ANTICOAGULATION CONTROL IN A STANDARD OF CARE VERSUS A PHARMACIST-MANAGED WARFARIN MONITORING SERVICE AT WINDHOEK CENTRAL HOSPITAL, NAMIBIA

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ABSTRACT

Introduction: Warfarin remains the drug of choice for treating thromboembolic diseases in Namibia. A historical control study reported a patient's mean time in the therapeutic range (TTR) at the Warfarin Outpatient Clinic of Windhoek Central Hospital (WCH) to be suboptimal (29.4%). Interventions to improve anticoagulation control were instituted and they involved a pharmacist-directed warfarin therapy. The main objective was to improve anticoagulation control in the intervention group and compare it to the historical control group.

Methods: A prospective cohort design was used. Adult patients who attended the warfarin clinic on Wednesdays and gave consent were exposed to the intervention study. The main outcome measure was the TTR computed using the Rosendaal method. Binary logistic regression was used to identify factors associated with poor anticoagulation control. A between groups comparison of anticoagulation control was based on the paired and unpaired patient cases. A p value < 0.05 was considered statistically significant. **Results**: A total of 330 patients were part of the present study (control (215) and intervention (115)). The majority (63.4%) of the patients in the intervention group were females. The mean (± SD) age was 45 ± 17 years. The top three prevalent clinical indications for warfarin in the intervention study were deep vein thrombosis (49.6%), mitral valve replacement (13.9%), and pulmonary embolism (13%). Only the baseline INR (OR 0.34 [95%CI: 0.13-0.86]) and warfarin dosage adherence (OR 0.17 [95%CI: 0.04-0.84]) were significant predictors of good anticoagulation control in the intervention group. The Mann-Whitney U test showed an 18% (p<0.050) improvement in the median %TTR when the unpaired cases between the groups were compared. The paired t-test showed a 10% (p=0.220) improvement in the mean %TTR when the paired patient cases between the groups were compared. **Conclusion**: Interventions involving a pharmacist-directed warfarin therapy were associated with improved anticoagulation control at the WCH warfarin clinic. Baseline INR and warfarin dosage adherence were statistically significant predictors of good anticoagulation control.

Keywords: Warfarin, Anticoagulation, Time in therapeutic Range, Pharmacist

LIST OF PUBLICATION(S)/CONFERENCE(S) PROCEEDINGS

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NB: A manuscript based on the results of the thesis is being prepared and will be submitted for publication before the viva examination.

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Table 1: Definition of Terms

Terms/abbreviations	Definition
INR	International Normalized Ratio: the ratio between the patient's prothrombin time and the standard prothrombin time raised to the international sensitivity index. The patient's prothrombin time is a measure of how long it takes for the patient's blood sample to clot.
INR range	Targeted therapeutic INR range as per the indication of warfarin.
NIP INR	Namibia Institute of Pathology INR: the INR value obtained using an ACL analyzer carried out at the NIP laboratory.
POC INR	Point-of-Care INR: the INR value obtained using a device called a CoaguChek® XS meter carried out at the clinic.
Intervention group	Patients who took part in the intervention study in 2021 at the Warfarin Outpatient Clinic of Windhoek Central Hospital.
Control group	Patients who took part in the control study carried out in 2017 at the Warfarin Outpatient Clinic of Windhoek Central Hospital.
New patient	A patient who attended the warfarin clinic and followed up for less than a month during the time of data collection or started on warfarin maintenance therapy during the intervention period.

Old patient	A patient who attended the warfarin clinic and followed up for more than a month before the beginning of the intervention period.
Warfarin initiation phase	Warfarin therapy (most likely at the different hospital wards) before the patient is referred to the warfarin outpatient clinic of Windhoek Central Hospital.
Warfarin maintenance phase	Warfarin therapy at the warfarin outpatient clinic of Windhoek Central Hospital.
% iTTR	Individual Time in Therapeutic Range: the number of days a patient's INR result falls within the therapeutic range (target or expanded INR range) of a given indication divided by the total number of days in the intervention period. This is then multiplied by 100.
%TTR	The mean or median time in the therapeutic range for all patients which was calculated from their % iTTR.
Target %TTR	Mean or median percentage time in therapeutic range calculated from the number of days that INR results were in the target INR ranges.
Expanded %TTR	Mean or median percentage time in therapeutic range calculated from the number of days that the INR results were in the expanded INR ranges adjusted by a tolerance of 0.4 units.
Good anticoagulation control	Target %TTR or expanded %TTR of ≥65%.

Poor Anticoagulation Control	Target %TTR or expanded %TTR of <65%.
Baseline INR	The first INR result of a patient obtained at the warfarin clinic.
Missed Follow-up	When the patient does not visit the clinic for more than 7 days from their scheduled follow-up date.

LIST OF ABBREVIATIONS AND ACRONYMS

AF:	Atrial Fibrillation
APOE:	Apolipoprotein E
BMI:	Body Mass Index
CALU:	Calumenin
CI:	Confidence Interval
CNS:	Central Nervous System
CYP:	Cytochrome P-450
DM:	Diabetes Mellitus
DOAC:	Direct Oral Anticoagulants
DVT:	Deep Vein Thrombosis
EPHX1:	Epoxide Hydroxylase
HAART:	Highly Active Antiretroviral Therapy
HCP:	Health Care Professional
HF:	Heart failure
HIV:	Human Immuno-deficiency Virus
HTN:	Hypertension
HREC:	Human Research Ethics Committee
IBM-SPSS:	Statistical Package for Social Sciences
IHK:	Intermediate Hospital Katutura
INR:	International Normalized Ratio
IQR:	Interquartile range
MMAS-8	Morisky Medication Adherence Scale
MO:	Medical Officer
MVR:	Mitral Valve Replacement

NCDs:	Non-Communicable Diseases
NIP:	Namibia Institute of Pathology
NTINR:	Non-therapeutic INR
OR:	Odds ratio
PAC:	Percentage Accuracy in Classification
PE:	Pulmonary Embolism
PGI_3:	Prostacyclin
POC:	Point of care
PT:	Prothrombin time
PVT:	Prosthetic Valve Thrombosis
RHD:	Rheumatic Heart Disease
RHE:	Rifampicin/ Isoniazid/ Ethambutol
ROS:	Reactive Oxygen Species
SADC:	Southern African Development Community
SAMe-TT2R2:	Sex; Age; Medical history; Treatment; Tobacco use; Race
SD:	Standard deviation
SDOH:	Social determinants of health
KS:	Kolmogorov-Smirnov Test
SW:	Shapiro-Wilk Test
TB:	Tuberculosis
TDM:	Therapeutic Drug Monitoring
TTR:	Time in Therapeutic Range
VKORC1:	Vitamin K Epoxide Reductase Complex 1
VTE:	Venous Thromboembolism
WCH:	Windhoek Central Hospital

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DEDICATION

I dedicate this thesis to me, Moses Thikukutu, for working hard and persevering through the hardship of my studies.

DECLARATION

I, Moses Mukwipure Thikukutu, hereby declare that this study is my work and is a true reflection of my research, and that this work, or any part thereof has not been submitted for a degree at any other institution.

……. 26 September 2024

Signature Date

1. INTRODUCTION.

1.1 Background to the study.

Thromboembolic diseases are an important health problem that will continue to be on the upsurge with increased incidence and prevalence of risk factors (1). A good number of these risk factors are non-modifiable including: age, sex, and genetics (2). Other risk factors of thromboembolism are a direct consequence of the aforementioned non-modifiable risk factors. For example, cancer, hypertension, congestive cardiac failure, and surgery are associated with advanced ages (2). Infectious diseases are also a common risk factor for thromboembolic diseases, including HIV/AIDS and COVID-19 (3).

Patients with a current thromboembolic disease or at risk for a thromboembolic event benefit from the use of anticoagulants. Warfarin is the most prescribed oral anticoagulant globally, especially in Sub-Saharan Africa. Warfarin is indicated to reduce the risk of thromboembolic events in patients with atrial fibrillation, mechanical heart valves, and venous thromboembolism (4). Its mechanism of action involves the inhibition of the vitamin-K reductase enzymes. This inhibition entails that the activation of vitamin-K-dependent clotting factors (II, VII, IX, and X) does not take place. In addition, warfarin inhibits the activation of factors with intrinsic anticoagulation properties, i.e. proteins C and S (4).

