OPINIONS OF HEALTHCARE WORKERS ON SAFE WARFARIN USE AT KENYATTA NATIONAL HOSPITAL: A DELPHI STUDY

BY

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DEDICATION

This thesis is dedicated to my parents who have continually supported me in all levels of my education life. I am truly grateful for their unwavering love.

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LIST OF ABBREVIATIONS

ABBREVIATION	TEXT EXPLANATION
ACC	Anticoagulation Clinic
ACCP	American College of Chest Physicians
AMS	Anticoagulation Monitoring Service
APTT	Activated Partial Thromboplastin Time
$CHADS_2$ score	Congestive heart failure, Hypertension, Age, Diabetes, Prior stroke score
CHA_2DS_2-VASc score	Congestive heart failure, Hypertension, Age (>75), Diabetes, Prior stroke score, Vascular disease, Age (65-74), Female
DVT	Deep Vein Thrombosis
HAS-BLED score	Hypertension, Abnormal renal and liver function, Stroke, Bleeding, Labile INR, Elderly (Age > 65 years) , Drugs or alcohol
$HAEMORR_2HAGES$ score	Hepatic or renal disease, Ethanol abuse, Malignancy, Old age, Reduced platelet count, Rebleeding risk, Hypertension, Anaemia, Genetic factors, Excessive fall risk, Stroke.
INR	International Normalized Ratio
KNH	Kenyatta National Hospital
KNH/UoN-ERC	University of Nairobi/Kenyatta National Hospital Ethics and Research committee
LMWH	Low Molecular Weight Heparins
MTRH	Moi Teaching and Referral Hospital
NTI	Narrow Therapeutic Index
OBRI score	Outpatient Bleeding Risk Index
RHD	Rheumatic Heart Disease
TTR	Therapeutic Time Range

ABSTRACT

Background: Warfarin is an anticoagulant used in treating patients with deep vein thrombosis to prevent the extension of the clot and to reduce the risk of developing pulmonary embolism. It is also used in patients with atrial fibrillation or artificial heart valves to reduce the risk of stroke. Despite all its benefits, it has a narrow therapeutic margin. It can cause major or fatal bleeding and treatment should be monitored regularly using the International normalized ratio (INR) test.

Study objectives: The objectives of the study were to: gather opinions of health care workers on risk assessment for patients receiving warfarin, collate opinions of health care workers on initial and subsequent maintenance dosing of warfarin, gather opinions of health care workers on monitoring of warfarin treatment and to collate opinions of health care workers on reversal of over-anticoagulation with warfarin.

Study design: A Delphi study comprising of three rounds was employed to determine the opinions of healthcare workers on safe warfarin use at Kenyatta National Hospital (KNH).

Study area: The study was carried out at Kenyatta National Hospital. The KNH cardiothoracic surgery clinic (number 24), haemato-oncology clinic (number 23) and medical clinic (number 17) which serve patients requiring specialized care on warfarin anticoagulation therapy.

Study participants: The Delphi panel comprised of 4 cardiologists, 4 physicians and 2 pharmacists who offer anticoagulation services to patients in KNH. These panelists met the inclusion criteria and gave informed consent.

Methods: Delphi panelists were sampled through purposive sampling and recruited from a list of KNH specialists (Cardiologists, physicians and clinical pharmacists) offering their expertise in the respective KNH clinics. The Delphi process involved three rounds of filling questionnaires where the subsequent questionnaire was formulated from the preceding questionnaire. The first round presented an open-ended questionnaire while the other two rounds involved closed ended questionnaires.

Data analysis: The qualitative data collected was entered into a password protected Microsoft word (2010) sheet while the quantitative data was entered into Microsoft Excel (2010) sheet. ATLAS.ti scientific software for qualitative data analysis was utilized. Quantitative data was analyzed using Stata® version 13 (Stata Corp, USA). Measures of central tendency (median and mean) were used to present information concerning demographics of panelists. Percentages were used to calculate the response rate of panelists and to present the judgements concerning the Delphi statements. Tables and charts were utilized to present the findings of the Delphi study.

Results: Patient education and counselling through face to face discussions about anticoagulation with warfarin was the most recommended way of alleviating risks associated with warfarin. $CHA_2DS_2VAS_c$ score was the most preferred method of assessing a patient's stroke risk factor while the $HAEMORR_2HAGES$ score was preferred for assessing the patient's bleeding risk. A standardized dosing algorithm for warfarin was suggested. The initial dosage of warfarin was recommended at 5mg per oral once daily. Warfarin dose adjustments should be made based on total weekly doses rather than daily doses. Bridging with a LMWH should be administered for 5 days until therapeutic INR was reached. The most recommended LMWH in KNH was enoxaparin.

Baseline INR test, full haemogram test and a pregnancy test were the mandatory tests to be done before initiating warfarin therapy. An INR of between 2-3 was found to be ideal for most disease

conditions requiring warfarin anticoagulation. INR levels should be checked every 2-3 days after initiation of warfarin until it lies within therapeutic range. Diet variations, concurrent medications, comorbidities and non-adherence to warfarin anticoagulation were the highest influencers of INR. In the case of any presence of clinically significant bleeding where warfarin-induced coagulopathy was considered a contributing factor, warfarin should be stopped, IV vitamin K given, blood transfusion and fresh frozen plasma should be administered.
Conclusion: In this study, more than 70% consensus or higher was reached for most statements. We were able to develop a consensus statement on safe warfarin use by cardiologists, physicians and pharmacists using the Delphi method.

1.0 CHAPTER ONE: INTRODUCTION

1.1 Background

Antagonists of vitamin K have been in use for ages for prevention and management of deep venous thrombosis and complications linked with atrial fibrillation and cardiac valve replacement. In spite of its advantages, numerous problems are encountered throughout management. The most favourable International normalized ratio (INR) range lies between 2.0-3.0. Maintaining this goal range requires very strict monitoring. Internationally, warfarin is the third drug on the list causing hospital admission due to side effects (Pirmohamed M, 2004). In an analysis where 6454 patients who had atrial fibrillation were assessed, it was noted that even with warfarin, approximately 50% of the time, their INR was still out of range (Boulanger L, 2006). In addition, the main side effect related with warfarin is haemorrhage. These haemorrhagic events can be major and fatal at rates of 7.2 and 1.3 per 100 patient years (Linkins LA, 2003). In a recent study done in Kenyatta National Hospital (KNH) and Mbagathi Hospital, the most common adverse effect of warfarin was haemorrhage (35.3 %), followed by headache, dizziness or weakness (17.6 %) and gastrointestinal disturbances at (11.8 %). Unusual body pains and swelling, alopecia, skin necrosis and hypersensitivity rash were uncommon (<10.0) % (David G Nyamu, 2017). Additionally, the need for recurrent INR observation and an increased possibility for drug interactions combine to challenge the use of warfarin, particularly in the older patients (Lowery S, 2005).

Due to these major complexities associated with warfarin administration, the American College of Chest Physicians (ACCP) guidelines suggest that medical professionals who deal with oral anticoagulation treatment ought to do so in an organized manner, integrating education of patients, coordinated INR monitoring and dosing choices (Holbrook A S. S., 2012). In Kenya, Moi Teaching and Referral Hospital (MTRH) has developed a model for providing anticoagulation services (Pastakia SD, 2009). An anticoagulation medical model has been created which includes community health professionals, pharmacists and their assistants and physicians to offer procedural-based care. This has been shown to increase the proportion of individuals within the goal range of INR (Curtis A. Franke, 2008). Facts also point out that this coordination is linked with few side effects compared to normal care (Witt DM, 2005) (Locke C, 2005).

At Kenyatta National Hospital, the process of anticoagulation with warfarin is not well structured. There is no evidence of a specific dosing nomogram. Anticoagulation management with warfarin is based on individual physician knowledge and experience (SW, 2000). In order to achieve better anticoagulation control, this study sought to develop a consensus statement for warfarin use through a Delphi study with a view to improving future practice.

1.2 Problem Statement

In a recent study at Kenyatta National Hospital to evaluate the management of warfarin related bleeding, ten (50%) of the prescribers managed warfarin related bleeding by administration of vitamin K injection. Approximately eight (40%) would stop warfarin administration when a patient presented with warfarin related bleeding while two (10%) would intensify the monitoring of INR in patients (David G Nyamu, 2017). These inter-individual management practices reveal the lack of standardized use of evidence based guidelines. In the same study, the availability and utilization of guidelines by the prescribers was explored as a factor which may impact on the ambulatory anticoagulation practice. Guidelines that govern anticoagulation practice are unavailable to over 75% of the prescribers (David G Nyamu, 2017).

Warfarin therapy is distinguished by a broad variation of doses between individuals. Consequently, precise dosing is vital for safe management of patients on the drug. Habitual monitoring of INR is an essential component in the management of individuals getting warfarin therapy. Several factors including remarkable alterations in nutrition or alcohol ingestion, medication interactions, coexisting illnesses and non adherence to dosage regimen can affect INR control. Health care workers are required to come up with tools for warfarin, to reduce the risks, increase the benefits of therapy and optimize health outcomes, by achieving tighter INR control (Garcia D, 2010).

In this respect, this study sought to gather opinions of healthcare workers on safe warfarin use at Kenyatta National Hospital.

1.3 Research questions

1. What are the views and opinions of healthcare workers on risk assessment and selection of initial and maintenance dosing of patients receiving warfarin?
2. What are the views of healthcare workers on monitoring and reversal of over-anticoagulation with warfarin treatment?

1.4. Objectives

1.4.1 Main objective

To develop a consensus statement for warfarin use to guide clinician decision making that will reduce adverse effects at Kenyatta National Hospital.

1.4.2 Specific objectives

a) To gather opinions of health care workers on risk assessment for patients receiving warfarin.

b) To collate opinions of health care workers on initial and subsequent maintenance dosing of warfarin.

c) To gather opinions of health care workers on monitoring of warfarin treatment.

d) To collate opinions of health care workers on reversal of over-anticoagulation with warfarin.

1.5 Study Justification

The Delphi study sought to create a consensus statement integrating knowledge from research together with the expert opinions of clinical professionals with a view to improving future practice. This will give consistent anticoagulation management to individuals getting warfarin whilst reducing the risks related with anticoagulation. The outcomes of this study will also assist in safeguarding patient safety during warfarin therapy, patient monitoring during therapy and dealing with warfarin toxicity. The information gathered in the study will be important in formulating treatment guidelines for warfarin use in Kenyatta National Hospital in the future.

2.0 CHAPTER TWO: LITERATURE REVIEW

Warfarin is one of the commonly used anticoagulant internationally (J. Hirsh, 2003). It was identified by Karl link in 1940 and the name is derived from *Warf* (Wisconsin Alumni Research Foundation) and–*arin* from the name coumarin (A, 1978). Individual factors such as hereditary differences, concomitant drug therapy and co morbidities contribute to inter-individual variation in warfarin dose requirements needed to achieve therapeutic level of anticoagulation.

2.1 Pharmacokinetics of Warfarin

Warfarin is a racemic mixture of two active enantiomers R and S forms. S- isomer is 2.5 times more potent than R- isomer (DrugBank, n.d.). It is quickly absorbed from the gastrointestinal tract and has high bioavailability of more than 79% (A, 1978; RA, 1976).It attains peak blood concentration in 90 minutes after being administered orally (Kelly JG, 1979). Warfarin has a half-life of between 36 hours and 42 hours. It binds to plasma proteins and accumulates in the liver, where the two isomers of warfarin are metabolically altered by dissimilar pathways (RA, The New Dimensions of Warfarin Prophylaxis: Advances in Experimental Medicine and Biology, 1986).

2.2 Mechanism of action of Warfarin

Warfarin inhibits vitamin K dependent clotting factors ii, vii, ix, x and proteins C and S production. Vitamin K promotes the synthesis of γ-carboxyglutamic acid residues in the proteins that are necessary for biological action. Warfarin is contemplated to impede clotting factor production by inhibition of the C1 subunit of vitamin K epoxide reductase enzyme complex, thus reducing the renewal of vitamin K1 epoxide (Gage BF, 2006) .

2.3 Clinical uses of Warfarin

For ages, warfarin has been used for the prevention and management of venous thrombosis and pulmonary embolism (PE), prevention and management of thromboembolic complications related with atrial fibrillation (AF) and cardiac valve replacement, decrease in myocardial infarction (MI) , stroke and systemic embolization (SW, 2000) (Ageno W, 2012) . At the Kenyatta National Hospital, 86.7% of patients getting warfarin treatment had deep vein

thrombosis, 33.3% had transient ischaemic attacks, while 16.7% had atrial fibrillation (David G Nyamu, 2017).

For individuals with venous thrombosis and pulmonary embolism, the least period of management is 3 months for transient risks such as surgery or 6-12 months for recurring idiopathic risks (Queensland, 2012). Further, individuals with Atrial fibrillation with Congestive heart failure, hypertension, age, Diabetes, prior stroke score ($CHADS_2$) score higher than or same as 2 or patients with irreversible clinically hypercoagulable states such as antiphospholipid syndrome, use anticoagulation treatment for their lifetime (Queensland, 2012).

Regardless of its uses, warfarin does not have a straight effect on a thrombus already formed, nor does it reverse ischemic tissue damage. When a thrombus has already been formed, the aim of anticoagulation therapy is to stop the spread of the clot and to avoid secondary thromboembolic complication that can lead to death (Queensland, 2012).

2.4 Risk assessment of patients on Warfarin therapy

This is the detection of potential risk factors that could endanger an individuals' wellbeing or recuperation during warfarin treatment (Rausand, 2013). Stroke risk assessment and bleeding risk assessment are used to determine whether or not therapy with anticoagulation is appropriate.

2.4.1 Risk of stroke in patients on Warfarin therapy

The possibility of stroke in individuals is evaluated using the $CHADS_2$ scoring system (Appendix VIII) (Gage BF W. A., 2001) (Queensland, 2012). In the $CHADS_2$ scoring system, every point signifies the yearly threat of stroke by a 1.5 factor. Warfarin treatment is suggested for $CHADS_2$ scores of 2 or higher. Individuals with a $CHADS_2$ score of 1 might gain from an oral anticoagulant and they should be evaluated with a complete risk assessment tool for example the Congestive heart failure, hypertension, age (>75), diabetes, prior stroke score, vascular disease, age (65-74), female (CHA_2DS_2-VASc) scoring system (Gage BF W. A., 2001) (Camm AJ, 2010) (Queensland, 2012).

2.4.2 Risk of bleeding in patients on Warfarin therapy

The threat of stroke ought to constantly be evaluated against the possibility of haemorrhage assessing the suitability of anticoagulation treatment. The main side effect of overcoagulation is

blood loss. The highest rates of major haemorrhage arise in the first three months of therapy (Clarke R, 2006) (Queensland, 2012). The risk of blood loss may be reviewed using the HAS-BLED scoring system (Appendix IX) (Pisters R, 2010) (Queensland, 2012) or other tools such as the hepatic or renal disease, ethanol abuse, malignancy, old age, reduced platelet count, re-bleeding risk, hypertension, anaemia, genetic factors, excessive fall risk, stroke ($HAEMORR_2HAGES$) score (Gage BF Y. Y., 2006). In the former, a haemorrhage risk score of 3 or higher signifies high risk. It is consequently imperative for clinicians to evaluate individuals for bleeding risk throughout treatment (Queensland, 2012).

2.4.3 Contraindications for Warfarin therapy

Contraindications for warfarin should be checked before initiation of treatment (Queensland, 2012). Warfarin ought not to be used in patients with haemorrhagic tendencies. These could include evident haemorrhage due to bacterial infections such as bacterial endocarditis or any system of the body such as the central nervous system, gastrointestinal system and respiratory system (Juurlink, 2007)

Warfarin therapy is also prohibited in patients who have had current surgery or those contemplating surgery of the central nervous system (Dharmarajan, 2008). It can have critical outcomes for individuals who have gone through threatened abortion, eclampsia, and preeclampsia. Its introduction during pregnancy is reported to cause a predictable blueprint of key innate malformations such as fetotoxicity, serious fetal bleeding and an increased threat of abortion and fetus death (Dharmarajan, 2008).

