

"Cost Effectiveness Analysis of Anticoagulation Clinic versus Standard Care in Monitoring or Coagulation Status in Kenya Tertiary Referral Hospitals".

Your proposal has been granted a Formal Approval Number: ***FAN: IREC 1896*** on 298th June, 2017. You are therefore permitted to begin your investigations.

Note that this approval is for 1 year; it will thus expire on 28th June, 2018. 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,

DR. S. NYABERA
DEPUTY-CHAIRMAN
INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE

cc	CEO	-	MTRH	Dean	-	SOP	Dean	-	SOM
	Principal	-	CHS	Dean	-	SON	Dean	-	SOD

MOI TEACHING AND REFERRAL HOSPITAL

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P. O. Box 3
ELDORET

Ref: ELD/MTRH/R&P/10/2/V.2/2010

7th July, 2017

Ms. Emmah Mongina Nyandigisi,
University of Nairobi,
School of Pharmacy,
P.O. Box 30197-00100,
NAIROBI-KENYA.

APPROVAL TO CONDUCT RESEARCH AT MTRH

Upon obtaining approval from the Institutional Research and Ethics Committee (IREC) to conduct your research proposal titled:-

"Cost Effectiveness Analysis of Anticoagulation Clinic versus Standard Care in Monitoring or Coagulation Status in Kenya Tertiary Referral Hospitals".

You are hereby permitted to commence your investigation at Moi Teaching and Referral Hospital.

07/07/2017
DR. WILSON K. ARUASA
CHIEF EXECUTIVE OFFICER
MOI TEACHING AND REFERRAL HOSPITAL

CC - Deputy Director (CS)
- Director of Nursing Services (DNS)
- HOD, HRISM

APPENDIX F: Institutional Letter of Authorization

KENYATTA NATIONAL HOSPITAL
P. O. Box 20723, 00202 Nairobi

Tel: 2726300/2726450/2726550
Fax: 2725272
Email: knhadmin@knh.or.ke

Ref: KNH/AD-MED/42B/VOL.I/

Date: 15th May 2017

Emma Mongina Nyandigisi
Department of Pharmacology & Pharmacognosy
School of Pharmacy
College of Health Sciences
University of Nairobi

RE:APPROVAL TO CONDUCT A STUDY IN MEDICINE DEPARTMENT

Following approval of your study by the KNH/UoN ERC and completion of the KNH study registration form, permission is hereby granted for you to collect data from the Medicine Department to enable you complete your study on ***"Cost effectiveness analysis of anticoagulation clinic versus standard care in monitoring of coagulation status in Kenyan tertiary referral hospitals"*** ***at*** Kenyatta *National Hospital, Nairobi County, Kenya.*

Kindly liaise with the Senior Nursing Officer Medicine Department for facilitation. By a copy of this letter, the Senior Nursing Officer Medicine Department is informed and requested to facilitate.

DR. M.MURAGE
AG. HOD - MEDICINE

Copy to: Senior Nursing Officer - Medicine