The management of warfarin therapy is often challenging as a consequence of its narrow therapeutic index and wide variability in dose-response relationship secondary to several factors (1,5). These numerous factors include diet, genetic variability, drug-drug interactions, and co-morbid conditions (1). Due to its narrow therapeutic window and an extensive variability in dose-response, it is not uncommon for patients on warfarin to have suboptimum anticoagulation. This has warranted the clinical

introduction of numerous interventions in an attempt to improve anticoagulation control. For optimal anticoagulation control, one of the interventions recommended is that warfarin therapy be managed through an anticoagulation management service such as the warfarin outpatient clinic of Windhoek Central Hospital (WCH) (4,6). In addition, pharmacist involvement and the use of point-of-care (POC) INR testing devices have been reported to positively impact the quality of anticoagulation services (7–10).

What is common in all the anticoagulation interventions thus far is the close therapeutic drug monitoring (TDM) of warfarin by measuring the international normalized ratio (INR) in the patients. An INR of 2.0-3.0 has been established as the therapeutic target for most of warfarin's indications, though a higher target of 2.5-3.5 is required for in the case of patients with mitral valve replacement or double valve replacement (11). Non-therapeutic INRs are INR results outside the stipulated therapeutic range and they can be either sub-therapeutic or supra-therapeutic. Sub-therapeutic INRs are INR results below the lower value of the normal range, that is below 2.0 or 2.5 depending on the indication of warfarin. Supra-therapeutic INRs on the other hand, are INRs above the upper value of the normal range, that is above 3.0 or 3.5 depending on the indication of warfarin.

The clinical responses to warfarin therapy are both efficacy-related and safety-related. Efficacy related responses relate to the ability of warfarin to prevent a thromboembolic event and is associated with the time that a patient's INR remains in a therapeutic range. Safety-related outcomes include adverse events from warfarin such as the bleeding risk. Both efficacy and safety are related to INR control. The patient's percentage individual time in the therapeutic range (%iTTR), calculated from the INR results, is commonly used to assess the adequacy of anticoagulation therapy with

warfarin (12,13). The %iTTR is calculated using numerous methods including the linear interpolation Rosendaal method (12). The %iTTR can be used to calculate the mean or median percentage time in the therapeutic range (%TTR) for an individual patient. The TTR is an objective measure of clinical response to warfarin therapy pertaining to both anticoagulation control and warfarin adverse effects. Good anticoagulation control is achieved when a minimum mean or median Time in Therapeutic Range (TTR) of 65% over a specified study period (usually, at least 3 months) is obtained and poor anticoagulation control is defined as TTR<65% over a specified study period (usually, at least 3 months) (14).

The current study aimed to assess whether the introduction of a pharmacist, a detailed data collection tool, and a standard dosing algorithm improved the quality of anticoagulation control at the warfarin outpatient clinic of WCH.

1.2 Statement of the problem.

Thrombotic diseases are a major health burden (2). Venous thromboembolism (pulmonary embolism and deep vein thrombosis) has an estimated yearly incidence of approximately 1 in 1000 world-wide (2). The high incidence rate is attributed to the many and common risk factors of thromboembolism such as old age, surgery, and obesity. Due to its high efficacy and high availability especially in low and middle-economy countries like Namibia, warfarin is and will continue to be one of the most prescribed anticoagulants in patients with thrombotic diseases. However, despite the long duration of clinical use thus far (more than 70 years), warfarin therapy remains an important clinical challenge in terms of attaining the desired clinical responses (1). While alternative agents that do not require as intense monitoring are available, these agents have an unacceptably low efficacy in certain populations including those with

mechanical valve replacements and those with valvular atrial fibrillation, both conditions with a high prevalence in Namibia.

Due to the well-known complexity of managing patients on warfarin, it is not uncommon for the quality of anticoagulation to be poor. In 2017, a retrospective study was carried out at the Warfarin Outpatient Clinic of WCH. The results showed that the patients' mean time in the therapeutic range was 29.4%, well below the target TTR of 65% (11). This was one of the lowest TTR reported from an anticoagulation clinic in Africa (3). Only 22 of the 215 patients included in the study, i.e. 10% of the patients, had a TTR of ≥65%. As a consequence, the majority of patients were at risk of either thrombotic or bleeding events.

On the basis of the results of this retrospective study, it was clear that interventions were needed to improve the quality of anticoagulation control at the clinic. A triad intervention consisting of: 1) involvement of a pharmacist, 2) an improved data collection tool, and 3) a standardized warfarin dosage adjustment guideline coupled with point-of-care INR testing (Fig. 1) were proposed. These covered many of the possible interventions proposed in the literature, namely: a specialized anticoagulation clinic, warfarin adherence intervention, dosing algorithms, and a possibility of patient-self INR monitoring (1). The intervention(s) used may depend on the phase of warfarin therapy, i.e. the initiation or maintenance phase. For example, dosing nomograms may be more useful in the initiation phase. On the other hand, outpatients in the warfarin maintenance phase, as was the case with the patients in this study, may benefit more from adherence interventions and contextually based dosing algorithms that account for patient-specific information collected with an improved data collection tool. Patient-self INR monitoring may be useful in well-trained and stable outpatients on warfarin maintenance therapy. Specialized anticoagulation clinics are

important in both phases of warfarin therapy. Nonetheless, specific combinations of interventions are dependent on the characteristics of the patients and the health facilities. The interventions made are further discussed in the paragraphs below.

Firstly, several studies have demonstrated that a pharmacist-managed anticoagulation clinic in a multidisciplinary setting offers not only safe and effective treatment but is superior concerning improvements in the quality of anticoagulation control consequently decreasing the incidence of thromboembolic events (7–10). Their major role has been attributed to their ability to apply their knowledge of warfarin-drug interactions and warfarin-food interactions to inform warfarin dosage adjustment. Another role of pharmacists in warfarin anticoagulation service is associated with adherence through counselling and regularly following up on patients.

Secondly, a detailed record should be kept of patient characteristics that may have a significant impact on the anticoagulant response to warfarin (e.g. co-morbidities, concurrent medications, diet, alcohol use, smoking, and missed or extra doses taken). Changes in these conditions during maintenance warfarin therapy should be reported and considered accordingly when adjusting the dosages (15). Decision-making about anticoagulation adjustment require a holistic view of patient management. This involves not only looking at the current dose and INR, but also other patient factors including the patient's historical response to warfarin.

Thirdly, a standardized warfarin dosage adjustment guideline would allow for a systematic approach to adjusting the patient's warfarin doses. Point-of-care (POC) INR meters (Fig. 1) provide more rapid and just as reliable INR values to those obtained from central laboratories (16,17). The benefit of these meters is the ability to rapidly assess anticoagulation and make prompt therapeutic adjustments while the patient is still in the anticoagulation clinic. Figure 2 below shows the Automated

Coagulation (ACL) analyzer currently used to measure INRs at the Namibia Institute of Pathology (NIP) laboratory of WCH.

Figure 1. The CoaguChek® XS INR meter from Roche Diagnostics.

Figure 2. Automated Coagulation (ACL) analyzer used to measure INR at Namibia Institute of Pathology (NIP) laboratories.

1.3 Objectives of the study.

1.3.1 Main objective.

To improve the quality of anticoagulation control in patients attending the warfarin clinic of Windhoek Central Hospital.

1.3.2 Research questions.

Based on findings from the literature review, the following research questions were designed according to the PICO (Patient, Intervention, Comparator, and Outcome) criteria. The ultimate question was whether patients requiring warfarin who receive pharmacist-supported anticoagulation management at the warfarin outpatient clinic at WCH have improved %iTTR compared to a historical control at the same clinic. Specific questions include:

1. What is the impact of a pharmacist on the quality of anticoagulation control (%TTR) in patients attending the warfarin outpatient clinic of WCH?
2. What is the difference in the quality of anticoagulation control between the historical control group (11) and the intervention study?
3. What factors affect the quality of anticoagulation control (%TTR) in patients attending the warfarin outpatient clinic of WCH?
4. What is the sensitivity and specificity of the CoaguChek® XS INR meter (Fig. 1) in comparison to NIP's automated coagulation analyzer (Fig. 2) in monitoring and managing patients on warfarin therapy attending the warfarin outpatient clinic of WCH?