Warfarin is also contraindicated in individuals with hypertension since they might present with a grave possibility of intra-cerebral bleeding. Treatment with oral anticoagulants should therefore be cautiously handled in these patients (Macina OT, 2007).

2.5 Dosing of Warfarin

2.5.1 Initial dosing of Warfarin

Many medical practitioners continue to use expert opinion alone as the source for starting and altering warfarin dosages in individuals who need oral anticoagulation (Horton JD, 1999). Several studies have confirmed methods to introduction of anticoagulation that offer quick anticoagulation with fewer risks. The two extensively used dosage choices on the introduction of warfarin treatment are 5 mg and 10 mg per day (Harrison L, 1997) (Crowther MA, 1999). A

number of studies proposed a 5-mg warfarin initiation algorithm whilst a supplementary study proposed a 10-mg warfarin initiation algorithm. The disparity may be partly due to differences in patient populations. The 5-mg algorithm seemed to perform better in inpatients who were also receiving heparin, whereas the 10-mg algorithm worked superiorly in outpatients who were getting low-molecular-weight heparin.

In other studies, two other ways for introducing warfarin, depending on the individuals risk for thrombotic events were projected; for low thrombotic risk individuals for example atrial fibrillation and high thrombotic risk individuals for example deep vein thrombosis (Queensland, 2012).For the former, no heparin was necessary and a low initial dosing course of warfarin therapy beginning at 3 mg was suggested. For 85% of individuals, after 29 days therapeutic INR was achieved (Clarke R, 2006) (Queensland, 2012). On the other hand, for individuals at high risk of thrombotic conditions, heparin was necessary. Warfarin 5mg was introduced on the same day as low molecular weight heparin. The two were used concurrently for at least five days and until the INR was in the goal range for at least two successive days.

2.5.2 Subsequent maintenance dosing using Warfarin

The maintenance dose of warfarin is the dose that maintains the INR between 2.0 and 3.0 for three consecutive measurements for atleast 6 weeks duration after initiation phase (Rosendaal FR1, 1993). To direct upcoming alterations in maintenance doses, practitioners are supposed to reflect on whether the individual has had INR disparities in the past (Queensland, 2012). Alterations are suggested depending on verification that usual every day doses have been taken correctly and the individual has had a steady diet. Clinicians should review accessible tablet strengths and the patient's capability to follow instructions when prescribing doses (Clarke R, 2006).

Most dosage adjustments are based on total weekly dosage of warfarin (Queensland, 2012). The weekly dosage can be given via a variety of dosing schedules. This can be through dosing on alternate days or taking different doses during the weekdays compared to the weekend. Dosage adjustments depending on total weekly dose also allow dosage alterations for low dosage regimens (Clarke R, 2006) (Queensland, 2012). Dose adjustment is also suggested for individuals with mechanical heart valves as the goal INR range is greater (2.5 – 3.5) (Clarke R, 2006).

2.6 Monitoring Warfarin treatment

The measurement of the anticoagulation status of individuals on oral anticoagulants requires standardization of prothrombin time with INR (Hirsh J, 1995). In a diversity of medical situations, the use of INR has been shown to allow efficient suggestions for use of oral anticoagulants. Many studies point out that in majority of scenarios an INR between 2-3 is necessary for efficient anticoagulation. The risk of haemorrhage is higher with an increasing INR, and can increase radically above an INR of 4.5 – 5 (Hirsh J, 1995) (Pisters R, 2010).

2.6.1 Frequency of monitoring

Regularity of monitoring is dependent on whether the individual is in the initiation stage, steady phase, transition phase and whether the individual is concomitantly taking heparin (Hirsh J, 1995). In the initiation stage of oral anticoagulant treatment, the individuals' status is supposed to be examined four to five times per week in anticipation of some level of stability in the INR response to be realized. Immediately the patient's INR and dose is stable, future INR measurements must be done on an individual patient basis. Universally, the INR ought to be checked once every four weeks at the least (Hirsh J, 1995). When there are alterations to prescription or a medical condition, it necessitates a transition phase to occur. Major nutritional alterations and a diversity of drugs can considerably alter the response to oral anticoagulant response. Consequently, it is vital to more directly check the INR when individuals in the stable phase go through alterations to drugs or nutrition (Hirsh J, 1995). It may be important to reverse to everyday observation if the INR gets out of range for any reason (Hirsh J, 1995).

2.7 Factors that influence INR

Warfarin is prone to interaction with many prescription and non-prescription drugs typically leading to an augmentation or a reduction in the anticoagulant effect. This may lead to critical and serious side effects and may necessitate clinical involvement to avert deleterious adverse effects (Juurlink, 2007).

2.7.1 Potential drug interactions

S-warfarin is metabolized primarily by CYP2C9 to 7-hydroxywarfarin (Kaminsky LS, 1997). Potential warfarin-drug interactions could occur with any of a very wide range of drugs that are metabolized by these CytochromeP450s (Kaminsky LS, 1997). Numerous antibiotics are reported to potentiate the outcome of warfarin. A number of examples include: cotrimoxazole, erythromycin, isoniazid, fluconazole, miconazole, and metronidazole (Juurlink, 2007). The

biphasic effect of sulfinpyrazone means an early potentiation of the anticoagulant effect is observed, thereafter an inhibition is observed. Aspirin, aspirin-like drugs (salicylates), and nonsteroidal anti-inflammatory drugs (NSAIDs such as ibuprofen, naproxen, and celecoxib) may possibly have outcomes similar to warfarin. These medications may potentiate the risk of haemorrhage if in use for the duration of therapy with warfarin (Steve A, 1999).

2.7.2 Potential interactions with complementary medications

In evaluating potential drug interactions, all concurrent treatments including complementary and over-the-counter medications ought to be considered (Queensland, 2012). Several complementary products interact with warfarin. These are dong quai, fenugreek, garlic, ginkgo biloba, ginseng, and St. John's wort, amongst others (Steve A, 1999).

2.7.3 Potential interactions with food

Remarkable alterations in nutrition can influence the INR owing to different levels of vitamin K in different foodstuff (Queensland, 2012). Vitamin K inhibits the hypoprothrombinemic effect of oral anticoagulants. The ingestion of vitamin K through vitamins or food reverses the effects of oral anticoagulants. Resistance to oral anticoagulants has been linked to ingestion of foodstuff high in vitamin K content which are green, leafy vegetables, avocados, soy beans, and green tea (Ansell J H. J., 2004).

Mango has been reported to increase warfarin effects. The mechanism of how this happens is unknown but may possibly be linked to the vitamin A content, which inhibits warfarin metabolism (Ansell J H. J., 2004). Warfarin and cranberry juice can lead to alterations in the INR and/or haemorrhage complications. The mechanism is unknown but may possibly entail changes in metabolism of warfarin stimulated by flavonoids found in cranberry juice (Tatro, 2010). Garlic, a very common seasoning in Kenya is also believed to have antithrombotic activity causing a major potentiation of the clinical effects of warfarin (Bordia A, 1978) (Banerjee SK, 2002). *In vitro* studies suggest that it inhibits CYP2C9, CYP3A, and CYP2D6 enzymes (Foster BC, 2001) (Zou L, 2002). Health care professionals are supposed to strictly monitor individuals to avoid severe bleeding or clotting problems (Tatro, 2010)

2.8 Warfarin reversal

There is a close association between the INR and possibility of haemorrhage. The possibility of blood loss is increased conspicuously once the INR surpasses 4 and the threat increases sharply with values larger than 5 (Steve A, 1999). The management of extreme anticoagulation is

dependent on the point of the INR, the existence or nonexistence of haemorrhage, and medical conditions. The choice of approach is based largely on clinical judgment, because no randomized trials have compared these strategies in terms of clinical outcomes (Steve A, 1999).

The turnaround of warfarin anticoagulation may possibly be obtained by stopping treatment and, if needed, by giving of oral or parenteral vitamin K. The utilization of vitamin K decreases the reaction to successive warfarin treatment and individuals may go back to a pretreatment thrombotic condition subsequent to the swift reversal of an extended INR (Steve A, 1999). If quick re-anticoagulation is required, heparin may be preferred for initial treatment. Prothrombin complex concentrate (PCC), fresh frozen plasma, or activated Factor VII management might be considered if the necessity to reverse the effect of warfarin is vital. Nevertheless, PCC and activated Factor VII are in addition linked to an augmented possibility of thrombosis. For that reason, these preparations ought to be used just in extraordinary or critical blood loss episodes resulting from warfarin over dosage (Baker RI & Group, 2004)

2.9 Warfarin use protocols

Numerous warfarin use guiding principles and procedures have been structured. They present suggestions for the use of anticoagulant drugs for quite a few indications that are significant in the main clinical setting. These guidelines set out consistent and medically efficient guides for the care of individuals taking warfarin that reduce the dangers related to anticoagulation. The American College of Chest Physicians, NHS Cumbria, HSSA Queensland health guidelines and British Columbia guidelines provide suggestions for the long-standing treatment with warfarin in individuals aged ≥19 years in the main clinical setting. The guiding principles illustrate warfarin initiation, international normalized ratio (INR) monitoring with most favourable ranges and warfarin dose modifications.

Warfarin use protocols have been seen to provide best possible management of INR control and give most favourable care to all patients getting warfarin treatment. A pharmacist-managed set of rules for warfarin administration generated at Baylor University Medical Center integrated modern medical guiding principles and evidence-based medicine. The patients attained therapeutic ranges of warfarin in 6 days, demonstrated a drift toward less adverse drug reactions and less supra therapeutic international normalized ratios compared to the control group, even though the dissimilarity was not statistically significant (David L, 2005).

Dosing guiding principles may help prevent errors in dosing warfarin. However, holding on to an inflexible protocol is inappropriate and may be risky (Wittkowsky AK, 2010). The vast number of patient factors such as age, body weight, nutritional status, acute and chronic disease states, and changes in concomitant drug therapy and diet can influence INR making warfarin dosing too complex to depend on a definite protocol (White PJ, 2010). A dosing protocol that was computer-based led to a progression of the INR time in the therapeutic range from 63.4% to 66.8% (Poller L, 2009). However, the protocol was unsuccessful in suggesting a dosage in about 6% of situations, and the suggested dose had to be overruled by the managing clinical specialist just about 27% of the time.

2.10 Delphi technique

The Delphi method is an agreement development technique used expansively in health care (Jones J, 1995). It is usually used when the prime basis of information is knowledgeable judgement (Ziglio E, 1996). It is a method that entails three to four rounds of feedback through survey. Normally, the first round is frequently used to identify main ideas from the open-ended questions. Subsequently the responses are assembled into survey forms that are the basis of the succeeding rounds. From the second round and beyond, the data is typically evaluated quantitatively, using rank order or rating procedure. The outcomes are evaluated in order to establish point of consensus in the ranking order. Outcomes from the rounds are summarised, assembled and returned to panelists. In succeeding iterations, panelists are allowed to re-examine responses of all the other panelists including their own (Dalkey NC, 1963).

Panelists are given an exclusive identifier only known to the investigator. This identifier increases the likelihood that judgments are unbiased by the one who articulated them. Furthermore, the Delphi method presents the benefit of merging panelists' responses, leading to a more dependable statement compared to estimation from a sole person (Murphy M, 1997) (Maher, 2015). Additionally, this method permits the exchange of information among persons in a restricted environment, restraining the potentially negative effects of interaction (Dalkey NC R. L., 1972) (Maher, 2015).

Kano et al in 2017 used the Delphi method to develop algorithms to monitor the use of warfarin by physicians (Kano EK, 2017). Recently, in 2018, Triller D et al, used the same method to develop a consensus list of requisite data elements (RDEs) that should accompany all anticoagulated patients at discharge (Triller D, 2018). In Kenyatta National Hospital, the Delphi

method has not been used before. This study aims to collect opinions on safe warfarin use based on medical experts.

2.11 Conceptual framework of the warfarin Delphi study

Goal 3E from the Joint Commission National Patient Safety Goals requirements for 2008 states the need to reduce the likelihood of anticoagulant therapy causing patient harm. This necessitates hospitals to develop processes that will ensure safe use of warfarin (Commission, 2008). Theoretically, guidelines on warfarin use provide recommendations on how to initiate, dose adjust and monitor warfarin therapy in the ambulatory setting. Evidence is based on the Antithrombotic therapy and Prevention of Thrombosis, 9th edition: American College of Chest Physicians Clinical Practice Guidelines. Guidelines on reversal of warfarin are also available within the (Gaston, 2015) (Holbrook A, 2012) (Ageno W, 2012). Figure 2.1 shows the conceptual framework of the warfarin Delphi study.

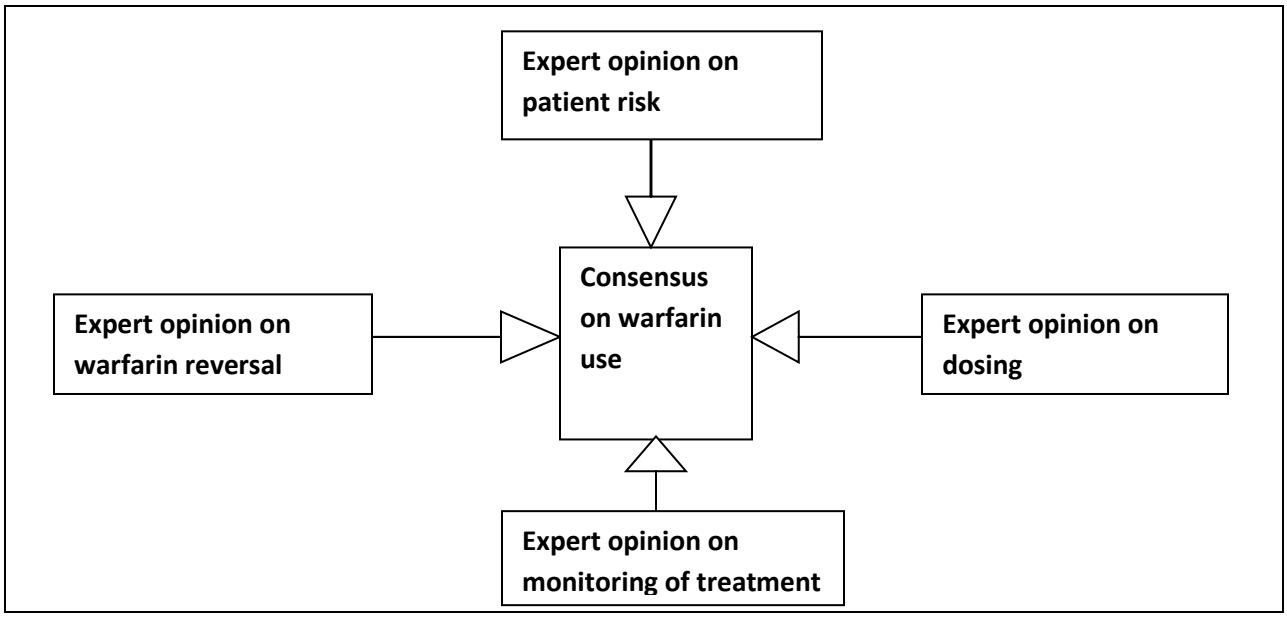

Figure 2. 1: Conceptual framework

3.0 CHAPTER THREE: METHODOLOGY

3.1 Study design

A Delphi study was employed to determine the opinions of healthcare workers on warfarin use at Kenyatta National Hospital. These opinions may in further studies be incorporated in warfarin use protocol development.

3.2 Study site

The study was conducted at the KNH which is the largest referral hospital in Kenya. It was built to fulfill the role of being a National Referral and Teaching Hospital, as well as to provide medical research environment. KNH has 50 wards, and 22 out-patient clinics. The KNH Cardiothoracic surgery clinic (clinic 24), haemato-oncology clinic (number 23) and medical (clinic number 17) serve patients requiring specialized care on warfarin anticoagulation therapy. In the year 2012 alone, there were 2467 and 8202 outpatients in the cardiothoracic and haemato-oncology clinic respectively (Kibiru AW, 2012) . This consensus statement will serve adult patients being initiated and maintained on warfarin therapy in the clinical setting.

3.3 Study population

A diversity of expertise in the group is reported to be a significant decisive factor for development of a consensus statement (Jamie J. Kirkham, 2015). The study population consisted of three relevant categories of experts who had important and valuable knowledge about anticoagulation services offered in KNH. These included 4 physicians, 4 cardiologists and 2 clinical pharmacists who offered anticoagulation services to patients who attended the KNH cardiothoracic surgery clinic, haemato-oncology clinic and medical clinic. The period of data collection was 5 months (Dec 2016- April 2017).

3.4 Eligibility criteria

Individuals were eligible to participate in the Delphi study if they had a related background in Cardiology, Internal Medicine and Clinical pharmacy and they served the population of patients requiring anticoagulation management at the Kenyatta National Hospital.

3.4.1 Inclusion criteria

The study sought to incorporate representatives from three key stakeholders that were mainly concerned with a consensus statement for safe warfarin use. These groups included: Cardiologists, physicians and clinical pharmacists who were health care providers at the Kenyatta National Hospital. The panelists had to be actively involved in the management of patients attending the KNH Cardiothoracic surgery clinic (number 24), haemato-oncology clinic (number 23) and medical clinic (number 17). They were also required to have their expertise in these clinics for a minimum of two years. The healthcare workers gave informed consent inorder to participate in the study.

3.4.2 Exclusion criteria

Cardiologists, physicians and clinical pharmacists who offered their expertise in any other areas apart from the cardiothoracic surgery clinic, haemato-oncology clinic and medical clinic of Kenyatta National Hospital were not included in the study.

3.5 Sample size estimation

The majority of Delphi studies have used between 15 and 20 members (Ludwig BG, 1994). In heterogeneous groups (people with expertise on a discipline but from different professional groups) it has been reported that only 5 to10 experts are needed (Clayton M J, 1997) (Jamie J. Kirkham, 2015). A panel of ten participants that included 4 physicians, 4 cardiologists and 2 clinical pharmacists who offered anticoagulation services to patients who attended the KNH cardiothoracic surgery clinic, haemato-oncology clinic and medical clinic were invited to participate in the Delphi survey. The estimated sample size scheduled above was suitably large to yield a significant statistical analysis even when non-responses/attrition was taken into account. Effort was put to maximise the response rate across stakeholders.

3.6 Sampling method

Delphi panelists were purposively sampled from a list of KNH specialists (cardiologists, physicians, clinical pharmacists) who offered their expertise in the KNH cardiothoracic surgery clinic, haemato-oncology clinic and medical clinic. After identification, a letter was sent to them

detailing the requirements of the study (Appendix III). The ones who responded were followed up through face to face meeting for consent. Recruitment was then carried out until the desired sample size was achieved. Only freely consenting participants were invited to participate in the study (Appendix IV).

3.7 Study procedures

The Delphi process consisted of three rounds of questionnaires, response and feedback. A series of three questionnaires were issued, each building on the previous one. Each panelist was issued a unique identifier that was only known to the researcher. Panelists were asked to complete each round of the Delphi exercise within three weeks. A reminder Email and phone message were sent at the end of week two to prompt completion of the survey. The questionnaires were physically collected by the researcher. Results from the rounds were analyzed, compiled and returned to panelists. The results were used to determine the levels of agreement in the panel and to formulate a consensus statement on warfarin use for Kenyatta National Hospital. No research assistants were employed in the study.

3.8 Data collection methods

Demographic characteristics (age, background, years of experience, field of interest and current position) of the expert panelists were obtained as part of the data filled in the first questionnaire. Data concerning the various aspects of warfarin use were also collected on questionnaires in three rounds of the Delphi process. The collected information was abstracted into data collection tool.

3.8.1 Delphi round one

In this round, an open ended questionnaire was issued to the panelists. The questionnaire was used for soliciting information about warfarin use from the Delphi panelists. After finishing the exercise, the questionnaires were collected.

3.8.2 Delphi round two

After getting responses from round one, the composed information was transformed into a well-structured questionnaire. Any added statements recommended in free text responses in round one

were included in this stage. In this round, each Delphi panelist was obligated to rank statements to establish preliminary priority. Statements in which a consensus was arrived at in the first round were not included in the second round.

3.8.3 Delphi round three

In this round, each Delphi participant received a compiled summary of statements in which a consensus was arrived in the second round. Furthermore, each panelist who participated in the previous round was shown the allocation of scores for each statement for all Delphi panelists separately and their own score from Round 2 (Jamie J. Kirkham, 2015). A third questionnaire detailing statements in which a consensus was not reached in the preceding round was administered. This round gave Delphi panelists a chance to make additional clarifications of the information gathered and their judgments.

3.8.4 Recruitment and consent process for expert panel

After selection of panelists, every one of them was sent a personal letter and Email expounding on the project (Appendix III). The preliminary letter consisted of a clear project explanation detailing the importance of finishing all rounds, an approximation of the amount of time required to complete filling the questionnaires and consent for participation. Involvement in the study was voluntary and informed consent was required before a panelist responded to the survey (Appendix IV). Thereafter, the first questionnaire (Appendix V) was administered.

Panelists were asked to complete round one of the Delphi exercise in three weeks. An email and phone message was sent in week two to encourage completion of the questionnaire. In round one of the Delphi study, demographic information gathered from panelists was used to offer the participant an exclusive identifier. Panelists were asked to give information on their age, background, years of practice and field of interest, to help characterize the composition of the Delphi group. All panelists who completed the first round of the Delphi study were asked to participate in the subsequent rounds as well.

After receiving responses from panelists, well-structured questionnaires were developed for the second and third round of the Delphi process. In these, the panelists were given three weeks to complete the questionnaires with a reminder email and phone message being sent at the end of week two.

3.9 Definition of terms

Consensus definition- Statements gained consensus if they got support from at least 70 % of panelists at a rate three or higher on a four point likert-type scale (Green PJ, 1982).

Case definition- An expert in the anticoagulation forum is a healthcare professional committed to the therapy of thromboembolic disorders predominantly through the use of anticoagulation management services. They also provide comprehensive monitoring, management and education for patients who require anticoagulation therapy. In this study, the cardiologists, clinical pharmacists and physicians participating had provided anticoagulation services for over two years.

Delphi scoring- In round two and three of the Delphi study, the panelists were requested to rank whether they thought the statement should be included (1 = 'definitely not include' to 4 = 'definitely include') on a four point likert scale and to give any remarks, in the form of open text, that may explain the implication of the statement (Queensland, 2012).

3.10 Data analysis

3.10.1 Data entry and Statistical analysis

In the Delphi process, data analysis involved both qualitative and quantitative data. Qualitative data was analysed in the first round of the Delphi study, where open-ended questionnaires were used to describe panelists views. The qualitative data collected in the data collection forms was entered into a password protected Microsoft Word (2010) sheet. ATLAS.ti scientific software was used for qualitative data analysis.

Quantitative data was entered into Microsoft Excel (2010) sheet. This data was analyzed using Stata® version 13 (Stata Corp, USA). Descriptive statistics was used to categorize and attain the preferred level of consensus among panelists. Measures of central tendency (median and mean) were utilized so as to display information regarding demographics of participants (Hasson F, 2000). Percentages were employed to compute the response rate of panelists and to represent information regarding consensus on statements.

3.10.2 First round analysis

The outcome of round one was evaluated using qualitative coding for open-ended questions. ATLAS.ti scientific software was employed for the analysis. The panelist's response rate was

computed as the totality of panelists who finished round one of the study as a proportion of those who gave informed consent.

3.10.3 Second round analysis

For every statement, the number of panelists who ranked the statement and the allocation of marks was summarised (Jamie J. Kirkham, 2015). The panelists' response rate was computed as the totality of respondents who finished round two of the questionnaires as a proportion of those who finished round one. As a result of round two, regions of similarity and dissimilarity were recognized. Consensus was created and definite conclusions were obtained among the panelists' responses. Statements in which a consensus was not reached were passed ahead to round three.

3.10.4 Third round analysis

For every statement, the totality of panelists who ranked it and the allocation of scores were reviewed. The number of panelists' finishing round three was recorded and the possibility of attrition bias evaluated by contrasting the number of panelists' who finished round three with those who provided informed consent. Statements for which consensus was attained was recognized.

3.10.5 Data presentation

Tables and charts were utilized after data analysis to present the findings of the Delphi study.

3.11 Data quality control

Every study tool was allocated a different serial number to avoid confusion and duplication of the data. The data collected was entered into password protected Microsoft Excel and Word (2010) sheets. Data entry was double checked by the investigator to ensure accuracy and completeness. It was backed up every four days on a flash disk.

Any documents linking the collected data to the source records were kept under lock and key. Such documents would only be accessible to the investigator and the K.N.H-UoN Ethics and Research Committee upon request.

3.12 Ethical considerations

Approval for the study was sought from the University of Nairobi/Kenyatta National Hospital Ethics and Research committee (KNH/UoN-ERC) (Appendix I). The study was also registered at

the KNH Research and Program department after permission to conduct the study was obtained (Appendix II).

Participants were only included in the study after giving informed consent. A signed copy declaration of consent was maintained as evidence of consent. Unique identifiers were assigned randomly to each of the panelists to ensure anonymity.

All the information collected was treated in strictest confidence without sharing with a third party. The filled data collection forms were filed and locked securely where only the researcher had access.

4.0 CHAPTER FOUR: RESULTS

4.1 Introduction

This chapter presents the results obtained from analysis of the questionnaires filled by Delphi panelists. It will also include results of a descriptive analysis of the Delphi study panel. Following the three Delphi rounds, consensus statements on patient risk assessment, initial and subsequent maintenance dosing of warfarin, monitoring of warfarin treatment and reversal of over-anticoagulation with warfarin were developed. Only two statements that were taken to the third round of the Delphi study did not gain consensus.

4.2 Delphi expert panel

The demographic characteristics of the Delphi expert panel are shown in Table 4.1. A total of 12 potential panelists were identified. Out of these, 10 of them gave informed consent and formed the Delphi expert panel. All the 10 participants completed the three Delphi rounds. The Delphi expert panel comprised of four cardiologists, four physicians and two pharmacists. This is a deviation from the targeted 3 cardiologists, 3 physicians and 4 pharmacists. There were a total of 6 males aged between 31-60 years and 4 females aged between 30-60 years. The males had a longer working experience with an average of 9.67 years compared to the female panelists who had mean of 3 years working experience. Cardiologists were found to be generally older (mean age of 47 years) and had a longer working experience (mean of 13 years) than the pharmacists and physicians.

Table 4.1 Demographic characteristics of the expert panel in the warfarin Delphi study

Characteristics	n (%)	Age (years) Mean (SD)	Experience (years) Mean (SD)
Gender			
Males	6 (60%)	42.3 (±10.74)	9.6 (±9.60)
Females	4 (40%)	33.5 (±3.87)	3 (±2)
Professional Qualification			
Physician	4 (40%)	34.5 (±2.64)	3 (±1.41)
Cardiologist	4 (40%)	47.25 (±9.84)	13.25 (±10.21)
Pharmacist	2 (20%)	30.5 (±0.70)	2.5 (±0.70)

4.3 Delphi round one

All the 10 Delphi expert panelists who gave informed consent completed the first round of the Delphi study. This was a 100% panelist response rate. The information gathered was subdivided into four domains which included patient risk assessment, initial and subsequent dosing of warfarin, monitoring of warfarin and reversal of over-anticoagulation with warfarin. At this stage, the statements that gained support from 70% of Delphi panelists were not carried forward to Delphi round two.

4.3.1 Patient Risk Assessment

The patient risk assessment features in round one of the warfarin Delphi study are shown in table 4.2. "n" represents the number of panelists that supported the statement out of the 10 panelists.

Table 4. 2 Patient risk assessment features for round one warfarin Delphi study

Characteristic	Panelist support n (%)
Patient information collected before warfarin therapy initiation	
Risk factor evaluation	1 (10%)
Social history	2 (20%)
Adverse reactions	3 (30%)
Drug history	5 (50%)
Blood work	7 (70%)
Medical history	7 (70%)
Tools for recording patient information	
Patient file	10 (100%)
Lab report	2 (20%)
Wells Criteria	1 (10%)
Patient information collected in clinic visits	
Clotting symptoms	1 (10%)
Bleeding tendencies	4 (40%)
INR	8 (80%)
Adverse drug reactions	5 (50%)
Blood work	1 (10%)
Patient adherence	1 (10%)
Information given about anticoagulation with warfarin	
Contraindications for warfarin	1 (10%)
Drug interactions	3 (30%)
Warfarin Adherence	5 (50%)
Monitoring INR	3 (30%)
Food interactions	3 (30%)
Risks that increase bleeding and thromboembolism	
Comorbidities	4 (40%)
Age	4 (40%)
Drug interactions	3 (30%)
Bleeding tendency	2 (20%)
INR range	2 (20%)
Drug compliance	2 (20%)
Genetics	2 (20%)
Alcohol intake	1 (10%)
Duration of treatment	1 (10%)
Clinical tools to assess bleeding risk	
$HAEMORR_2HAGES$ score	5 (50%)
Clinical tools to assess stroke risk	
$CHA_2DS_2VAS_C$ score	6 (60%)
SRAT	1 (10%)
Comorbidities/stroke/age/cardiovascular risk profile	1 (10%)

All the panelists (10) stated that there should be collection of patient information before initiating warfarin therapy. Blood work-up, medical history and medication history were among the most critical information to be collected before initiating warfarin therapy. Patient file was the most preferred method of collecting patient information. All the panelists stated that there should be treatment assessment for every patient at every clinic visit. International Normalized Ratio (INR), bleeding tendencies and cases of adverse drug reaction were among the most important information to be collected during clinic visits for the patients.

Patient education on warfarin use was seen to be paramount. Amongst the ways to educate patients on the use of warfarin, 10 (100%) of panelists suggested face to face discussions with the patients while 1 (100%) also suggested patient leaflets as additional visual tools of relaying information. The leaflets were found to be practical as the patients would carry them home and would act as reference material. All panelists stated patients should be counselled before, during and after initiation of the anticoagulation process using warfarin. Side effects of warfarin, adherence to the warfarin, need to monitor INR, drug and food interactions were among the most significant information the patients should be informed about warfarin therapy.

Before initiating warfarin therapy, the panelists suggested several risk factors that may increase the risk of bleeding and thromboembolic events that should be assessed. These included age, comorbidities, drug interactions, INR range and bleeding tendencies among others. Five (50%) panelists recommended the use of HAEMORR$_2$HAGE score and cases of previous bleeding as the best ways to determine whether a patient was at high bleeding risk. However, about 3 (30%) and 1 (10%) of panelists also suggested the use of HAS-BLED score and OBRI score respectively. Unfortunately, 2 (20%) of panelists were not aware of the clinical tools available to assess patient bleeding risk. CHA_2DS_2VASc score was the most preferred method as seen in 6 (60%) of panelists in assessing a patient's stroke risk factor. However, there were other methods such as previous stroke history, age, cardiovascular risk profiles and comorbidities that were suggested. The most critical signs and symptoms of adverse side effects of warfarin were bleeding and pain.

4.3.2 Warfarin dosing

4.3.2.1 Initial Warfarin dosing

The factors affecting initial warfarin dosing in round one of the Delphi study are shown in Table 4.3.

Table 4. 3 Factors affecting initial dosing of warfarin in round one Delphi study

Characteristic	Panelist support n (%)
Available strengths of warfarin at KNH	
5mg	9 (90%)
3mg	3 (30%)
1mg	2 (20%)
2mg	1 (10%)
10mg	1 (10%)
Factors considered before warfarin initiation	
Bleeding and clotting risk	6 (60%)
Contraindications of warfarin	6 (60%)
Drug interactions	3 (30%)
Duration of warfarin use	3 (30%)
Comorbidities	2 (20%)
Sensitivity to warfarin	1 (10%)
Drug/herbs/food interactions with warfarin	
Can increase or decrease dosage	7 (70%)
Drugs inducing cytochrome p450 increase warfarin	1 (10%)
Patient nutritional counseling	1 (10%)
Increased bleeding risk	1 (10%)
Prevent warfarin from working	1 (10%)
When to consider LMWH therapy	
Patients with DVT	4 (40%)
All patients starting warfarin	3 (30%)
Patients with atrial fibrillation history/ presence of mechanical heart valves/ inpatients/ patients with renal dysfunction/ before surgery	1 (10%)
Duration patient should receive another form of anticoagulation	
For 5 days until therapeutic INR is reached	9 (90%)
Atleast 3 days	1 (10%)
Reason enoxaparin is recommended in KNH	
Availability	7 (70%)
Less side effects	2 (20%)
Convenience	1 (10%)
Affordability	1 (10%)

All the panelists (10) stated that it is important to have a dosing algorithm for initiation of warfarin therapy. However, warfarin dosing algorithms were not in the scope of our study, therefore we did not go further to discuss. Nine (90%) of the panelists involved in the study stated that the initial dosage of warfarin should be 5 mg per oral once daily (p.o. OD). This is related to the fact that 9 (90%) were aware of the 5 mg strength of warfarin to be readily available in KNH. However, 1 (10%) stated that a dose of 2.5 mg p.o. OD of warfarin should be the initiation dose. None of the medical practitioners stated a dose of 10 mg p.o. OD as a suitable initiation dose. Contraindications to the use of warfarin such as bleeding risks/clotting risks, duration of warfarin use and drug interactions were among the most preferred factors to be considered prior to initial warfarin use.