1.4 Hypothesis of the study.

Ho: There is no statistically significant difference between the quality of anticoagulation control (%TTR) achieved from the control study and the quality of anticoagulation control (%TTR) achieved by the intervention study among patients on warfarin therapy attending the Warfarin Outpatient Clinic of Windhoek Central Hospital.

Ha: There is a statistically significant difference between the quality of anticoagulation control (%TTR) achieved from the control study and the quality of anticoagulation control (%TTR) achieved by the intervention study among patients on warfarin therapy attending the Warfarin Outpatient Clinic of Windhoek Central Hospital.

1.5 Significance of the study.

The results of a retrospective study, henceforth referred to as the control study, showed that anticoagulation control at the Warfarin Outpatient Clinic of WCH was poor (TTR = 29.4%) (11). This puts the patients attending this warfarin clinic at risk of serious, potentially life-threatening warfarin adverse effects, i.e. thromboembolic or haemorrhagic events. This intervention aimed to improve anticoagulation control (%TTR) at the clinic. If the results of the study show a clinically significant improvement in the %TTR it could be used to recommend the permanent implementation of these interventions at the Warfarin Outpatient Clinic of Windhoek Central Hospital. It was reckoned that this was the first study in Namibia to explore factors affecting the quality of anticoagulation control in patients attending the warfarin outpatient clinic of WCH. These factors could be used to design targeted interventions meant to improve the quality of anticoagulation control consequently

reducing the risk of warfarin-associated adverse events. The study also looked into the clinical agreement between INR results obtained from a POC INR meter and the laboratory INR measurements. The results enabled an evidence-based recommendation for the use of POC-INR meters in patients on warfarin therapy at the clinic.

1.6 Limitations of the study.

The intervention study did not recruit all the patients involved in the control study. Another limitation of the study is that the Point-of-Care (POC) INR testing could not be carried out in all patients recruited in the intervention study due to the limited availability of funds to purchase the test strips.

1.7 Delimitation of the study.

First, the study was limited to the Warfarin Outpatient Clinic of Windhoek Central hospital (WCH). It is one of the two anticoagulation clinics in Namibia, the other being at Oshakati Intermediate Hospital. The Warfarin Outpatient Clinic of WCH was the preferred site of the study since, in comparison to Oshakati Intermediate Hospital's anticoagulation clinic, it caters for the majority of patients on warfarin in Namibia. Second, the study was delimited to patients on warfarin who attend the warfarin clinic on Wednesdays.

2. LITERATURE REVIEW.

2.1 Introduction.

Many factors contribute to the complexity of managing patients on warfarin therapy. Such factors need to be adequately examined for targeted interventions to improve the quality of anticoagulation control. The research questions guided the literature search and subsequent review. The aim was to explore what is already known regarding the factors affecting the quality of anticoagulation control and the impact that pharmacists may have on the quality of anticoagulation control. The literature review also aimed to study what has been reported about the sensitivity and specificity of point-of-care INR devices in comparison to mainstream laboratory monitoring of INR in patients on warfarin therapy. The following advanced searches on the research questions were carried out in the COCHRANE library and PubMed.

Research question 1: ("*Pharmacist*" NEXT (*involvement** or *run** or *managed**) **AND** ("*Warfarin*" NEXT (*treatment** or *maintenance** or *therapy**)) **AND** *("International Normalized Ratio" NEXT control)* **OR** *("INR"* NEXT *control)* **AND** ("*Anticoagulation*" NEXT (*clinic** or *service*)).* The MeSH descriptors were "**Pharmacists**", "**Warfarin**", "**International Normalized Ratio**", and "**Anticoagulation**."

Research question 2: *("Factors"* NEXT *affecting)* **OR** *("Factors"* NEXT *influencing)* **AND** *("International normalized ratio"* NEXT *control)* **OR** *("INR"* NEXT *control)* **AND** *("Warfarin"* NEXT *(treatment** or *maintenance** or *therapy*))* **OR** *("VKA"* NEXT *(treatment** or *maintenance** or *therapy*)).* The MeSH descriptors were "**Factors**", "**Warfarin**" and "**International Normalized Ratio**."

Research question 3: ("*point of care testing*" NEXT (*device** or *system**)) **AND** ("*Accuracy"* OR *"precision")* **OR** ("*sensitivity"* AND *"specificity*") **AND**

*("International normalized ratio" NEXT (measurement** or *monitoring*))* **OR** *("INR" NEXT (measurement** or *monitoring*))* **AND** *("Warfarin"* NEXT *(treatment** or *therapy** or *management** or *maintenance*))* **OR** *("Coumadin"* NEXT *(treatment** or *therapy** or *management** or *maintenance*)).* The MeSH descriptors used for this search were "**Point-of-Care Systems**", "**International Normalized Ratio**", and "**Warfarin**."

These searches were carried out between the 19th of May, 2022, and the 27th of September, 2023. Reviewed articles were assessed for appropriateness based on their titles and abstracts. Due to the large number of studies on warfarin and the factors affecting anticoagulation control, systematic reviews and meta-analyses were given precedence. Relevant studies were also found in the reference list of the included studies.

2.2 Warfarin.

Warfarin also known as 4-hydroxy-3-(3-oxo-1-phenylbutyl)chromen-2-one (18), is an oral anticoagulant used in the management of thromboembolic conditions such as deep vein thrombosis and pulmonary embolism (4,5). These conditions are of major importance in public health. Due to its associated low cost of procurement, e.g. in rural Zambia, 5 mg warfarin tablet costs 8 US cents (19) and high efficacy in treating these conditions, warfarin is the most commonly prescribed oral anticoagulant. It has been clinically utilized for longer than 70 years now (1). In Namibia, a 5 mg warfarin tablet at the wholesale pharmacy costs N$1.57 which currently (N$1 = 0.053 USD) translates to 0.08 US cents. Warfarin is a racemic mixture of two enantiomers which are the S- and R-enantiomer (1). The S-enantiomer is thought to be responsible for the anticoagulation properties of warfarin as it is 3 to 5 times more potent at inhibiting

vitamin K reductases than the R-enantiomer (20). Figure 3 below shows the chemical structure of warfarin.

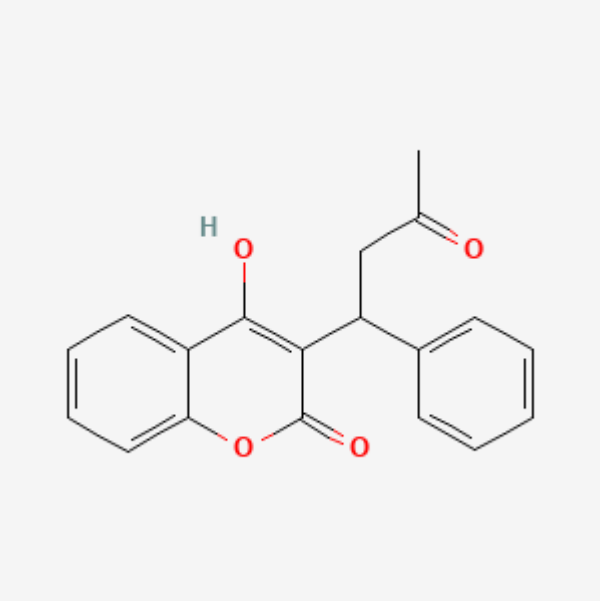

Figure 3. The chemical structure of warfarin (C19H16O4) (18).

2.3 Pharmacokinetics of warfarin.

2.3.1 Absorption.

Warfarin is administered orally and its bioavailability following oral administration is at least 90% (21). The Tmax ranges from 2 to 6 hours with a much longer Tmax of approximately 9 hours obtained following oral administration of starch-based warfarin tablets.

2.3.2 Distribution.

Warfarin (both enantiomers) has a small apparent volume of distribution of about 10 L/70kg (21). The distribution phase following an intravenous or oral solution of warfarin lasts for about 6 to 12 hours. Following an oral dosing of warfarin, a one compartment model is usually sufficient to characterize the disposition of warfarin

(21). It is essentially a weak acid with a pKa of 5.05 bound to albumin in plasma. Its plasma protein binding is estimated to be 99% (21).

2.3.3 Biotransformation and excretion.

Warfarin is mainly eliminated by biotransforming the two enantiomers into 2 inactive and 2 less active metabolites (20). This biotransformation occurs in the liver and it is mediated through the cytochrome P450 enzymes. The main route of biotransformation is the hydroxylation of the S- and R-enantiomer of warfarin into the inactive 7-hydroxy warfarin and 8-hydroxywarfarin (20). Cytochrome P450 2C9 mainly metabolizes the S-enantiomer into the inactive 7-hydroxy warfarin. On the other hand, cytochrome P450 2C19 metabolizes the R-enantiomer into the inactive 8-hydroxy warfarin.

The hepatic extraction of warfarin is small and hence the low plasma clearance of 0.2 L/h/70kg (21). It has been established that the clearance of the S-enantiomer is twice that of the R-enantiomer. Therefore, assuming a one compartment model and a similar volume of distribution of the racemic mixture, the half-life ($= {}^{0.693 \times Vd}/_{Cl}$) of the S-enantiomer (21-43 hours) is much shorter than that of the R-enantiomer (37-89 hours) (21). While the effective half-life of warfarin is between 20-60 hours, the terminal half-life of warfarin is approximated at 35 hours (21). Generally, it takes about 5 half-lives for a drug to reach new a steady state in plasma. Consequently, after a change in dosage, warfarin reaches a new steady state in about a week ($= 5 \times 35\ hours\ = 175\ hours\ \cong 168\ hours\ \ in\ a\ week$) (21).

2.4 Pharmacodynamics.

The mechanism of action of warfarin requires an understanding of the activation of vitamin K-dependent clotting factors (21). The vitamin K-dependent clotting factors

are either procoagulants, i.e. factors 10, 9, 7, and 2, or anticoagulants, i.e. proteins C and S. These clotting factors have glutamic acid residues which undergo vitamin-dependent decarboxylation (21). Vitamin K reductases are needed for vitamin K-dependent carboxylation converting the precursor vitamin-K dependent clotting factors into the activated clotting factors. These vitamin K reductases are namely: vitamin K reductase and vitamin K epoxide reductase. Warfarin antagonizes these vitamin K reductases resulting in its short-term pro-coagulation and long-term anticoagulation effects (21). Essentially, warfarin interrupts the body's handling of vitamin K. Reduced vitamin K (vitamin K hydroquinone) is essential for the vitamin K-dependent carboxylation process. The formation of vitamin K hydroquinone is mediated by the enzyme vitamin K reductase. Vitamin K hydroquinone is converted into vitamin K epoxide during vitamin K-dependent carboxylation of the glutamic acid residues of vitamin K-dependent clotting factors. Vitamin K epoxide is then reduced into vitamin K by the enzyme vitamin K epoxide reductase. The vitamin K is further reduced by vitamin K reductase to form vitamin K hydroquinone and the cycle continues (21). Figure 4 below illustrates the pharmacodynamic properties of warfarin.

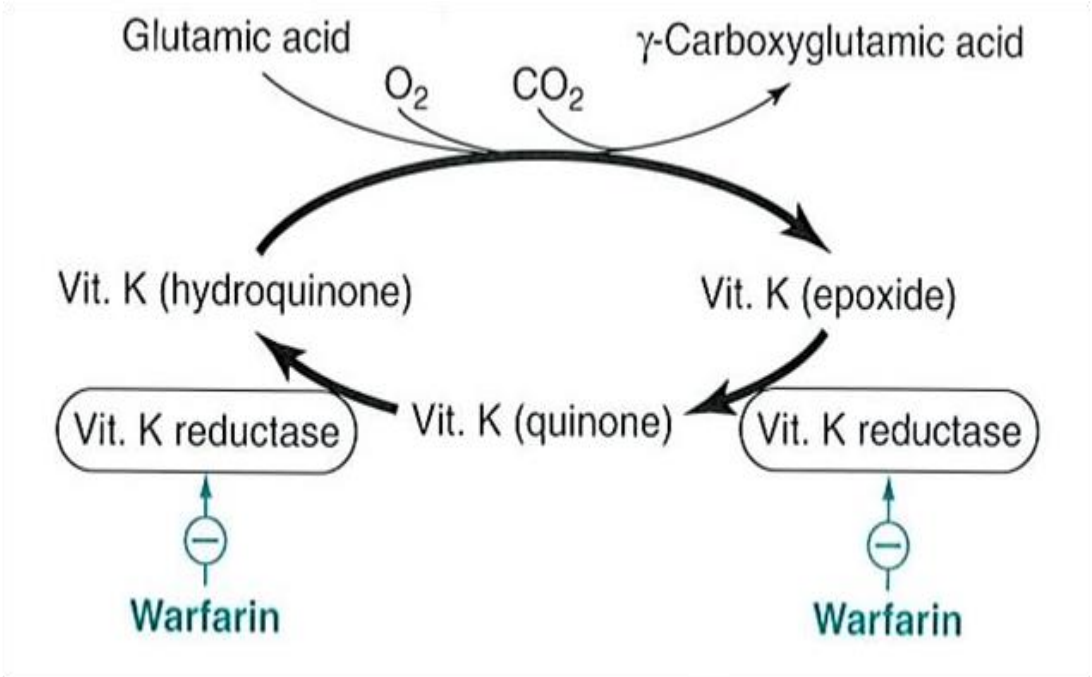

Figure 4. The pharmacodynamic properties of warfarin (21).

2.5 Challenges of warfarin as an anticoagulant.

While warfarin is highly effective, there are certain challenges to its use. The first established reason is that warfarin has a narrow therapeutic window (1). This means that there is a small difference in the dose of warfarin associated with desired clinical responses (good anticoagulation control and minimal to no adverse events while on warfarin therapy) and the dose of warfarin associated with undesired clinical responses (poor anticoagulation control and presence of adverse events). The therapeutic window of warfarin is a measure of response to warfarin based on the patient's prothrombin time. The prothrombin time is used to calculate the patient's International Normalized Ratio (INR). Essentially, the therapeutic window of warfarin is based on the INR. The INR is expressed as a range that is either 2-3 or 2.5-3.5 depending on the indication of warfarin. For example, the therapeutic window of warfarin in a patient with a diagnosis of DVT is an INR of 2-3. However, due to the high prothrombotic tendencies of

prosthetic heart valves in certain positions, the INR for a patient who has a mechanical prosthetic mitral valve will be 2.5 – 3.5, while a standalone mechanical aortic valve has a goal of 2-3.

Both clinical efficacy and adverse events associated with warfarin are related to INR. An INR below the therapeutic INR range is associated with an increased risk of thrombosis. On the other hand, an INR above the therapeutic INR range is associated with an increased risk of haemorrhaging. Therefore, to maximize clinical efficacy and minimize the risk of adverse events to warfarin, the patient's INR results have to be within the target INR range all or at least 65% of the time while on warfarin anticoagulation. In addition, it is worth noting that the two INR ranges have a difference of 1 unit. To better appreciate this narrow therapeutic window (narrow INR range), although individual patient variability in warfarin sensitivity has to be considered, it has been shown that adjusting the weekly maintenance dose of warfarin by approximately 1 mg/day can induce a change in the INR by 0.5 units (1).

Secondly, for many medicines, the dose-response relationship is quite easy to predict. Such medicines are relatively easy to use in managing clinical conditions for which they are indicated. For warfarin, however, there is limited predictability of the dose-response relationship (21). The clinical translation of this is that you might use a wide range of warfarin dosages which will result in a similar clinical response or that the same warfarin dosage can result in a wide range of clinical responses in different patients. The clinical implication, therefore, is the large inter- and intra-patient variability to warfarin therapy. To combat this, a better understanding of the dose-response relationship of warfarin is required. The dose-response relationship of warfarin is composed of at least three important models: first, is the pharmacokinetic model which studies the dose-concentration relationship of a medicine; second, is the

pharmacodynamics model which studies the concentration-effect relationship; and lastly, the physiologic model which studies the effect-response relationship (21). Any factor or a combination of factors influencing any of these models has the potential to alter clinical responses to warfarin. These factors can be classified as modifiable (such as warfarin-food interactions and warfarin-drug interactions) or non-modifiable (such as age, sex, indication for warfarin, co-diagnosis, and genetics). A third group of factors affecting warfarin therapy is the social determinants of health (22). The patient's geographic location, which is the distance between the patient's home and the nearest warfarin clinic, is an example of a factor classified in this group. Nontherapeutic INRs associated with the geographic location (for example, distance to the closest clinic) are usually sub-therapeutic in nature and are secondary to increases in the interval of clinic visits (22).