All the panelists stated that patients with high bleeding risk should be initiated on the lowest warfarin dose. More than half 8 (80%) also suggested that patients who were sensitive to warfarin should be initiated on a lower dose of warfarin. However, most 6 (60%) of the panelists stated that the indication for anticoagulation and the goal of INR range does not affect initial dosing of warfarin. Seven (70%) of the study panelists stated that interactions with herb/food/drug can either lead to an increase or decrease in initial dosing of warfarin. The participants based their views on the fact that there were limited evidence based studies on complementary medicine and their effect on concurrent administration with anticoagulation medicines. Due to this uncertainty, the panelists strongly recommended that patients should be warned against using any herbal preparations during warfarin therapy. Diet should also be strictly controlled and monitored during warfarin use.

Three (30%) and 4 (40%) of panelists respectively stated that patients with deep venous thrombosis (DVT) and all others starting warfarin dosage should be initiated on low molecular weight heparins (LMWH). Others suggested that patients who were obese, with renal dysfunction and those with a previous history of atrial fibrillation ought to be on LMWH. Nine (90%) of panelists stated that a patient should be initiated on another form of anticoagulation for five days until therapeutic INR is reached. All the panelists stated that enoxaparin was the recommended low molecular weight heparin in Kenyatta National Hospital. Of these 7 (70%) of the panelists stated that it was because enoxaparin was more readily available, while others stated it had less side effects compared to other alternatives that were not stocked at KNH.

4.3.2.2 Long-term maintenance dosing using Warfarin

All of the panelists stated that long-term maintenance dosing protocols for warfarin should be available to guide clinician decision making regarding warfarin use. This was foreseen to create standardized treatment of patients especially because in the KNH clinic setting, patients are not examined by the same medical practitioners at every visit. Eight (80%) of the panelists cited INR levels to be the most important factor to consider before warfarin dose adjustments were made. Other parameters to consider included adverse drug reactions of warfarin and diet. Seven (70%) of the panelists stated that warfarin dose adjustments of warfarin should be based on total weekly doses of warfarin. Long-term maintenance dosing in round one of warfarin Delphi study are shown in Table 4.4.

Table 4. 4 Long-term maintenance dosing of warfarin in round one Delphi study

Characteristic	Panelist support n (%)
Factors for warfarin dose adjustments	
INR levels	8 (80%)
Adverse drug reactions	6 (60%)
Diet	6 (60%)
Drug interactions	4 (40%)
Adherence to warfarin	4 (40%)
Comorbidities	2 (20%)
Contraindications	2 (20%)
Indications of warfarin	1 (10%)
Basis of warfarin dose adjustments	
Weekly doses of warfarin	7 (70%)
Daily doses of warfarin	3 (30%)
Frequency of monitoring INR levels	
Weekly	6 (60%)
Every 3 days	2 (20%)
3-5 days after adjusting doses then weekly	2 (20%)

4.3.3 Monitoring of warfarin treatment

4.3.3.1 Laboratory monitoring during warfarin therapy

Features of laboratory monitoring in round one of warfarin Delphi study are shown in Table 4.5.

Table 4.5 Laboratory monitoring of warfarin in round one Delphi study

Characteristic	Panelist support n (%)
Laboratory tests carried out before and during warfarin therapy	
INR test	9 (90%)
Full haemogram	6 (60%)
Pregnancy	6 (60%)
UECs	1 (10%)
Liver function tests	1 (10%)
Prothrombin time	6 (60%)
Frequency of monitoring INR after initiation of warfarin therapy	
Weekly	4 (40%)
Every 3 days	3 (30%)
Daily/alternate days	2 (20%)
Four times during 1st week of therapy	1 (10%)
INR levels <0.5	
Increase dose of INR	8 (80%)
Investigate diet	4 (40%)
Investigate possible drug interactions	3 (30%)
Check warfarin adherence	4 (40%)
Introduce LMWH	2 (20%)
INR check after discharge from hospital	
After 1 week	4 (40%)
After 2 days	4 (40%)
After 3 days	2 (20%)
INR check when bridging with LMWH	
After 3 days	6 (60%)
After 2 days	4 (40%)

INR test, full haemogram, pregnancy test and prothrombin time are the main tests to be conducted before initiating warfarin therapy. Eight (80%) of the panelists stated that the targeted INR levels for patients who undergo major surgeries should be between 2.5 to 3.5. All of the respondents proposed that for patients with DVT, Rheumatic Heart Disease and Atrial fibrillation, the targeted INR levels should between 2.0 to 3.0. Seven (70%) of the study panelists also stated that for patients with a previous history of pulmonary embolism, an INR of 2.0-3.0 was suitable. Nine (90%) of the panelists also recommended INR levels of between 2.0-3.0 for patients with transient ischaemic attacks. The reasons for variations of INR levels depending on indication for warfarin therapy was not provided. Nine (90%) of the respondents stated that a baseline INR test should be done before the initial dosing of warfarin.

Four (40%) of the panelists stated that INR monitoring should be done weekly with 3 (30%) recommending after every three days. All the respondents recommended that in addition INR levels should be obtained in every clinic visit for every patient. As a precaution, a pregnancy test should be carried out for every woman of child bearing age before initiating them on warfarin therapy. This was deemed very important because warfarin had been shown to cause fetotoxicity in-utero. In the case that after an INR test, the patient presented with very low INR levels, 8 (80%) of the panelists stated that there should be an increase in warfarin dose. Around 4 (40%) suggested investigating the diet, checking adherence, checking drug interactions so as to ascertain the cause of the decrease in INR.

There are other instances whereby INR levels are supposed to be monitored. In patients who are discharged on warfarin therapy, study panelists had differing views on the time duration they should use the medication before an INR test is then carried out. Almost half of the study panelists suggested an INR test should be done two days later for patients newly initiated on warfarin, while the others recommended three days later. Six (60%) of the panelists recommended that in another instance whereby there is bridging with LMWH, INR levels should also be checked if it still lies in the therapeutic range.

The study panelists recommended five circumstances whereby there should be a repeat of INR test in the subsequent 2-3 days after initiation with warfarin. This is illustrated in Figure 4.1.

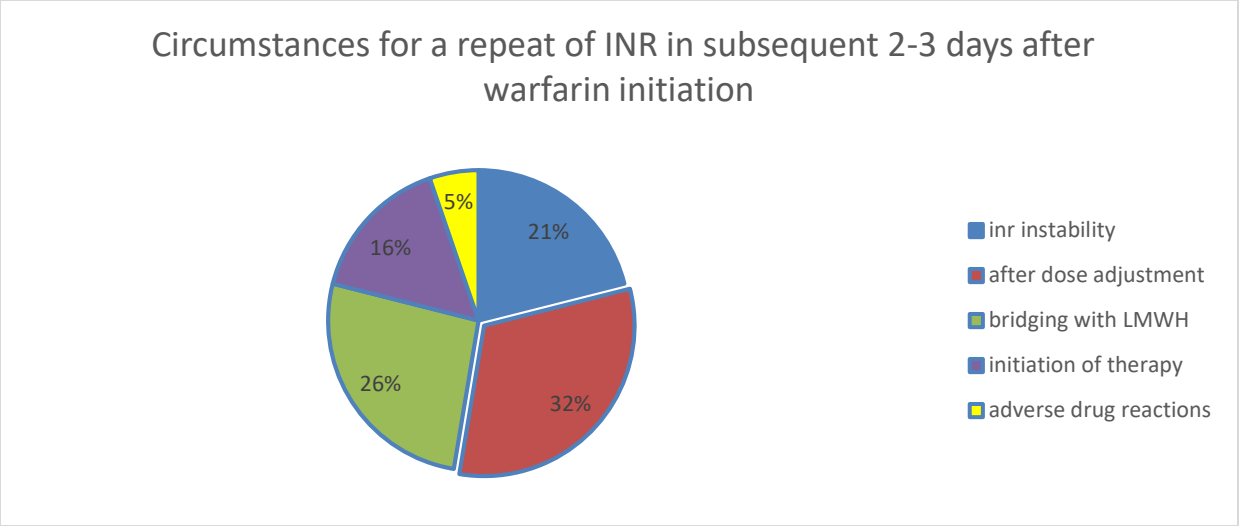

Figure 4. 1: Circumstances for a repeat INR test in the next 2-3 days after warfarin initiation

4.3.3.2 Factors that affect the levels of INR during warfarin therapy

According to the panelists, factors such as diet, concurrent medication, comorbidities, laboratory test errors and non-adherence to warfarin therapy regimens affect INR. The panelists also recognized that some medications are contraindicated when one is taking warfarin. Aspirin, antifungals, paracetamol and other anticoagulants are amongst the concurrent medications that are contraindicated.

Most of the respondents stated that vitamin k supplements, anticonvulsants, anti-TB drugs and griseofulvin were among the medications that reduce INR levels. The panelists also strongly recommended that patients on warfarin therapy should have a controlled diet. This was because some foods were seen to affect INR levels. Six (60%) of the panelists stated that food with low vitamin k increase the levels of INR. Some of the other food stuffs that are known to increase INR levels include cranberry juice, garlic and mango. Foods such as green vegetables, green tea, soya beans and avocado were reported to be among those which reduce INR levels. Six (60%) of the panelists advised to avoid dietary supplements that contain vitamin K during warfarin therapy. Six (60%) of the panelists recommended that patients using warfarin should avoid foods with vitamin K while 5 (50%) recommended use in moderation. In conclusion, all the Delphi panelists recommended that patients using warfarin should avoid use of herbal and or complementary medicines. Factors that were reported to affect the level of INR in round one of the warfarin Delphi study are shown in Table 4.6

Table 4. 6 Factors that affect INR in round one Warfarin Delphi study

Characteristic	Panelist support n (%)
Factors that affect levels of INR	
Diet	9 (90%)
Concurrent medication	6 (60%)
Comorbidities	6 (60%)
Non adherence to warfarin/ lab errors	1 (10%)
Contraindicated medications during warfarin therapy	
Aspirin	7 (70%)
Antifungals	5 (50%)
Paracetamol	3 (30%)
Other anticoagulants	1 (10%)
Food precautions during warfarin use	
Avoid green vegetables	8 (80%)
Avoid foods with vitamin K	6 (60%)
Foods that increase INR levels	
Foods low in vitamin K	6 (60%)
Cranberry juice	2 (20%)
Garlic	2 (20%)
Mango	1 (10%)
Foods that decrease INR levels	
Foods high in vitamin K	3 (30%)
Green vegetables/ green tea/ avocado	2 (20%)
Soya beans	1 (10%)

Medications that increase or decrease levels of INR are shown in Table 4.7

Table 4.7 Medications that increase or decrease INR during Warfarin therapy

Medications that increase INR	Medications that decrease INR
Aspirin	Vitamin K supplements
Fluconazole	Carbamazepine
Ritonavir	Rifampicin
Amiodarone	Enzyme inducers
Levothyroxine	Griseofulvin
Isoniazid	Carbimazole
Azithromycin	Propythiouracil
Clopidogrel	Barbiturates
Disulfuram	

4.3.4 Reversal of over-anticoagulation with Warfarin

Four (40%) of the panelists stated that INR levels greater than 5.0 is likely to put a patient at the risk of bleeding. However, all of the panelists stated that INR levels that are greater than 3.0 are likely to put the patient at a risk of bleeding. Five (50%) of the panelists recommended that when the INR is greater than therapeutic value but less than 5 and there is no bleeding, the warfarin dose should be titrated down and INR repeated in 3 days. Three (30%) of panelists recommended withholding the dose and restarting at a lower warfarin dose and 2 (20%) supported stopping warfarin till the INR levels were within the normal range.

Figure 4.2 shows the recommended actions that were given by the Delphi panelists in the case of an INR between 5-9 and no bleeding. All the Delphi panelists agreed on the recommended action in the presence of clinically significant bleeding where warfarin induced coagulopathy was considered a contributing factor. All of them stated that warfarin should be stopped, IV vitamin K administered, blood transfusion and Fresh Frozen Plasma (FFB) if available should also be administered.

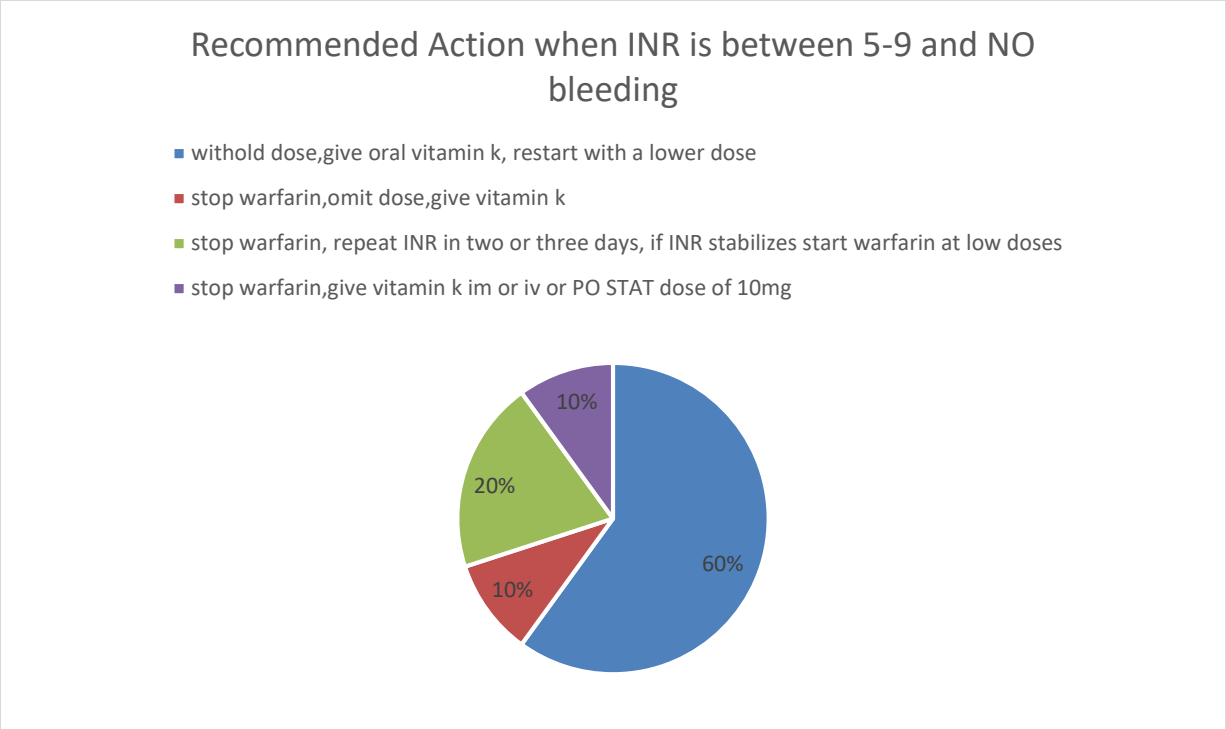

Figure 4. 2: The recommended action when INR is between 5-9 and NO bleeding

Figure 4.3 shows differing opinions on the actions to be taken when an INR is greater than 9 but there is no bleeding.

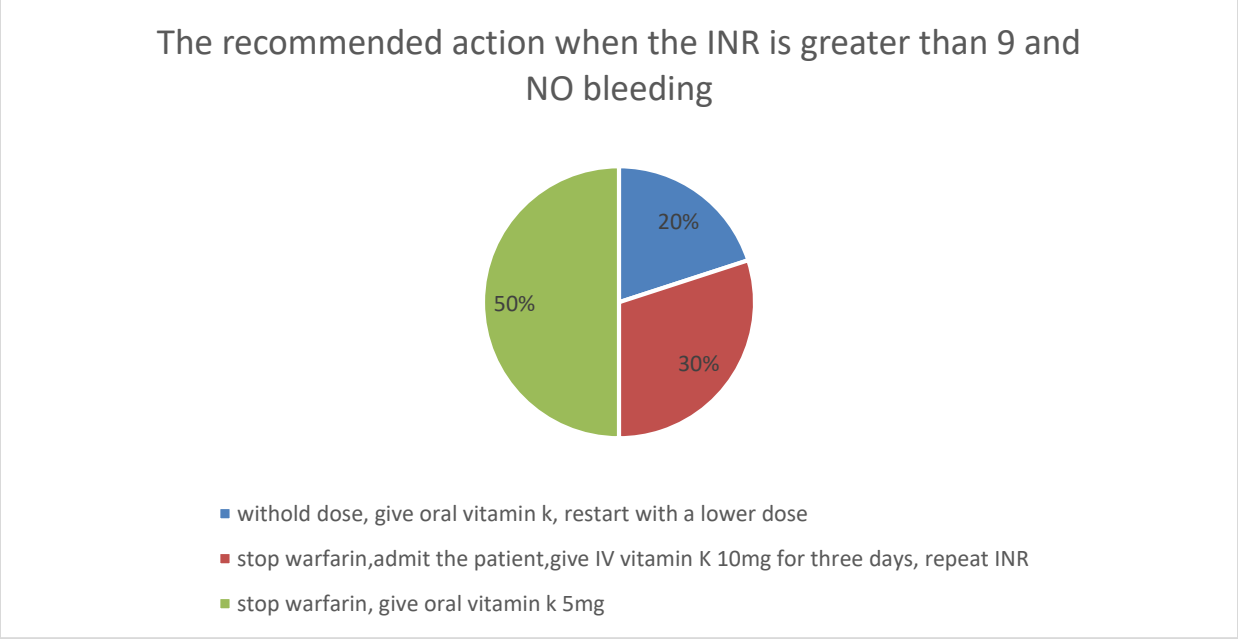

Figure 4. 3: The recommended action when INR is greater than 9 and NO bleeding

4.4 Delphi round two

After getting panelists responses from the first round of the Delphi study, the composed information was transformed into a well-structured questionnaire. There were no added statements recommended in the free text responses in round one. Each Delphi panelist was given a second questionnaire to assess the statements detailed by the researcher based on the information compiled in the first round. Consequently, a Delphi panelist was obligated to rank statements in a likert scale format (1-4) whereby '1' represented 'definitely not include' and '4' represented 'definitely include' to establish preliminary priority among statements (Appendix VI).

For every statement, the number of panelists who had ranked the statement and the allocation of marks were summarized. The panelists' response rate was computed as the total number of panelists who completed round two of the questionnaires as a proportion of those who completed round one. There was a 100% response rate. From the results of round two Delphi study, areas of similarity and dissimilarity were recognized. Consensus was created and definite conclusions were obtained among the panelists' responses. Statements were prioritized if they got support from at least 70 % of panelists' at a rate of three or higher on a four point Likert-type scale and the median was at 3 or higher. There were two statements that did not gain consensus at this stage. Those were carried forward to Delphi round 3.

4.4.1 Patient risk assessment

The patient risk assessment features that gained consensus in round two of warfarin Delphi study are shown in Table 4.8.

Table 4. 8 Patient risk assessment features in round two warfarin Delphi study

	LIKERT SCALE RESPONSES			
Characteristic	**Definitely not include n (%)**	**Maybe not include n (%)**	**Maybe include n (%)**	**Definitely include n (%)**
Patient information prior to warfarin initiation				
Risk factor evaluation	0	0	0	10 (100%)
Social history	0	0	0	10 (100%)
Adverse reactions	0	0	0	10 (100%)
Drug history	0	0	4 (40%)	6 (60%)
Blood workup	0	0	0	10 (100%)
Medical history	0	0	0	10 (100%)
Patient information to collect in clinic visits				
Clotting symptoms	0	0	0	9 (90%)
Bleeding tendencies	0	0	0	10 (100%)
INR	0	0	0	10 (100%)
Adverse drug reactions	0	0	0	10 (100%)
Blood workup	0	4 (40%)	2 (20%)	4 (40%)
Patient adherence	0	0	6 (60%)	4 (40%)
Information to convey about warfarin anticoagulation				
Contraindications for warfarin	2 (20%)	0	2 (20%)	6 (60%)
Drug interactions	0	0	0	10 (100%)
Warfarin Adherence	0	0	0	10 (100%)
Need for monitoring INR	0	0	0	10 (100%)
Food interactions	0	0	0	10 (100%)
Side effects of warfarin	0	0	0	10 (100%)
Warfarin pharmacology	0	10 (100%)	0	0
Risks that increase bleeding and thromboembolism				
Comorbidities	0	0	0	10 (100%)
Age	0	0	0	10 (100%)
Medication interactions	0	2 (20%)	0	8 (80%)
Bleeding tendency	0	2 (20%)	0	8 (80%)
INR range	0	4 (40%)	0	6 (60%)
Adherence to warfarin	0	2 (20%)	0	8 (80%)
Genetics	0	5 (50%)	0	5 (50%)
Alcohol intake	0	0	0	10 (100%)
Duration of treatment	0	3 (30%)	0	6 (60%)
Clinical tools to assess bleeding risk				
$HAEMORR_2HAGES$ score	0	0	0	10 (100%)
HAS-BLED score	0	9 (90%)	0	0
OBRI	0	9 (90%)	0	0
INR test	0	0	0	10 (100%)
Clinical tools to assess stroke risk				
$CHA_2DS_2VAS_C$	0	0	0	10 (100%)
SRAT	0	5 (50%)	5 (50%)	0
Comorbidities	2 (20%)	4 (40%)	0	4 (40%)
Stroke	0	6 (60%)	0	4 (40%)
Age	0	6 (60%)	0	4 (40%)
Cardiovascular risk profile	0	6 (60%)	0	4 (40%)

All the panelists 10 (100%) fully supported the collection of medical history, blood workup, adverse drug reactions, social history and risk factors during the initial assessment prior to initiation of warfarin therapy. Six (60%) of the panelists thought it is necessary to collect patient's drug history. Bleeding tendencies, INR levels, and adverse drug reactions should always be collected during every patients' clinic visit according to all study participants. Nine (90%) of the panelists proposed the inclusion of patients' clotting symptoms onto the medical report of every clinic visits. Blood workup and adherence to warfarin therapy did not gain adequate consensus to be included in the consensus statement.

The Delphi panelists recommended that patients should know about side effects and food interactions associated with warfarin therapy. Also, patients should know about the importance of monitoring INR levels. Six (60%) of the respondents supported the communication of warfarin contraindications to the patients. In addition, all of the respondents suggested that it may not be of much importance to let the patients know about the warfarin pharmacology because of the complexity of such information to non-scholars of medicine. All of the panelists suggested that age, comorbidities, drug interactions, bleeding tendancies, adherence to warfarin and alcohol intake are among the risk factors that may increase bleeding and thrombotic events. Six (60%) of the panelists suggested that treatment duration was a factor affecting bleeding tendencies. Five (50%) of the participating panelists suggested that genetics affect bleeding and thrombotic events.

All of the panelists stated that HAEMORR$_2$HAGES score clinical tool was available to assess a patients' bleeding risk, though it was used on informed basis by clinicians rather than as a standard tool. Nine (90%) of the panelists suggested that OBRI and HAS-BLED score tools were not widely used tools in their clinical setting to measure bleeding tendencies.

All the panelists stated that CHA_2DS_2VASc Score was a good tool to measure patients' stroke risk. Four (40%) of the respondents did not think that cardiovascular risk could be used as a measure of stroke risk for a patient. Age of the patient, Stroke, comorbidities and SRAT did not gain consensus from the Delphi panelists. Bruising and bleeding from anywhere in the body should be checked every time a medical specialist meets a patient on warfarin therapy. Pain and weakness were other symptoms that could be present but might not be directly related to warfarin therapy.

4.4.2 Warfarin dosing

4.4.2.1 Initial Warfarin dosing

All of the panelists stated that 5 mg was an available strength at Kenyatta National Hospital. However, most of them were not aware of the availability 2 mg, 3 mg, 1 mg strengths of warfarin. All of the panelists supported the initial dose of 5 mg p.o. OD for warfarin. Four (40%) of Delphi panelists stated a dose of 2.5 mg p.o OD could be used as an initial dose.

The Delphi panelists fully supported consideration of warfarin contraindications, drug interactions and bleeding risks versus clotting risk prior to initial dosing of warfarin. Comorbidities, sensitivity to warfarin and duration of warfarin use did not gain consensus among the panelists. All patients starting warfarin therapy, atrial fibrillation history, DVT patients, mechanical heart valves, inpatients and obese patients were deemed suitable to be on bridging with LMWH. All of the panelists recommended that the patients should receive the LMWH for 5 days until therapeutic INR was reached. Factors identified as affecting initial dosing in round two of warfarin Delphi study are shown in Table 4.9

Table 4. 9 Factors affecting initial warfarin dosing in round two Delphi study

	LIKERT SCALE RESPONSES			
Characteristic	**Definitely not include n (%)**	**Maybe not include n (%)**	**Maybe include n (%)**	**Definitely include n (%)**
Available strengths of warfarin at KNH				
5mg	0	0	0	10 (100%)
3mg	0	0	6 (60%)	4 (40%)
1mg	0	0	6 (60%)	4 (40%)
2mg	0	0	6 (60%)	4 (40%)
10mg	0	2 (20%)	8 (80%)	0
Factors to consider before warfarin initiation				
Bleeding and clotting risk	0	0	0	10 (100%)
Contraindications of warfarin	0	0	0	10 (100%)
Drug interactions	0	0	0	10 (100%)
Duration of warfarin use	1 (10%)	5 (50%)	0	4 (40%)
Comorbidities	0	2 (20%)	4 (40%)	4 (40%)
Sensitivity to warfarin	3 (30%)	3 (30%)	2 (20%)	2 (20%)
When to consider LMWH therapy				
Patients with DVT	0	0	8 (80%)	2 (20%)
All patients starting warfarin	0	2 (20%)	0	8 (80%)
Patients with afib history	0	2 (20%)	8 (80%)	0
Presence of mechanical heart valves	0	2 (20%)	8 (80%)	0
Obese patients	0	2 (20%)	8 (80%)	0
Patients with renal dysfunction	0	2 (20%)	8 (80%)	0
Before surgery	0	0	0	10 (100%)
Inpatients	0	2 (20%)	8 (80%)	0
Duration to receive another form of anticoagulation				
For 5 days until therapeutic INR is reached	0	0	0	10 (100%)
Atleast 3 days	2 (20%)	8 (80%)	0	0

4.4.2.2. Long-term maintenance dosing of patients on warfarin

All of the respondents recommended various factors to be considered before warfarin dose adjustments. These include INR levels, diet, adherence to warfarin, drug interactions and adverse drug interactions.

Seven (70%) of the panelists also suggested that it is important to consider comorbidities and warfarin contraindications before adjusting warfarin dose while 7 (70%) of the panelists suggested that indication for warfarin use might not be important to consider before warfarin dose adjustments. Nine (90%) of the respondents suggested that dose adjustments of warfarin should be based on total weekly doses while 7 (70%) of responses did not support the use of daily doses of warfarin as a basis for dose adjustments. There was a lot of differing opinions when deciding on how INR levels should be monitored to ensure stability when altering the dose of warfarin whereby a consensus was not reached. Therefore, this statement was carried forward to round three of the Delphi study. Features of long-term maintenance dosing in round two of warfarin Delphi study are shown in Table 4.10

Table 4. 10 Features of warfarin maintenance dosing in round two Delphi study

	LIKERT SCALE RESPONSES			
Characteristic	**Definitely not include n (%)**	**Maybe not include n (%)**	**Maybe include n (%)**	**Definitely include n (%)**
Factors to consider before warfarin dose adjustments				
INR levels	0	0	0	10 (100%)
Adverse drug reactions	0	0	0	10 (100%)
Diet	0	0	0	10 (100%)
Drug interactions	0	0	0	10 (100%)
Adherence to warfarin	0	0	0	10 (100%)
Comorbidities	0	0	3 (30%)	7 (70%)
Contraindications	0	2 (20%)	0	8 (80%)
Indications of warfarin	0	7 (70%)	3 (30%)	0
Basis of warfarin dose adjustments				
Weekly doses of warfarin	0	0	0	9 (90%)
Daily doses of warfarin	7(70%)	0	3 (30%)	0
Frequency of monitoring INR levels to ensure stability				
Weekly	0	4 (40%)	2 (20%)	2 (20%)
Every 3 days	2 (20%)	6 (60%)	1 (10%)	2 (20%)
Taken 3-5 days after adjusting doses then weekly thereafter	2 (20%)	0	0	6 (60%)

4.4.3 Monitoring of Warfarin treatment

4.4.3.1. Laboratory monitoring

Nine (90%) of the panelists supported that INR, full haemogram and pregnancy tests should be carried out on patients before initiation and during warfarin therapy. Liver function tests, urea electrolytes creatinine tests and prothrombin time were also stated as important tests but not crucial to be done. Nine (90%) of the panelists recommended that INR levels should be monitored daily/alternate days after warfarin initiation until it is stable and lies within a suitable INR range. The study also considered another group of patients who have been newly discharged on warfarin therapy. In this case, all of the panelists proposed that INR levels should be obtained after two days. In yet another special circumstance whereby there is bridging with LMWH, All of the panelists advised that INR can be checked if it is within therapeutic range, in either 2 or 3 days after warfarin initiation.

The study also sought to find out in which situations a repeat INR is most suitable. From the list derived from round one of the Delphi study, all of the panelists submitted that, a repeat of INR levels in the next 2-3 days is useful in cases of INR instability, during warfarin initiation, after warfarin dose adjustment and when bridging with LMWH. In the instance whereby a patient presents with INR less than 0.5, all of the panelists suggested that investigations should be done on their diets, dose should then be increased and warfarin adherence investigated. Nine (90%) of the panelists also recommended that drug interactions should be investigated in this situation. The features of laboratory monitoring in round two of warfarin Delphi study are shown in Table 4.11.

Table 4. 11 Features of laboratory monitoring of warfarin in round two Delphi study

	LIKERT SCALE RESPONSES			
Characteristic	**Definitely not include n (%)**	**Maybe not include n (%)**	**Maybe include n (%)**	**Definitely include n (%)**
Laboratory tests before and during warfarin therapy				
INR test	0	0	0	10 (100%)
Full haemogram	0	0	0	9 (90%)
Pregnancy	0	0	0	10 (100%)
UECs	0	0	6 (60%)	4 (40%)
Liver function tests	0	6 (60%)	0	4 (40%)
Prothrombin time	0	6 (60%)	0	4 (40%)
Frequency of monitoring INR after warfarin initiation				
Daily/alternate days	0	0	0	9 (90%)
Every 3 days	0	6 (60%)	3 (30%)	1 (10%)
Four times during 1st week of therapy	0	6 (60%)	3 (30%)	0
Weekly	3 (30%)	3 (30%)	3 (30%)	0
INR levels <0.5				
Increase dose of warfarin	0	0	0	10 (100%)
Investigate diet	0	0	0	10 (100%)
Investigate possible drug interactions	0	0	0	9 (90%)
Check warfarin adherence	0	0	0	10 (100%)
Introduce LMWH	0	6 (60%)	4 (40%)	0
INR check after hospital discharge				
After 1 week	0	3 (30%)	0	6 (60%)
After 2 days	0	0	0	10 (100%)
After 3 days	0	3 (30%)	3 (30%)	4 (40%)

4.4.3.2 Factors that affect levels of INR

The study sought to find out which factors that influence INR levels are critical to maintaining a suitable therapeutic range. All of the panelists stated that diet, administering concurrent medication, non-adherence to warfarin therapy and comorbidities were the main factors influencing INR levels. All the Delphi panelists strongly indicated that aspirin, paracetamol and fluconazole were among the medications that should be prescribed with care when a patient is to

be initiated on warfarin therapy. They also suggested that warfarin guidelines should be present in every prescribing station. This would prevent mistakes during prescribing of warfarin. The panelists also advised on avoiding dietary supplements and foods with vitamin K or taking them under strict supervision of the primary care giver. Factors that affected INR levels in round two of warfarin Delphi study are shown in Table 4.12.