Due to the narrow therapeutic window of warfarin and the numerous factors with potentially clinically significant interactions with the dose-response relationship of warfarin, it is not uncommon for: 1) the quality of anticoagulation control to be poor, and 2) for the probability of adverse effects of warfarin to be increased (1).

2.6 Evidence for poor quality of anticoagulation in Africa.

Reports of poor anticoagulation control among patients on warfarin in Africa have been published from mostly observational studies as early as 2008 (23). A median time in therapeutic range (PTR) of 36% was reported amongst 189 patients with mechanical heart valves in Dar Es Salaam, Tanzania (23). Eight years later, a time in therapeutic range (TTR) of 48% was reported in 27 patients with atrial fibrillation (AF) from Yaoundé, Cameroon (24). In 2016, 4 more studies reported a TTR or PTR ranging from 30% to 49% (3,25). A study carried out at district hospital in Durban, South

Africa reported a TTR of 30% (3), Ethiopia teaching hospital, Ethiopia reported a PTR of 34% (25), Kenya teaching hospital, Kenya reported a PTR of 44% (26), and a district hospital in Cape Town, South Africa reported a PTR of 49% (27). A much recent study involving two countries: Uganda and South Africa, reported a TTR of 41% in 229 patients attending 5 different anticoagulation clinics (28).

It appears that poor anticoagulation control in patients on warfarin is more evident in Sub-Saharan Africa. For instance, even under the well-designed conditions of clinical trials, patients in 3 clinical trials in South Africa reported mean TTRs of 46% (22), 55% (14), and 58% (29) well below the acceptable standard of >65% TTR. One of the lowest TTR of 29% in Africa was reported from the warfarin outpatient clinic of Windhoek Central Hospital, Namibia (11). Table 2 below shows these results.

Table 2: Evidence for poor anticoagulation control in Africa.

Author, year	Setting	Patient description	Sample size	Mean/median TTR (%)
Makubi, 2008	Dar Es Salaam, Tanzania National referral hospital	Patients with mechanical heart valves	189	36
Menanga, 2015	Yaoundé, Cameroon general and a central hospital	Adult patients with atrial fibrillation	27	48
Sadhabiriss, 2016	Durban, South Africa District-level hospital	Patients with atrial fibrillation	177	30
Daba, 2016	Addis Ababa, Ethiopia Teaching hospital	Adult patients with venous thromboembolism	91	34
Mariita, 2016	Nairobi, Kenya Teaching hospital	Adults attending the anticoagulation monitoring service	147	44
Sonuga, 2016	Cape Town, South Africa District hospital	Adults attending the anticoagulation clinic	136	49
Semakula, 2020	Kampala, Uganda and Cape Town, South Africa	Patients attending five anticoagulation clinics	299	41
Singer, 2013	45 countries	Patients on warfarin	6983	46
Connolly, 2008	526 centres, 15 countries	Patients on warfarin vs aspirin plus dabigatran combination	6706	15
Wallentin, 2010	951 sites	Patients on dabigatran vs warfarin	18 113	58

2.7 Therapeutic Drug Monitoring of warfarin.

The clinical complexity of managing patients on warfarin therapy due to its narrow therapeutic window and large interpatient variability is crystal clear. To this effect, a number of interventions have been studied, proposed, and introduced into clinical care. The interventions are targeted at patients on warfarin in the initiation phase and/or in their maintenance phase. Examples of these interventions include specialized anticoagulation clinics, standardized dosing algorithms, adherence interventions, and patient INR self-monitoring (1). The common practice in each of these interventions is warfarin therapeutic drug monitoring (TDM). This is achieved by measuring and monitoring the patients' INR results (1). An objective assessment of the clinical responses to warfarin is made based on INR results. Anticoagulation control, as a form of clinical response to warfarin therapy, is assessed by determining the time that the patients' INRs are within the therapeutic range (TTR). Different methods, including the Rosendaal method, are used to calculate TTR (12). While the goal of anticoagulation control is a TTR as high as possible, good anticoagulation control is defined as a TTR of $\geq$ 65% calculated over a minimum of three months (12). On the other hand, poor anticoagulation control is generally defined when the TTR <65% which occurs when the patients obtain non-therapeutic INRs (NTINR) for much of the study duration (14). NTINR is either a result of subtherapeutic INRs or supratherapeutic INRs (30). A subtherapeutic INR is when a patient's INR result is below the lower limit of the normal INR range for their clinical indication of warfarin. A supratherapeutic INR on the other hand is when the patient's INR result is above the upper limit of the normal INR range for their clinical indication of warfarin. In patients with atrial fibrillation, it has been shown that the risk of warfarin side effects is significantly lower in patients with good anticoagulation control (31). The

haemorrhagic and thrombotic side effects make warfarin an important high-risk medicine, meaning it is an important cause of medicines-related harm.

2.8 Factors affecting clinical responses to warfarin.

Warfarin was first introduced into the market in the early 1950s (9). The first two systematic reviews looking into warfarin-drug and warfarin-food interactions were published in 1994 and 2005 (32) respectively. Until the year 2005, factors affecting the quality of anticoagulation were primarily reported in case reports, case series, and to a certain extent descriptive reviews. Even then, it was clear that several factors affected the clinical response to warfarin. The high variability in the effects of these factors explain how warfarin doses could differ by more than 15-fold between patients (33). These factors influence warfarin response by interfering with the dose-response relationship (pharmacokinetic, pharmacodynamic, and physiological model) of warfarin (21). On a more general scale, these factors can be classified as patient-related or setting-related factors which are either modifiable or non-modifiable (3). Examples of patient-related factors important in Sub-Saharan Africa (SSA) include pharmacogenetics, disease burden (TB and HIV) and associated drug-interactions, and poor patient knowledge of anticoagulation (3). On the other hand, setting-related factors in SSA include low availability of warfarin in state hospitals, lack of dedicated anticoagulation clinics, health-care worker's deficiencies in warfarin knowledge, in particular, drug interactions, and cost of INR testing.

2.9 Factors affecting the pharmacokinetic model of warfarin.

The pharmacokinetics of any medicine is described in terms of four main processes, i.e. absorption, distribution, metabolism, and excretion (34). Consequently, factors

affecting the pharmacokinetics of warfarin should be affecting one or a combination of these pharmacokinetic processes. Pharmacokinetic variability may involve alteration in warfarin absorption and plasma protein binding (34). However, metabolism is the most studied pharmacokinetic process contributing to variability in response to warfarin (20). The metabolism of warfarin is carried out in the liver by certain cytochrome P450 enzymes (CYP450) (20). Factors affecting the metabolism of warfarin do so by either potentiating or inhibiting the activity of these CYP450 enzymes (32). The activity of these enzymes is related to both the extent of expression (amount/concentration) and functionality (20). As stated earlier, warfarin structurally consists of two active enantiomers: the more potent *S*-enantiomer and the less potent *R*-enantiomer (20). The *S*-enantiomer is metabolized by *CYP2C9* and the *R*-enantiomer by *CYP2C19*, *CYP1A2*, and *CYP3A4* liver enzymes. Changes in the activity of these enzymes will affect the clearance of warfarin which will subsequently affect the area under the curve (AUC). AUC is a measure of drug concentration over time or the systemic exposure of the patient to the drug. The equation $AUC = Dose \times F/Cl$ (35), can help us understand the effect of factors involved in the metabolism of warfarin. When a factor potentiates the activity of CYP450 enzymes, the clearance of warfarin increases leading to reduced warfarin plasma concentrations. The reverse is true when a factor leads to inhibition of the CYP450 enzymes, the clearance reduces and the patient is exposed to much higher concentrations of warfarin.