Table 4. 12 Factors that affect INR in round two Delphi study

	LIKERT SCALE RESPONSES			
Characteristic	**Definitely not include n (%)**	**Maybe not include n (%)**	**Maybe include n (%)**	**Definitely include n (%)**
Factors affecting INR levels				
Lab errors	0	1 (10%)	6 (60%)	3 (30%)
Diet	0	0	0	10 (100%)
Concurrent medication	0	0	0	10 (100%)
Non-adherence to warfarin therapy	0	0	0	10 (100%)
Comorbidities	0	0	0	10 (100%)
Medications contraindicated when on warfarin				
Other anticoagulants	6 (60%)	0	0	4 (40%)
Aspirin	0	0	0	10 (100%)
Paracetamol	0	3 (30%)	7 (70%)	0
Antifungals	0	0	0	10 (100%)
Dietary supplements when on warfarin				
Avoid if possible	0	0	0	10 (100%)
Avoid supplements with vitamin K	0	0	0	10 (100%)
Vitamin K containing foods when on warfarin				
Avoid them if possible	0	0	10 (100%)	0
Take them in moderation	0	0	0	10 (100%)

4.4.4 Reversal of over-anticoagulation with Warfarin

In the process of warfarin therapy, INR levels may abruptly rise to high levels increasing the chances of bleeding in patients. So as to prevent this from occurring, the study sought to discuss the instances in which INR levels may be high and how medical practitioners should handle such situations appropriately. All the panelists stated that INR levels of greater than 5 put all patients at an increased risk of bleeding. From the various suggestions offered in the first round of the Delphi study, in a case whereby INR is greater than the therapeutic range but less than 5 and no bleeding, all the panelists recommended titrating the dose down and repeating INR in three days. However, in a case whereby INR is between 5-9 and no bleeding, the Delphi panelists did not reach a consensus. This statement was then presented to the third round of the Delphi study. However, in the case whereby INR is greater than 9 and NO bleeding, warfarin administration should be stopped immediately and an oral dose of vitamin K 5 mg administered. Features of reversal of over-anticoagulation with warfarin in round two are shown in Table 4.13

Table 4. 13 Reversal of anticoagulation with warfarin in round two Delphi study

	LIKERT SCALE RESPONSES			
Characteristic	**Definitely not include n (%)**	**Maybe not include n (%)**	**Maybe include n (%)**	**Definitely include n (%)**
INR level high posing risk of bleeding				
>3	0	6 (60%)	0	3 (30%)
>4	3 (30%)	6 (60%)	0	0
>5	0	0	0	10 (100%)
Action when INR is > therapeutic value but < 5 and NO bleeding				
Withhold dose, restart with lower dose	3 (30%)	6 (60%)	1 (10%)	0
Titrate dose down, repeat INR in three days	0	0	0	10 (100%)
Stop warfarin, skip dose, monitor INR	3 (30%)	6 (60%)	0	0
Action when INR is 5-9 , NO bleeding				
Withhold dose, give oral vitamin K, restart with a lower dose	0	3 (30%)	0	5 (50%)
Stop warfarin, omit dose, give vitamin K	0	3 (30%)	0	5 (50%)
Stop warfarin, repeat INR in 2-3 days, if INR stabilizes start warfarin at low doses	0	5 (50%)	0	4 (40%)
Stop warfarin, give vitamin K intramuscularly/ intravenously or orally STAT dose of 10 mg	5 (50%)	3 (30%)	0	0
Recommended action when the INR is > 9 and NO bleeding				
Withhold dose, give oral vitamin K, restart with a lower dose	0	5 (50%)	3 (30%)	0
Stop warfarin, admit the patient, give IV vitamin k 10mg for three days, repeat INR	0	5 (50%)	3 (30%)	1 (10%)
Stop warfarin, give oral	0	0	0	10 (100%)

vitamin k 5 mg				

4.5 Delphi round three

In this round, each Delphi panelist received a third questionnaire which had all statements that reached consensus and those that did not reach consensus in the preceding round. It was noted that only two statements did not reach consensus from round two. Each panelist who participated in round two of the Delphi study was shown the scores for each of the two statements carried forward. The panelists then considered the ranks assigned by the other panelists. Even after a repeat of the ranking process, the two statements did not gain sufficient support. However, the panelist response rate still remained at 100%. The two statements that did not gain consensus after the third round of the Delphi study are shown in Appendix VII.

4.5.1 Warfarin dosing

4.5.1.1 Initial Warfarin dosing

When altering the dose of warfarin, INR levels should be monitored keenly so as to ensure the therapeutic levels are maintained. The study panelists did not reach a consensus on this statement. Most of them stated that the frequency of monitoring INR levels varied depending on a number of reasons. In scenarios whereby it was not possible for a patient to return to KNH every three to five days due to financial constraints, they were given an appointment on a weekly or biweekly basis. Further, the patient turnover in the clinics was seen to be very high. This led to clinic appointments being scheduled to accommodate the high population served by the outpatient clinics.

4.5.2 Reversal of over- anticoagulation with Warfarin

The recommended action in the case whereby INR is between 5-9 but there is no evidence of bleeding, the study panelists gave varied ways of dealing with the situation. All of them stated they had used more than one procedure. This was informed by their own judgement of the situation as there was no standardized procedure to deal with this scenario. All of the panelists proposed that warfarin should be stopped. However, the action to follow next was not clear. It was also not clear what dose, strength, frequency of administration, route of administration and duration of administration of Vitamin K should be given. Five (50%) of the panelists advised on adjusting the dose of warfarin downwards. However, it was not clear how this should be done.

5.0 CHAPTER FIVE: DISCUSSIONS, CONCLUSIONS AND RECOMMENDATIONS

This chapter considers the results generated and evaluates them according to previous studies done. It also attempts to describe the inconsistencies between the study findings and other studies as well. Study limitations, conclusions and recommendations are also included.

5.1 Discussion

The Delphi study design was employed to develop a consensus statement for warfarin use that will guide clinician decision making. This is the first study that has utilized the Delphi design to identify opinions of healthcare workers on safe warfarin use at KNH. The following were the major findings of the warfarin Delphi study.

The study also revealed that the patient file was the best tool to collect patient information whereas face to face discussions about anticoagulation with warfarin was the most recommended way of preventing risks associated with the drug. $CHA_2DS_2VAS_c$ score was the most preferred method of assessing a patient's stroke risk factor while the $HAEMORR_2HAGE$ score was preferred for assessing the patient's bleeding risk. The initial dosage of warfarin was recommended at 5 mg per oral once daily. The study strongly recommended that patients should avoid the use of complementary medicines during warfarin therapy whereas diet had to be strictly controlled.

The most recommended LMWH in KNH is enoxaparin. Warfarin dose adjustments should be made based on total weekly doses rather than daily doses. Warfarin should be closely monitored throughout its use. An INR of between 2-3 was found to be ideal for most disease conditions requiring warfarin anticoagulation. In the presence of clinically significant bleeding, the study recommended warfarin to be stopped, IV vitamin K given, blood transfusion and fresh frozen plasma administered.

These observations will form the pillars of enhanced safe use of warfarin at KNH. Specifically the focus will be on safeguarding patient safety during warfarin therapy, regular patient monitoring, a local warfarin dosing algorithm, ensuring patient safety during long term warfarin therapy and how to deal with warfarin toxicity.

5.1.1 Safeguarding patient safety during Warfarin therapy

Warfarin is a high alert medicine that has a very narrow therapeutic index. For this reason, its use is associated with complications of bleeding and thromboembolic events (Ageno W, 2012). As

revealed in our study and in a study done by Lekshmi et al (Dharmarajan, 2008), the basics of patient risk assessment before initiating warfarin therapy are paramount. A focused history taking including comorbidities, concurrent medication (prescribed drugs, over the counter drugs and complementary medications), social history including alcohol intake form part of critical information required. Laboratory tests such as baseline INR and full haemogram were also strongly recommended.

Patient counselling was found to be important. The health and social care board (HSCB) in Northern Ireland recommends this should be done before initiation of warfarin therapy, after a patient is discharged from hospital and it should be an ongoing process as part of every clinic visit. In this study, face to face counselling sessions were highly prioritised 9 (91%). In the same study done by Lekshmi et al (Dharmarajan, 2008), patient education was summarised into "3 Ds" namely Drug, Disease and Diet. The drugs the patient is currently taking including complementary medicines and over the counter drugs should be assessed. This was because medications such as antibiotics and analgesics have been stipulated to cause changes in INR. Many diseases may also alter INR levels. These mostly include thyroid disorders and liver disease. Dietary preferences of every individual should also be reviewed critically. Patients should be counselled on avoiding drastic variations in their diet. This is especially for foods containing Vitamin K (Dharmarajan, 2008) (Beier MT, 2005). Herbs such as garlic were found to cause a potentiation of clinical effects of warfarin (Bordia A, 1978). However, in a placebo-controlled study in 48 patients stabilized on warfarin, there was no change in INR in those receiving 5 mL of aged Garlic extract (Kyolic) twice daily for twelve weeks. (Macan H, 2006).

There are a number of risk factors that may increase the risk of bleeding and thromboembolic events that the patient should be assessed for. In accordance with our findings, stroke risk, active bleeding lesions and bleeding tendencies (such as Thrombocytopenia), comorbidities (such as chronic kidney disease and liver diseases) were among the most important. In a study done by Gwent healthcare NHS Trust (Gwent healthcare NHS Trust, 2010), a comprehensive Risk assessment tool was developed. This tool outlined all the risk factors that can increase the risk of bleeding and thromboembolic events in an individual. This tool is in agreement with this study. However, it had additional parameters that were not among the risk factors considered in this study. The tool suggested laboratory parameters such as prothrombin time, activated partial

thromboplastin time (APTT), platelet count and INR levels are important in formation that could increase the bleeding and thromboembolic risk in a patient.

According to the European society of cardiology (European Society of Cardiology, 2012) , the CHA_2DS_2VASc score was recommended for assessing patient stroke risk while the $HAEMORR_2HAGES$ score was recommended for assessing patient bleeding risk. The results of this study also proposed that the above tools were ideal for the Kenyan setting. Furthermore, in the case of adverse reactions after warfarin is taken, this study revealed that unusual bleeding occurring should be immediately assessed by a physician. However, our study did not look into the bleeding scores that would warrant immediate attention.

5.1.2 Warfarin dosing algorithm

In this study, all panelists were in consensus that a standardized warfarin dosing algorithm should be in place to facilitate initial warfarin therapy. This tool is however not currently in use in KNH. As much as the standardized warfarin dosing algorithm gained consensus from all the panelists, a study by Scott et al (Scott E. K, 2016), showed that 16% of patients were found to require human intervention over a standardized dosing algorithm. This was mostly evident in patients who had congestive heart failure.

All the panelists stated that they were aware of the availability of the warfarin sodium 5 mg tablet. This strength was also enlisted in the Kenya essential medicines list (KEML) (Ministry of Health, 2016) and was readily available in KNH. In this study, an initial 5 mg per oral once daily dose of warfarin was fully supported. However, in a systematic review done by Carl et al (Carl H, 2010), there is still a lot of uncertainty surrounding a 5mg or 10mg starting dose of warfarin. They revealed that different starting doses were appropriate for different populations. For instance in the elderly, a lower starting warfarin dose led to lower INR therefore it was more suitable.

In this study, patients to be newly initiated on warfarin therapy should be assessed for features that might predispose them to side effects of warfarin. The instances in which this study proposed a lower initiation dose were situations in which a patient had a high bleeding risk or when a patient was highly sensitive to warfarin. This is consistent with a study done by Ageno et al (Ageno W, 2012) that indicated initial warfarin dosing should be specifically tailored depending on patient bleeding risk, goal of INR, sensitivity to warfarin and potential drug/food /herb interactions. This study also revealed that bridging therapy with LMWH was strongly

suggested in patients who required surgical or invasive procedures. In the same respect, a study by Pengo et al (Pengo V, 2009)showed no suitably recognized bridging regimen tailored for patients who require surgical or invasive procedures. In another study by Mark et al in (Mark L, 1996), other patients with conditions such as Deep vein thrombosis (DVT) were deemed to also benefit from LMWH more than unfractionated Heparin as the former does not require hospitalization. LMWH should be administered for 5 days until therapeutic INR was reached. This is in agreement with the Chest guidelines (Ageno W, 2012).

5.1.3 Long-term Warfarin therapy

Medical practitioners should consider the strengths of warfarin available in prescribing doses. The state of Queensland guidelines and protocol advisory committee (Queensland, 2012), formulated a subsequent maintenance dosing regimen for warfarin (INR range 2-3). A separate dose modification regimen was proposed for an INR range (2.5-3.5) for patients with mechanical heart valves. The same institution agreed with this study in that warfarin dose adjustments of warfarin should be based on total weekly doses for warfarin rather than daily doses. This was because total weekly doses allow for dose adjustments for lower dose regimens that would not be possible with daily doses of warfarin.

The guidelines also suggested that warfarin dose adjustments should be made based on whether the patient has had previous INR level variations. In addition to that, variations in diet and compliance with the dosing regimen should also guide dose adjustments. After altering the dose of warfarin, ambulatory clinical practice guidelines (University of Wisconsin, 2012) recommended INR levels to be checked every 3-5 days if there is any start/ stop of an interacting medication, change in diet, change in activity or any other change that could affect INR. INR levels should also be checked every 1-2 weeks if warfarin doses needed adjustment by 5-10%.

5.1.4 Patient monitoring during Warfarin therapy

As evident in this study, when initiating and during warfarin therapy, the most important tests to be carried out include baseline INR, full blood count and pregnancy tests. In a study by Anich et al (Anich KV, 2005), a full blood count was shown to detect occult bleeding when haemoglobin levels decreased from the baseline. This is in agreement with the results in this study. However, the same study showed that although routine complete blood count monitoring provided some information, the decrease in haemoglobin levels was marginal. The study therefore concluded that routine blood count was unnecessary. The British Committee for Standards in Haematology

Guidelines (British Committee for Standards in Haematology, 2011) outlines in detail the targeted INR levels for various indications and the duration of treatment with warfarin. In this study, for most indications such as major surgery, DVT, Atrial fibrillation, rheumatic heart disease and transient ischemic attacks, the INR should be between 2-3. This conforms to the above international guidelines.

INR should be frequently monitored after initiation of warfarin until it is stable. In this study panelists suggested that INR levels should be checked every 2-3 days or on alternate days until INR is within therapeutic range on 2 consecutive INR checks. The Adult-Ambulatory clinical practice guidelines (University of Wisconsin, 2012) agrees with this finding. INR levels of recently discharged patients should be checked every 2 days until stability is achieved whereas in instances where there is bridging with LMWH, every 2-3 days is sufficient.

It is paramount that in prescribing of warfarin, all factors that affect INR are considered. The guidelines on oral anticoagulation with warfarin (British Committee for Standards in Haematology, 2011) proposed that periods of acute illness such as infections might trigger significant changes in INR. In this respect, medical practitioners in this study recommended the consideration of drug interactions, herbal and vitamin products, alcohol intake, foods/drinks/ food supplements and clinical indications among the factors that may affect INR. Guidelines for primary care on warfarin suggest the use of the latest British National Formulary in detecting drug interactions with warfarin (Joint Formulary Committee, 2013). In the findings, analgesics such as paracetamol and Aspirin were highlighted as medications that readily alter INR levels. The British society of Hematology recommends an INR to be performed after 3-5 days when an interacting drug is prescribed to a patient on warfarin (British Committee for Standards in Haematology, 2011). Patients are advised to inform their clinicians when they start taking new herbal, vitamin products, foods and supplements. In the study, most panelists recommended herbal products should be completely avoided and if this was impossible, these patients should be closely monitored.

Foods can also affect INR. This is because drastic changes in diet greatly influence INR levels and can lead to hindrances in anticoagulation control. Foods especially leafy green vegetables such as broccoli, kales and sprouts have been found to affect the control of anticoagulation due to their vitamin K content. The same guidelines proposed by HSCB (British Committee for

Standards in Haematology, 2011) support the study findings in ensuring foods are also carefully monitored so as to keep the INR stable during the duration of warfarin therapy.

5.1.5 Warfarin toxicity

In this study, an INR level of >5 was found to be considerably high to put a patient at bleeding risk. Several studies and guidelines have varying procedures to follow when INR levels are higher than the target INR range. For instance, when INR is higher than 5-9 and No bleeding is present, the health and social care board (British Committee for Standards in Haematology, 2011) recommends stopping warfarin by 1-2 doses and lowering the maintenance dose when the INR drops to below 5 while investigating the cause. In another study (Husband A, 2009), it was suggested that for asymptomatic patients in this category, the patient's usual dose of warfarin should be omitted, a repeat INR should then be done a few days after the fact and warfarin restated once the INR fell below 5. The United states guidelines on the same suggest omitting warfarin and monitoring more frequently if there is no bleeding present. However, if there is a high risk of bleeding, they recommend administration of Vitamin K (1–2.5 mg orally; 2–4 mg orally if more urgent reduction needed (Ansell J, 2001).The differing opinions amongst study panelists in this study did not yield a consensus. This provides a gap for future research to be conducted so as to yield suitable consensus on safe warfarin reversal procedures.

5.1.6 Study limitations

One of the main challenges encountered when carrying out the Delphi study was time delays in data collection process. The formulation of questionnaires for the subsequent rounds of the study was labour intensive and time consuming. This study was based on subjective reasoning. The disagreement in responses between the expert panel was evident in the three rounds of questionnaires.

Our study was conducted based on the subjective reasoning of the experts. Thus, besides the frequent disagreement in responses between the consulted health professionals, other experts who were not included in our study may not agree with the results obtained.

Response bias was another limitation encountered in this study. This is common in a likert scale type survey. The statements presented in the second and third round of the Delphi study required the panelists to indicate whether the response whether the statement should be included in the consensus statement. The categories included a range of 1-4, where 1= "definitely not include", 2= "maybe not include", 3= "maybe include" and 4= "definitely include". It was discovered that

in most statements the panelists selected either 1 or 4. Due to the nature of this study, it was not possible to eliminate response bias.

5.2 Conclusion

Warfarin is a high alert medication that is complex. It requires consistent monitoring to prevent unwanted adverse effects such as bleeding when the INR is higher than the target therapeutic range. When the INR is sub therapeutic, a patient is also at an increased risk of developing thromboembolic events.

The study was able to develop a consensus statement for safe warfarin use by an expert panel using the Delphi method. This consensus statement can be used to offer warfarin anticoagulation services in the cardiothoracic surgery clinic, haemato-oncology clinic and medical clinic. Further studies are however required in low resource settings to validate the consensus statement so that it can be used in clinical practice.

5.3 Recommendations

5.3.1 Recommendations for local guidelines for anticoagulation with warfarin in KNH

A consensus statement is a backbone for further research that would lead to the development of local guidelines concerning anticoagulation using warfarin. Local guidelines would promote easier translation of knowledge into practice. This is because the guidelines would utilize available resources in anticoagulation service delivery in the Kenyan setting.

5.3.2 Recommendations for future research

This study has revealed more gaps for future research in the field of ambulatory anticoagulation with warfarin. For instance, it was evident that warfarin reversal procedures are not clear. In this setting, there was no consensus arrived at in the statement dealing with suitable warfarin reversal procedure when INR was between 5-9 but there is no bleeding. This statement will require further research. When altering the dose of warfarin, INR levels should also be monitored to ensure their stability. The study did not gain a consensus on this statement. There were varying responses on the frequency of monitoring INR in this case. Some responses stated INR should be checked every three to five days while others stated weekly. Further studies can be done to look

for standardized time durations while monitoring INR that is suitable for the KNH setting and its patients.

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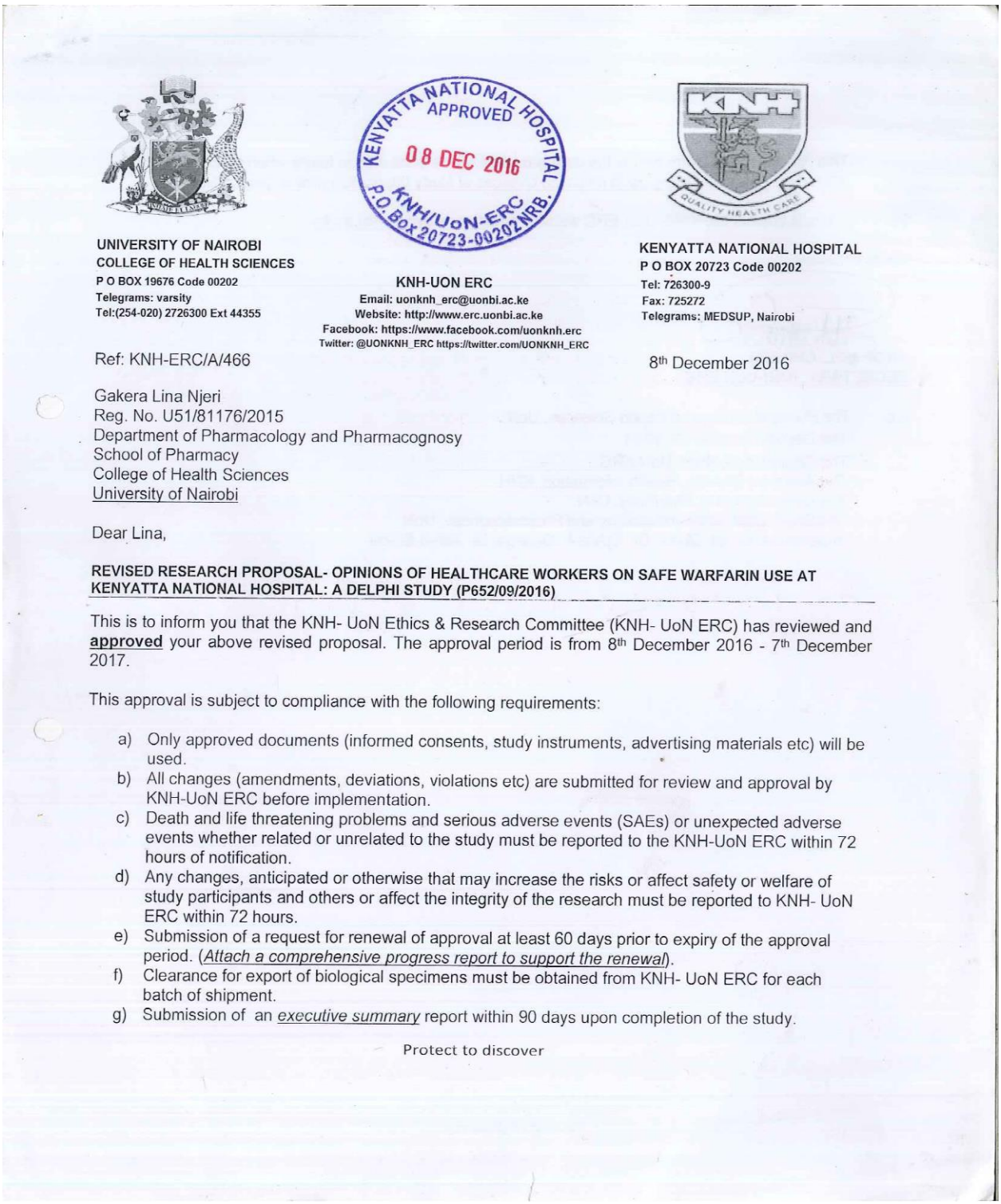
APPENDICES

Appendix I: Study Approval Letter from KNH-UoN / ERC



KENYATTA NATIONAL HOSPITAL APPROVED 08 DEC 2016 KNH/UoN-ERC P.O. Box 20723-00202 NRB.

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Ref: KNH-ERC/A/466

8th December 2016

Gakera Lina Njeri
Reg. No. U51/81176/2015
Department of Pharmacology and Pharmacognosy
School of Pharmacy
College of Health Sciences
University of Nairobi

Dear Lina,

REVISED RESEARCH PROPOSAL- OPINIONS OF HEALTHCARE WORKERS ON SAFE WARFARIN USE AT KENYATTA NATIONAL HOSPITAL: A DELPHI STUDY (P652/09/2016)

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 8th December 2016 - 7th December 2017.

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.

Protect to discover

Appendix II: Study Approval Letter from Kenyatta National Hospital

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

Lina Njeri Gakera
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 Medicine Department to enable you complete your study on ***"Opinions of healthcare workers on safe warfin use"*** at Kenyatta *National Hospital, Nairobi County, Kenya.*

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

DR. M. MURAGE
AG. HOD - MEDICINE

Copy to: Senior Nursing Officer Incharge - Medicine Department

Vision: A world class patient-centered specialized care hospital

ISO 9001: 2008 CERTIFIED

Appendix III: Consent Explanation Form for Healthcare Providers.

Serial Number…….

Study Title: Opinions of Healthcare workers on safe warfarin use at Kenyatta National Hospital: A Delphi study.

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

Principle Investigator: Dr. Gakera Lina Njeri, B.Pharm (Pharmacoepidemiology and Pharmacovigilance) P.O. Box 68397-00100, Nairobi. Mobile: +254725722395.

Supervisors:

Dr. Margaret Oluka, PhD. Department of Pharmacology and Pharmacognosy, School of Pharmacy, University of Nairobi.

Dr. Sylvia Adisa Opanga, Clinical Pharmacist, Department of Pharmaceutics and Pharmacy practice, School of Pharmacy, University of Nairobi.

I am Dr. Gakera Lina Njeri, conducting the above mentioned study to partly fulfill the requirements for a Master Degree of Pharmacy in Pharmacoepidemiology and Pharmacovigilance of the University of Nairobi.

Ethical Approval: Kenyatta National Hospital- University of Nairobi Ethical Research Committee, P.O.BOX 20723-00100, Nairobi. Tel 2726300 / 2716450 Ext 44102

The study

The Delphi technique is a well-known method to systematically explore priorities of groups of experts. The experts are usually selected to reflect current knowledge and perceptions in the field under consideration. The Delphi technique is based on a series of stages or iterations, where informed judgments on specific issues are collected from experts. The experts respond individually and anonymously to questions, to avoid influence of contextual factors such as personal characteristics, seniority and experience.

Purpose of the study

The purpose of this Delphi study is to develop a consensus statement for warfarin use to guide clinician decision making that will reduce adverse effects and improve anticoagulation management in Kenyatta National Hospital.

Participation

Why have I been invited to participate?

You have been approached as a participant based on your knowledge, training and experience in warfarin anticoagulation management in Kenyatta National Hospital.

What is expected of me as a participant?

Should you agree to participate in the study, your expertise shall be sought as a member of a Delphi panel of experts on anticoagulation with warfarin. Each participant of the Delphi panel will be issued a unique identifier that is only known to the researcher.

The Delphi process will consist of three rounds of questionnaires, response and feedback. A series of three questionnaires will be issued, each building on the previous one. Results from the rounds will be analyzed, compiled and returned to participants. In successive iterations, participants will be able to reevaluate responses of all the other participants and in turn their own.

Participants will be asked to complete each round of the Delphi exercise within three weeks. A reminder Email and phone message will be sent at the end of week two to prompt completion of the survey. The results will determine the levels of agreement in the panel and will be used to formulate a consensus statement on warfarin use for Kenyatta National Hospital.

Benefits for participation

There are no financial incentives or other direct benefits to you. However, the findings will be useful in improving the quality of care to patients on warfarin therapy. This will be through a systematic process of developing and refining a warfarin use consensus statement that will guide clinician decision making in anticoagulation management.

Risks associated with participation

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

Voluntary participation

Your participation is completely voluntary. 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.

Confidentiality

All data collected during this analysis shall be available only to the principle investigator. All information obtained from you will be kept in confidence. It shall be entered into a password protected computer to maintain confidentiality. It shall be availed to the KNH-UoN Ethics and Research Committee upon request

Appendix IV: Consent Form for Healthcare Providers.

STATEMENT OF CONSENT

I _____ willingly give my consent to participate and use the information obtained in this study. Dr. Gakera Lina Njeri has explained the nature of the study, my responsibilities as a participant and all the inconveniencies associated with voluntary participation.

Respondent Signature_____ Date_____

Mobile phone number_____

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.

Signature_____ Date_____

In case of any concern, you may contact the principle investigator on E-mail: linagakera@gmail.com or mobile: +254725722395 or KNH-UoN Ethics and Research Committee Secretary: Prof. Mark Chindia Tel +254 207 726300 ext. 44355, E-mail uonknh_erc@uonbi.ac.ke

Appendix V: Data collection tool for expert panelist: ROUND 1

Serial number----------

INSTRUCTIONS

The questionnaire has four sections labelled A, B, C, and D. The questions are open ended.

You are requested to answer the questions as honestly as possible in order to help us gather correct data for optimal utilization. You may contact Lina Njeri Gakera on 0725 722395 in case you wish to get further clarification.

DEMOGRAPHICS

1. Age----------Years
2. Gender----------1.M[ ] 2.F[ ]
3. Academic Qualifications
4. Years of experience in the institution--------Years

A. PATIENT RISK ASSESSMENT

1. Should there be patient initial assessment prior to initiating warfarin therapy?
    a) What patient information should be collected?
    b) What kind of tools should be used to record this?
2. Should there be treatment assessment for every patient for every clinic visit?
    a) What patient information should be recorded?
3. Is it important to educate patients on warfarin use?
    a) How should this be done?
4. Should a patient undergo counseling before initiation and during anticoagulation with warfarin therapy?
    a) What information regarding warfarin therapy should be communicated to the patient?
5. Before initiating warfarin therapy, what risk factors that may increase the risk of bleeding and thromboembolic events should the patient be assessed for?
    a) What clinical tools are available to assess a patients bleeding risk?
    b) What clinical tools should be used to assess a patient's stroke risk factor?
    c) At each encounter with a patient taking warfarin, what critical symptoms and signs of adverse effects should be assessed?

B. WARFARIN DOSING

Initial warfarin dosing

1. Should a warfarin dosing algorithm be in place to facilitate initial warfarin therapy?
2. What are the available strengths of warfarin in Kenyatta National Hospital?
    a) What should the initial dose of warfarin given to patients be?
3. What factors should be considered prior to initial dosing of warfarin?
    a) How should the patient bleeding risk affect initial dosing of warfarin?
    b) How should potential sensitivity to warfarin affect initial dosing?
    c) How does the indication for anticoagulation affect initial dosing?
    d) How does the goal on INR range affect initial dosing?
    e) How do potential drug /herb/food interactions affect initial dosing?
4. When should bridging therapy with a low molecular weight heparin be considered?
    a) For how long should a patient receive another form of anticoagulation such as low molecular weight heparins together with warfarin?
    b) Which low molecular weight heparins are recommended in KNH setting?
    c) Why do you recommend the above LMWH?

Subsequent maintenance dosing using warfarin

1. Should there be a standard warfarin maintenance dosing protocol with INR goals?
2. What factors are considered before dose adjustments of warfarin is made?
3. Should dose adjustments of warfarin be based on total weekly doses of warfarin or daily doses of warfarin?
4. When altering the dose of warfarin, how should INR levels be monitored to ensure stability?