Drug interactions with warfarin are an important modifiable factor increasing or decreasing the metabolism of warfarin. Examples include conventional medicines such as amiodarone, herbal medicines such as ginseng capsules, and substances such as alcohol (32). Due to a wide range of conventional medicines shown to interfere with

the metabolism of warfarin, they are usually reported by classifying them into drug groups such as antimicrobials, cardiovascular drugs, analgesics/ immunomodulators, and central nervous system (CNS) drugs (32). Examples of conventional medicines with a probability of inhibiting the metabolism and possibly potentiating the anticoagulation effects of warfarin are: cotrimoxazole, amiodarone, and fluoroquinolones. On the other hand, certain conventional medicines have a probability to potentiate the metabolism of warfarin consequently inhibiting its anticoagulation effects. Examples include; rifampicin and carbamazepine (32). To expound on this, rifampicin is a potent inducer of CYP450 enzymes including those involved in the biotransformation of warfarin, i.e. *CYP2C9, CYP2C19, CYP1A2,* and *CYP3A4*. Similarly, carbamazepine is a potent inducer of *CYP2C9,* the enzyme mainly responsible for the metabolism of the more active S-enantiomer. In addition, it is also an inducer of *CYP3A4,* one of the oxidative enzymes involved in the metabolism of warfarin (32). Other drugs like cholestyramine interact with warfarin by reducing its absorption (36). Cholestyramine, a bile-acid sequestrant, is a basic anion-exchange resin used for a variety of clinical indications including lipid reduction. Following oral administration, cholestyramine is not absorbed from the gastrointestinal tract. It can bind several drugs taken orally preventing the absorption of the drugs into the portal system and eventually into the systemic circulation (36).

Second, warfarin-food interactions are another modifiable factor affecting the metabolism of warfarin. Mango and grapefruit juice have been shown with a high probability to induce clinically significant increase in the metabolism of warfarin (32). Other foods have been shown with a high probability as well to induce clinically significant inhibition of warfarin metabolism (32). Examples are soy milk and avocado. Food with a high vitamin K content will be discussed under the

pharmacodynamic model.

Lastly, genetic polymorphisms are an important non-modifiable factor affecting warfarin metabolism. Genetic polymorphism in CYP450 enzymes metabolizing warfarin can affect the activity of these enzymes resulting in altered clearance and the AUC of warfarin. *CYP2C9* metabolizes the more active S-enantiomer into the inactive 7-hydroxywarfarin (20). The S-enantiomer is responsible for 60 - 70% of the anticoagulating effect of warfarin. Amongst white Europeans, the *CYP2C9* gene exists in three variants: *CYP2C9*1*, *CYP2C9*2*, and *CYP2C9*3* (20). The *CYP2C9*1* (Arg144/ Tyr358/Ile359/Gly417) is the wild variant and the allelic variants being *CYP2C9*2* (Arg144Cys) and *CYP2C9*3* (Ile359Leu). The allelic variants contribute a maximum of 12% of the biotransformation activity of CYP2C9 (20). Therefore, in the order of increasing enzymatic activity, the following order has been established: *3/*3, *3/*2, *2/*2, *3/*1, *2/*1, and the most potent *1/*1 (20). Patients with allelic variants of *CYP2C9*, especially homozygous *CYP2C9*3/*3* have a reduced warfarin clearance capacity and may be classified as slow metabolizers. Therefore, they tend to require smaller starting doses than those with homozygous *CYP2C9*1/*1* (20). Such patients tend to be at high risk of haemorrhagic events with standard warfarin dosage. Surprisingly, it has been demonstrated that up to 30% of patients on warfarin requiring lower dosages and a low plasma clearance defined as free clearance of less than 129 mL/min had a homozygous *CYP2C9*1* (20). However, among African-Americans in the United States, some studies have reported higher rates of alleles of *CYP2C9* associated with the reduced function of the enzyme (37). This suggests that studies involving warfarin pharmacogenetics may need to be carried out in other ethnic groups, including in a multi-ethnic country such as Namibia. The R-enantiomer, on the other hand, contributes to the anticoagulation properties of warfarin to a lesser

extent. It is metabolized mainly by *CYP2C19* and to a lesser extent other CYP450 enzymes to form the inactive 8-hydroxywarfarin (20). The *CYP2C19* gene has two variants: *CYP2C19*2* and *CYP2C19*3*. Genetic polymorphisms are linked to ethnic origin; genotyping-based dosing algorithms for warfarin have been proposed (20), though in practice are not routinely used. The effects of these enzymes are less clear in other populations, including in Africa.

2.10 Factors affecting the pharmacodynamic model of warfarin.

Warfarin exerts its acute pro-coagulation and anticoagulation effect by inhibiting the enzymatic activity of vitamin K reductases (21). These enzymes are crucial for the body's handling of vitamin K and are needed to activate pro-coagulation (factors XX, IX, VII, and II) and anticoagulation (protein C and S) vitamin K-dependent clotting factors. To begin with, foods containing a high content of vitamin K are an important source of pharmacodynamic warfarin-food interaction (32). An example includes green leafy vegetables such as cabbage and broccoli, and animal liver. Periodic consumption of these has been shown to reduce the efficacy of warfarin resulting in one of the most common causes of subtherapeutic INRs may contribute to poor anticoagulation control. In addition, certain drugs such as cephalosporins and levothyroxine contribute to warfarin-drug pharmacodynamic interaction (32). Cephalosporins interaction with warfarin is dependent on the presence or absence of the N-methyl-thio-tetrazole side chain (NMTT) (38). Cephalosporins with an NMTT side chain have been shown to downregulate the formation of clotting factors therefore reducing warfarin effect. Conversely, cephalosporins without an NMTT side chain have been shown to enhance warfarin effect. Examples of cephalosporins with an NMTT side chain include the second generation cephalosporins such as cefmetazole

and third generation cephalosporins such as cefoperazone (39). Lastly, warfarin-genetic interaction can influence the patient's response to warfarin therapy. The production of vitamin K reductases are dependent on genes and the processes of transcription and translation (1). In this regard, the Vitamin K Epoxide Reductase Complex 1 (*VKORC1*) is the most studied gene. *VKORC1* encodes for the production of vitamin K epoxide reductase enzyme, one of the enzymes that warfarin inhibits during the vitamin K cycle. Warfarin response may vary depending on the expression of the gene (1). There are other genes that may influence the warfarin effect. However, these genes have not been well studied thus far. For instance, the activation of enzymatic activity of vitamin K epoxide reductase is mediated through the enzyme microsomal epoxide hydroxylase (EPHX1) (1). Therefore, alterations in the *EPHX1* gene may induce changes in the activity of EPHX and vitamin K epoxide reductase subsequently affecting response to warfarin. Calumenin (CALU), a calcium-binding protein, is highly involved in the carboxylation of glutamic residues of vitamin K-dependent clotting factors (1). Variations in calumenin activity can influence response to warfarin. Vitamin K is a lipid-soluble vitamin whose absorption is dependent on the lymphatic system. The uptake of vitamin K by the liver is dependent upon the binding of vitamin K-containing chylomicrons to apolipoprotein E (APOE) (1). *APOE* gene activity can influence hepatic uptake of vitamin K, the vitamin K cycle, and subsequent response to warfarin. Lastly, modifications to the genes coding for vitamin K-dependent clotting factors can influence clinical response to warfarin (1).

2.11 Factors affecting the physiologic model of warfarin.

The physiologic model of warfarin encompasses factors that are commonly described in the literature as patient-associated factors. The primary modifiable patient factor is

body weight, which has been better studied as body mass index (BMI). The majority of the patient-related factors are non-modifiable, including but not limited to age, sex, a co-diagnosis of heart failure, acute coronary syndrome, biochemical abnormalities such as diabetes mellitus, thyroid disease, liver disease, cancer, and the indication for anticoagulation (1,40–42).

Since all these physiologic factors may affect one or more of the aforementioned models (pharmacokinetic and pharmacodynamic) of the warfarin dose-response relationship, they may contribute to poor anticoagulation control. The predictors of poor anticoagulation control are discussed below.