C. MONITORING OF WARFARIN TREATMENT

Laboratory monitoring

1. What laboratory tests should be carried out on patients before initiation and during warfarin therapy?
2. What are the targeted INR levels for various indications?
    a) Major surgery (please give details/type of surgery) e.g. valve replacement
    b) Deep venous thrombosis (DVT)
    c) History of pulmonary embolism
    d) Rheumatic heart disease
    e) Atrial fibrillation
    f) Transient ischaemic attacks
    g) Other indication (please specify)
3. Should a baseline INR be done prior to initial dosing of warfarin?
4. How frequent should INR be monitored after initiation of warfarin until it is stable
5. Should INR levels be obtained for every clinic visit?
6. For women of child bearing age, should a pregnancy test be recommended before initiating warfarin?
7. If using INR monitoring services, what do you do if the patient presents with very low INR e.g. < 0.5?
8. Upon discharge from the hospital, after how many days should an INR be obtained for patients newly initiated on warfarin?
9. If bridging warfarin with Low molecular weight heparins, after how many days should INR be checked if it is within the therapeutic range?
10. A repeat INR in the next 2-3 days is useful in which circumstances?

Factors that affect INR

1. What are the factors that influence INR?
2. What medications are contraindicated when one is taking warfarin?
    a) Which medications increase INR?
    b) Which medications decrease INR?
3. What foods precaution should be taken when one is taking warfarin?
    a) Which foods increase INR?
    b) Which foods decrease INR?

4. How should dietary supplements be handled when one is taking warfarin?
5. How should Vitamin K containing foods be handled in patients taking warfarin?
6. How should herbal/complementary medicines be handled when one is taking warfarin?

D. WARFARIN REVERSAL

1. What INR level is considered high and puts a patient at a risk of bleeding?
2. What is the recommended action when the INR is greater than therapeutic value but less than 5 and NO bleeding?
3. What is the recommended action when the INR is between 5-9 and NO bleeding?
4. What is the recommended action when the INR is greater than 9 and NO bleeding?
5. What is the recommended action in the presence of any clinically significant bleeding where warfarin –induced coagulopathy is considered a contributing factor?

Appendix VI: Data Collection Tool for Expert Panelist: ROUND 2

Serial number----------

INSTRUCTIONS

The questionnaire has four sections labelled A, B, C, and D. The questions are structured with statements on a 4 point likert scale ranging from "1= Definitely not include" to "4= Definitely include". As a Delphi participant, please rank statements to establish preliminary priority among statements.

You are requested to answer the questions as honestly as possible in order to help us gather correct data for optimal utilization. You may contact Lina Njeri Gakera on 0725 722395 in case you wish to get further clarification.

DEMOGRAPHICS

1. Age----------Years
2. Gender----------1.M[ ] 2.F[ ]
3. Academic Qualifications

4. Years of experience in the institution--------Years

A. PATIENT RISK ASSESSMENT

For each of the following questions below, circle the response that best characterizes whether the statement should be included in the consensus document, where 1=definitely not include, 2=maybe not include, 3= maybe include and 4= definitely include.

1. What patient information should be collected in the initial assessment prior to initiating warfarin therapy?

	Definitely not include	Maybe not include	Maybe include	Definitely include
Medical history	1	2	3	4
Blood work	1	2	3	4
Drug history	1	2	3	4
Adverse drug reactions	1	2	3	4
Social history e.g. alcohol intake	1	2	3	4
Risk factor evaluation e.g. stroke risk, bleeding risk	1	2	3	4

2. What patient information should be recorded as treatment assessment for every clinic visit?

	Definitely not include	Maybe not include	Maybe include	Definitely include
Bleeding tendencies	1	2	3	4
INR	1	2	3	4
Adverse drug reactions	1	2	3	4
Blood work e.g. PT	1	2	3	4
Patient adherence to warfarin	1	2	3	4
Clotting symptoms	1	2	3	4

3. What information regarding warfarin therapy should be communicated to the patient?

	Definitely not include	Maybe not include	Maybe include	Definitely include
Warfarin pharmacology	1	2	3	4
Side effects	1	2	3	4
Food interactions	1	2	3	4
Drug interactions	1	2	3	4
Need for monitoring INR	1	2	3	4
Contraindications of warfarin	1	2	3	4

4. Before initiating warfarin therapy, what risk factors that may increase the risk of bleeding and thromboembolic events should the patient be assessed for?

	Definitely not include	Maybe not include	Maybe include	Definitely include
Age	1	2	3	4
Duration of treatment with warfarin	1	2	3	4
Genetics	1	2	3	4
Comorbidities	1	2	3	4
Alcohol intake	1	2	3	4
Compliance to warfarin treatment	1	2	3	4
Drug interactions	1	2	3	4
INR range	1	2	3	4
Bleeding tendency	1	2	3	4

a.) What clinical tools are available to assess a patients bleeding risk?

	Definitely not include	Maybe not include	Maybe include	Definitely include
HAEMORHAGES	1	2	3	4
INR	1	2	3	4
HAS-BLED	1	2	3	4
OBRI	1	2	3	4

b). what clinical tools should be used to assess a patient's stroke risk factor?

	Definitely not include	Maybe not include	Maybe include	Definitely include
Cardiovascular risk profile	1	2	3	4
CHADS2VAS2 score	1	2	3	4
Age	1	2	3	4
Stroke	1	2	3	4
Comorbidities	1	2	3	4
SRAT	1	2	3	4

c). At each encounter with a patient taking warfarin, what critical symptoms and signs of adverse effects should be assessed?

	Definitely not include	Maybe not include	Maybe include	Definitely include
Bleeding from anywhere	1	2	3	4
Bruising	1	2	3	4
Pain	1	2	3	4
Weakness	1	2	3	4

B. WARFARIN DOSING

Initial warfarin dosing

1. What are the available strengths of warfarin in Kenyatta National Hospital?

	Definitely not include	Maybe not include	Maybe include	Definitely include
1mg	1	2	3	4
2mg	1	2	3	4
3mg	1	2	3	4
5mg	1	2	3	4
10mg	1	2	3	4

a). What should the initial dose of warfarin given to patients be?

	Definitely not include	Maybe not include	Maybe include	Definitely include
5mg p.o OD	1	2	3	4
2.5mg p.o OD	1	2	3	4

2. What factors should be considered prior to initial dosing of warfarin?

	Definitely not include	Maybe not include	Maybe include	Definitely include
Contraindications of warfarin	1	2	3	4
Drug interactions	1	2	3	4
Bleeding risk vs. clotting risk	1	2	3	4
Comorbidities	1	2	3	4
Sensitivity to warfarin	1	2	3	4
Duration of warfarin use	1	2	3	4

3. When bridging therapy with a low molecular weight heparin should be considered?

	Definitely not include	Maybe not include	Maybe include	Definitely include
All patients starting warfarin	1	2	3	4
Patients with afib history	1	2	3	4
Presence of mechanical heart valves	1	2	3	4
DVT patients	1	2	3	4
Inpatients	1	2	3	4
Obese patients	1	2	3	4
Patients with renal dysfunction	1	2	3	4
Before surgery	1	2	3	4

a). For how long should a patient receive another form of anticoagulation such as low molecular weight heparins together with warfarin?

	Definitely not include	Maybe not include	Maybe include	Definitely include
For 5 days to until therapeutic INR is reached	1	2	3	4
Atleast 3 days	1	2	3	4

Subsequent maintenance dosing using warfarin

1. What factors are considered before dose adjustments of warfarin is made?

	Definitely not include	Maybe not include	Maybe include	Definitely include
INR levels	1	2	3	4
Diet	1	2	3	4
Adherence to warfarin	1	2	3	4
Drug interactions	1	2	3	4
Adverse drug reactions	1	2	3	4
Indications of warfarin	1	2	3	4
Comorbidities	1	2	3	4
Contraindications of warfarin	1	2	3	4

2. Should dose adjustments of warfarin be based on total weekly doses of warfarin or daily doses of warfarin?

	Definitely not include	Maybe not include	Maybe include	Definitely include
Total weekly doses	1	2	3	4
Daily doses of warfarin	1	2	3	4

3. When altering the dose of warfarin, how should INR levels be monitored to ensure stability?

	Definitely not include	Maybe not include	Maybe include	Definitely include
Weekly	1	2	3	4
Every 3 days	1	2	3	4
Taken 3-5 days after adjusting dose then weekly	1	2	3	4

C. MONITORING OF WARFARIN TREATMENT

Laboratory monitoring

1. What laboratory tests should be carried out on patients before initiation and during warfarin therapy?

	Definitely not include	Maybe not include	Maybe include	Definitely include
INR	1	2	3	4
FHG	1	2	3	4
Pregnancy test	1	2	3	4
UECs	1	2	3	4
LFTs	1	2	3	4
Prothrombin time	1	2	3	4

2. How frequent should INR be monitored after initiation of warfarin until it is stable?

	Definitely not include	Maybe not include	Maybe include	Definitely include
daily/alternate days	1	2	3	4
Weekly	1	2	3	4
every 3 days	1	2	3	4
four times during 1st week of therapy	1	2	3	4

3. If using INR monitoring services, what do you do if the patient presents with very low INR e.g. < 0.5?

	Definitely not include	Maybe not include	Maybe include	Definitely include
Increase dose of INR	1	2	3	4
Investigate diet	1	2	3	4
Investigate drug interactions	1	2	3	4
Check patient adherence	1	2	3	4
Introduce LMWH	1	2	3	4

4. Upon discharge from the hospital, after how many days should an INR be obtained for patients newly initiated on warfarin?

	Definitely not include	Maybe not include	Maybe include	Definitely include
After 1 week	1	2	3	4
After 2 days	1	2	3	4
After 3 days	1	2	3	4

5. If bridging warfarin with Low molecular weight heparins, after how many days should INR be checked if it is within the therapeutic range?

	Definitely not include	Maybe not include	Maybe include	Definitely include
After 2 days	1	2	3	4
After 3 days	1	2	3	4

6. A repeat INR in the next 2-3 days is useful in which circumstances?

	Definitely not include	Maybe not include	Maybe include	Definitely include
INR instability	1	2	3	4
Initiation of warfarin therapy	1	2	3	4
After warfarin dose adjustment	1	2	3	4
Bridging with LMWH	1	2	3	4
Presence of Adverse drug reactions	1	2	3	4

Factors that affect INR

1. What are the factors that influence INR?

	Definitely not include	Maybe not include	Maybe include	Definitely include
Lab errors	1	2	3	4
Diet	1	2	3	4
Concurrent medication	1	2	3	4
Non-adherence to warfarin	1	2	3	4
Comorbidities	1	2	3	4

2. What medications are contraindicated when one is taking warfarin?

	Definitely not include	Maybe not include	Maybe include	Definitely include
Other anticoagulants	1	2	3	4
Aspirin	1	2	3	4
Paracetamol	1	2	3	4
Antifungals e.g. fluconazole	1	2	3	4

3. How should dietary supplements be handled when one is taking warfarin?

	Definitely not include	Maybe not include	Maybe include	Definitely include
Avoid if possible	1	2	3	4
Avoid supplements with vitamin k	1	2	3	4

4. How should Vitamin K containing foods be handled in patients taking warfarin?

	Definitely not include	Maybe not include	Maybe include	Definitely include
Avoid them if possible	1	2	3	4
Take them in moderation	1	2	3	4

D. WARFARIN REVERSAL

1. What INR level is considered high and puts a patient at a risk of bleeding?

	Definitely not include	Maybe not include	Maybe include	Definitely include
>3	1	2	3	4
>4	1	2	3	4
>5	1	2	3	4

2. What is the recommended action when the INR is greater than therapeutic value but less than 5 and NO bleeding?

	Definitely not include	Maybe not include	Maybe include	Definitely include
Withhold dose, restart with a lower dose	1	2	3	4
Titrate the dose down, repeat INR in three days	1	2	3	4
Stop warfarin, skip dose, monitor INR	1	2	3	4

3. What is the recommended action when the INR is between 5-9 and NO bleeding?

	Definitely not include	Maybe not include	Maybe include	Definitely include
withhold dose, give oral vitamin k, restart with a lower dose	1	2	3	4
stop warfarin, omit dose, give vitamin k	1	2	3	4
stop warfarin, repeat INR in two or three days, if INR stabilizes start warfarin at low doses	1	2	3	4
stop warfarin, give vitamin k im or iv or PO STAT dose of 10mg	1	2	3	4

4. What is the recommended action when the INR is greater than 9 and NO bleeding?

	Definitely not include	Maybe not include	Maybe include	Definitely include
withhold dose, give oral vitamin k, restart with a lower dose	1	2	3	4
stop warfarin, admit the patient, give IV vitamin K 10mg for three days, repeat INR	1	2	3	4
Stop warfarin, give oral vitamin k 5mg	1	2	3	4

Appendix VII: Data Collection Tool for Expert Panelist : ROUND 3

Serial number----------

INSTRUCTIONS

The questionnaire has four sections labelled A, B, C, and D. The questions are structured with statements on a 4 point likert scale ranging from "1= Definitely not include" to "4= Definitely include". As a Delphi participant, please rank statements to establish preliminary priority among statements.

You are requested to answer the questions as honestly as possible in order to help us gather correct data for optimal utilization. You may contact Lina Njeri Gakera on 0725 722395 in case you wish to get further clarification.

DEMOGRAPHICS

1. Age----------Years
2. Gender----------1.M[ ] 2.F[ ]
3. Academic Qualifications

4. Years of experience in the institution--------Years

For each of the following questions below, circle the response that best characterizes whether the statement should be included in the consensus document, where 1=definitely not include, 2=maybe not include, 3= maybe include and 4= definitely include.

B. WARFARIN DOSING

Initial warfarin dosing

1. When altering the dose of warfarin, how should INR levels be monitored to ensure stability?

	Definitely not include	Maybe not include	Maybe include	Definitely include
Weekly	1	2	3	4
Every 3 days	1	2	3	4
Taken 3-5 days after adjusting dose then weekly	1	2	3	4

D. WARFARIN REVERSAL

1. What is the recommended action when the INR is between 5-9 and NO bleeding?

	Definitely not include	Maybe not include	Maybe include	Definitely include
withhold dose, give oral vitamin k, restart with a lower dose	1	2	3	4
stop warfarin, omit dose, give vitamin k	1	2	3	4
stop warfarin, repeat INR in two or three days, if INR stabilizes start warfarin at low doses	1	2	3	4
stop warfarin, give vitamin k im or iv or PO STAT dose of 10mg	1	2	3	4

Appendix VIII: CHADS2 Scoring System

	$CHADS_2$ Clinical characteristics	**Add points**
C	**Congestive Heart Failure**	**1**
H	**History of Hypertension**	**1**
A	**Age 75 years or older**	**1**
D	**Diabetes Mellitus**	**1**
S_2	**History of Stroke or Transient ischaemic attack**	**2**
	TOTAL SCORE(max 6)=	

Source: Adapted from Gage et al. 2001[22]

Appendix IX: HAS-BLED Scoring System

	HAS-BLED Clinical characteristic	Add points
H	**Hypertension (uncontrolled, greater than 160 mm Hg systolic)**	**1**
A	**Abnormal renal and liver function (1 point each)**	**1 or 2**
S	**Stroke (previous history)**	**1**
B	**Bleeding (history or predisposition e.g. anaemia)**	**1**
L	**Labile International INRs (i.e. time in therapeutic range is less than 60 per cent)**	**1**
E	**Elderly (older than 65 years)**	**1**
D	**Drugs (e.g. non-steroidal anti-inflammatory or antiplatelet drugs, heparin or thrombolysis) OR alcohol (1 point each)**	**1 or 2**
	TOTAL SCORE (out of maximum 9 points) =	

Source: Adapted from Pisters R et al, 2010[26, 63]

Appendix X: Regimen for maintenance dosing using Warfarin: Target range of INR 2 – 3

INR	Dosage adjustment
Less than 1.5	Increase weekly dose by 20%
1.5 – 1.9	Increase weekly dose by 10%
2 – 3	No change
3.1 – 3.9	No change – recheck in one week If persistent, decrease weekly dose by 10%–20%
4 – 4.9	Omit one dose Decrease weekly dose by 10%–20% Re-check INR in two to five days
Greater than or equal to 5	Management of High INR

Source: Adapted from Clarke R, et al.2006[36]

Appendix XI: Delphi Technique Statement Inclusion Key

Statement result[62]	Threshold applied[62]
Definitely include	**1.≥80% of panel rate statement as[62] = 4** **OR** **2.Median rating of[62] ≥3**
Maybe include	**1. ≥70% of panel rate statement as[62] = 4** **OR** **2. Median rating of ≥2**
Definitely not include	**1.Median ≤2** **OR** **2.Major revisions suggested**