2.12 Predictors of poor anticoagulation control.

Marcato et al. (2016) studied the association between age and time in the therapeutic range among patients with atrial fibrillation (43). Their results showed that patients less than 65 years of age had a higher rate of suboptimal quality of anticoagulation control. Female patients generally have a decreased probability of achieving good anticoagulation control. This finding was reported by Connolly et al. (2008) and later by Ciurus et al. (2015) (14,44). The reasons for this observation remain to be expounded and may be related to cyclical changes in oestrogen exposure or other environmental or social factors.

A diagnosis of MVR and prolonged warfarin treatment are associated with lower rates of anticoagulation control (45,46). These two factors could be interconnected as patients with a mechanical MVR typically require life-long warfarin therapy. In explaining the negative influence of prolonged treatment durations on the quality of anticoagulation control, social determinants of health may need to be considered. For instance, finances have a bearing on adherence to follow-up dates which may become

more significant with prolonged durations of treatment. Poor adherence has a direct negative link to poor quality of anticoagulation (37). In terms of chronic comorbidities, Ciurus et al. (2015) have shown that a diagnosis of hypertension can reduce the quality of anticoagulation control (44). In addition, congestive cardiac failure as a co-diagnosis also makes it difficult to achieve good anticoagulation control (44).

Infectious comorbid conditions such as HIV and tuberculosis are of importance in Sub-Saharan Africa and they are associated with poor anticoagulation control (3). Patients with these diagnoses require more clinic visits to achieve good anticoagulation control (3). A study carried out in Kenya amongst VTE patients with a co-diagnosis of HIV and TB found that patients required a median of eight additional appointments before achieving good anticoagulation control (47). Labile INRs have been shown to be associated with the use of antiretrovirals in patients living with HIV and rifampicin in patients with TB (48). Rifampicin is a potent inducer of a number of CYP450 enzyme isoforms including those involved in warfarin metabolism (3). The resultant effect is decreased plasma concentrations of warfarin and associated decreased effect and decreased response to warfarin. Cotrimoxazole, on the other hand, is a standard addition for patients with HIV in Namibia as it reduces the risk of certain opportunistic infections (49). The drug has been shown to inhibit *CYP1A2* and *CYP3A4*. These oxidative enzymes metabolize the relatively lesser active *R*-enantiomer of warfarin which may inadvertently exaggerate the effects of warfarin (32).

2.13 Status quo on the predictors of anticoagulation control in the clinical setting.

From a review of the literature, it is clear that many factors affect the quality of anticoagulation control. Attempts to standardize these factors in different

anticoagulation clinics have been made. The commonly reported clinical score: SAMe-TT_2R_2 (Sex, female; Age, < 60 years; Medical history [more than two comorbidities]; Treatment [interacting drugs such as amiodarone]; Tobacco use [given two points]; Race [also given two points]) was used to predict mean %TTR control in several studies (50,51). However, a recent systematic review and meta-analysis showed that the score might not be clinically significant and may not be generalized to other settings outside of the US (52). The need to study and understand setting- and context-specific factors affecting the quality of anticoagulation control cannot be overemphasized.

2.14 Pharmacist involvement in anticoagulation services.

During the past 2 decades, a paradigm shift in the management of oral anticoagulation therapy has occurred. A multidisciplinary approach has been implemented in certain settings and has proved beneficial from both a cost and quality perspective of managing warfarin therapy. This approach has allowed pharmacists, nurses, and other health care providers (HCPs) such as doctors to actively manage anticoagulation therapy under defined treatment guidelines. Pharmacists bring in a different clinical perspective focusing on patient warfarin education, health status evaluation, adherence, and warfarin-drug interactions with concomitantly administered medications (9,10).

Several studies have shown that pharmacist-managed anticoagulation monitoring services improved anticoagulation control and reduced the risk of warfarin adverse events (7–10,53). For example, Noor et al. (2021) conducted a retrospective study comparing a pharmacist versus a haematologist-led anticoagulation service (54). The pharmacist-led anticoagulation service had a median TTR of 71%, IQR (60.8-83.8) in

comparison to a median TTR of 65%, IQR (43.5-79.1) obtained by the haematologist-led anticoagulation service. This difference was noted to be statistically significant, however, they also reported that there was no statistically significant difference in the thrombotic and haemorrhagic events in the two groups (54). This finding was in part supported by the results of a systematic review and meta-analysis carried out a few years earlier in 2017 (55). The study involved 8 randomized controlled trials and 9 observational studies with 9919 patients. In line with the finding by Noor et al. (2021), there was no difference in major haemorrhagic events and mortality between the pharmacist-led versus standard-of-care anticoagulation service (55). Although there was a decreased total haemorrhagic, minor bleeding, and thrombotic events in the pharmacist managed anticoagulation service, the authors showed that there was no significant difference in the quality of anticoagulation control between the two groups. In the same year, another systematic review carried out on the subject reported contradictory findings to those by Hou et al. (2017) (55) (56). Manzoor et al. (2017) did not only show that a pharmacist-managed anticoagulation service resulted in a better quality of anticoagulation control, they also showed that pharmacist involvement was associated with decreased haemorrhagic and thrombotic events which resulted in reduced healthcare visits (56). Although many studies have demonstrated the positive impact of pharmacist-led anticoagulation services, there is evidence that there may be no difference in the quality of anticoagulation service between a pharmacist-led versus other healthcare professionals such as nurses. Besides this study, no comparisons have been made between a pharmacist-led and a standard-of-care anticoagulation service at Windhoek Central Hospital.

2.15 Sensitivity and precision of point-of-care devices for INR monitoring.

Point-of-care (POC) tests are the tests performed at or near the patient's site of care, rather than requiring the sample to be transferred to a laboratory for testing. Their application is increasing as they enable swift clinical decisions due to the rapid turnaround time of INR results (57). In the haematology field, several POC tests (activated clotting time, thromboelastography, platelet function, D-dimer) are available but measurement of international normalized ratio (INR) for monitoring warfarin therapy is the main test in this domain (58). POC testing of INR involves three stages: the pre-analytical, analytical, and post-analytical (59). The pre-analytical stage involves obtaining a drop of blood (10µl to about 35µl) from a fingerprick. The blood sample is then transferred onto a test strip which is inserted into the INR meter. The analytical stage then follows. The test areas of the test strips contain a prothrombin reagent. Upon application of the blood sample to the test area, the prothrombin reagent is dissolved, resulting into an electrochemical reaction. This reaction measures the thromboplastin-mediated clotting time which is then converted into a plasma prothrombin time upon activation of blood coagulation with human recombinant tissue factor. This prothrombin time, also known as the "clotting time", is then used to calculate the patient's INR value. Lastly, the post-analytical stage involves the display of the INR. The clinician can then assess the INR value as being subtherapeutic, therapeutic, or supratherapeutic.

Despite the emergence of novel oral anticoagulants, warfarin is still the most commonly used oral anticoagulant worldwide (60). Warfarin is monitored through INR which is a mathematical calculation based on prothrombin time. To determine INR, POC testing could be performed easily without the delay of a formal blood draw and the time required to perform an INR in the laboratory. Additionally, INR-POC

testing allows the reduction of problems related to venepuncture, particularly in patients with difficult venous access, therefore, possibly minimizing errors in the assessment of patients' coagulation status (61). POC INR testing can allow for clinicians to view a patient's INR in real-time (without the laboratory delay) and can allow the clinician to query out-of-range INRs while the patient is present rather than attempting to contact the patient 12-24 hours later. It also provides greater convenience for patients living in remote locations and has been advocated for home monitoring and patient self-dose adjustment (16).

Quality assurance for INR-POC testing is no less important than for conventional laboratory-based analyses. It incorporates all measures taken to ensure the reliability of testing and reporting. The CoaguChek® XS INR meter from Roche Diagnostics (which was used in the intervention study) has been shown in several studies to give accurate and precise results when compared to laboratory-based determination of INR (17,62). The conventional laboratories in these studies used the STAGO®- Star coagulometers and not the Werfen® elite pro Automated Coagulation (ACL) meter used at Windhoek Central Hospital NIP laboratory. Although strong positive correlations such as r = 0.97 (95%CI: 0.95 – 0.97) have been shown between the CoaguChek® XS INR meter and the STAGO®-Star coagulometers, an increase in the differences between the methods was observed with INR results above 5.0 (17). The increase in the difference between the two methods was also reported in South Africa but at a much lower INR result of 3.6 (62). In 2010, one study determined the sensitivity and specificity between the CoaguChek® XS INR meter and the STAGO® Compact Analyzer to be 65.5% and 67.6% respectively (63). The sensitivity of the CoaguChek® XS INR meter defined as the percentage accuracy in detecting therapeutic INR and specificity as the percentage accuracy in correctly detecting sub-

therapeutic and supra-therapeutic INR values. In this study, the highest correlation between the two methods was observed in the INR range of 2.0 to 3.0. The sensitivity and specificity of the POC INR meters were not reported in most of the comparison studies. A study in Korea looked at the agreement between the CoaguChek® XS INR meter and the ACL-based laboratory INR meter. They reported a good positive correlation ($r=0.97$, $p<0.001$) between the two methods, however, the authors concluded that the two methods may need to be run together from time to time in patients with low serum fibrinogen levels (<130 mg/dl) as low serum fibrinogen levels reduce the correlation between the two methods (64). While POC-INR devices can be used in the clinical settings, it is pertinent to be vigilant about the possibility of errors in INR results by these devices. In 2010, a case report was published on the use of a CoaguChek® S INR meter which resulted in the thrombosis of the patient's prosthetic tricuspid valve (65). At the time, the patient was self-monitoring his INRs using the device. Since then, the much more accurate CoaguChek® XS INR meter was introduced into the clinical market (66).

2.16 Summary of literature review.

Many factors influence clinical response to warfarin. Generalized interventions such as close INR monitoring may be of use in managing the non-modifiable factors. Modifiable factors such as geographic location on the other hand warrant the need to determine clinic/facility-specific factors that influence the quality of anticoagulation control. Patient knowledge of warfarin therapy is another important common factor which may improve INR control. Pharmacists have been shown to positively impact the level of knowledge of warfarin therapy, improve adherence, and ultimately the quality of anticoagulation control. In the anticoagulation field, the CoaguChek® XS

INR meters have been extensively studied and shown to be comparable to centralized laboratory methods of INR monitoring. Background information from the nurses at the clinic revealed that point-of-care INR meters were used to test INRs at the clinic years back. However, there was no evidence to show how the INRs from the POC INR meters correlated or agreed with the INR results from NIP's ACL. Interventions included in this study involved the introduction of a pharmacist and POC INR testing to manage anticoagulation therapy at the warfarin outpatient clinic of Windhoek Central Hospital.

3. RESEARCH METHODOLOGY.

3.1 Research design and study site.

To test the study hypothesis, a quantitative prospective cohort design was used. The outcome of interest was the quality of anticoagulation control defined by %TTR which is a quantitative measure. Data collection was carried out prospectively from January 20th, 2021 to July 28th, 2021.

The study was carried out in a defined cohort of patients on warfarin therapy attending the warfarin outpatient clinic of WCH. WCH is a specialist-level hospital situated in Windhoek, the capital city of Namibia. According to the Health Information office of WCH, the hospital has a bed capacity of 855 patients serving a population of over 25 000 inpatients and 100 000 outpatients annually. Since it is a specialist-level hospital, the catchment area is essentially the entire country (2.596 million people in 2022) (67). The hospital provides several specialty clinics, including the cardiac clinic. The cardiac clinic is organised into different 'sub-clinics' on different days of the week. These are as follows: Mondays – thoracic clinic, Tuesdays – adult cardiology & paediatric congenital clinic, Wednesdays – INR/warfarin clinic, Thursdays – adult & paediatric congenital clinic, and Fridays – Mixed clinic. The Warfarin Outpatient Clinic is responsible for the maintenance therapy of patients on warfarin. These patients are referrals primarily from the cardiac ward of WCH and from Intermediate Hospital Katutura -the referral hospital for the Southern half of Namibia and the district hospital for Windhoek. According to the Ministry of Health and Social Services' Cardiac Outpatient Quarterly Report of 2022, the clinic attended to about 10 000 patients of which 27% (2746) were patients on warfarin maintenance therapy and 1.6% (158) were new referrals for warfarin maintenance (68). This translates into an average of 228 patients a month or 57 patients every Wednesday of the week. An

average of 13 patients a month were referred to the clinic which translates into 4 new patients requiring warfarin counselling every week.

3.2 Patient population.

All outpatients on warfarin therapy who attended the Warfarin Outpatient Clinic on Wednesdays and gave informed consent were enrolled in the study. The study took place from January 20th, 2021 to July 28th, 2021.

3.2.1 Inclusion criteria.

Only patients who attended the warfarin clinic on Wednesdays were exposed to the intervention study. In addition, only data from patients 18 years or older who gave informed written consent was collected for analysis. Patients with at least three INR readings during the follow-up period were included in the data analysis of the study.

3.2.2 Exclusion criteria.

Patients on warfarin who visited the cardiac clinic on days other than Wednesdays were not part of the intervention study. In addition, data from patients below the age of 18 years and those 18 years or older who did not give informed written consent was not collected. Patients with less than three INR readings during the follow-up period were excluded from the data analysis of the study.

3.3 Sampling procedure.

Due to the interventional nature of the study, all patients who attended the warfarin clinic on Wednesdays during the study period were eligible for the study and offered the interventions. Convenience sampling was employed as the study participants were

recruited when the pharmacist was at the clinic on Wednesdays during the intervention period. Written informed consent was sought from the patients permitting us to use their clinical data for this study. Each outpatient on warfarin who attended the warfarin clinic had an equal chance of giving informed consent for their data to be used in the study.

3.3.1 Sample size calculation.

The sample size was calculated based on the main objective. The median TTR of 25% was calculated from data received from the historical control study ((11). This median TTR translates into a proportion of 0.25 of patients with good anticoagulation control in the historical control group (standard of care). The literature review revealed an improvement in the quality of anticoagulation control ranging from 6.4% to 17.7% in a pharmacist-directed warfarin therapy compared to standard of care warfarin therapy (8,9,54,69). In view of this, a target improvement in the quality of anticoagulation control was set at 18%. Since the proportion of patients in the control group with good quality of anticoagulation control was 0.25, a 0.18 improvement results in the expected quality of anticoagulation control in the intervention group of 0.43.

Statulator®, an online sample size calculator, was used to determine the sample size in the intervention group. Since 25% of the patients in the control group had good quality of anticoagulation control, after applying continuity correction, the intervention study required a sample size of 116 for the intervention and 116 for the historical control (i.e. a total sample size of 232, assuming equal group sizes), to achieve a power of 80% for detecting a difference in proportions of 0.18 between the two groups (control - intervention group) at a two-sided p-value of 0.05 (70).

3.4 The intervention vs the standard of care (Data collection procedure).

Patients attending the warfarin outpatient clinic on Wednesdays began by getting their bloods drawn for INR testing at the Namibia Institute of Pathology (NIP) hospital laboratory. The laboratory (NIP) then calculated the INR results derived from the patient's prothrombin testing. The INR results were available later in the day and these were traced using a computer stationed at the cardiac clinic. An automatically generated printout of a unique code of the patient's blood sample was provided in the patient's health passport by laboratory staff. After their bloods were drawn, the patient proceeded to the cardiac clinic where they engaged with the pharmacist and nurses about their anticoagulation care. In the historical control group, nurses noted down the patients' names, diagnosis, date of birth, cell phone numbers, NIP's unique code (to trace INR results later), previous weekly dosage of warfarin, and the previous INR results. These were recorded in a "Cardiac Clinic INR book." However, a more structured and detailed interview of the patients was carried out in the intervention group. For this, the pharmacist interviewed each patient and the nurses assisted with actively translating the questions and responses for patients who were not fluent in English. Data collected during the interview included patient demographics (including the unique code of their blood sample and their cell phone number), previous INR results, and warfarin dosage. In addition, the pharmacist also interviewed the patients about what they anticipated their INR result would be and asked that they provided any possible reasons for such anticipation. For example, the patient reported that they thought their INR result would be low and a possible explanation could have been that they missed several doses of warfarin. Other than self-reporting, the pharmacist also asked direct questions pertaining to certain factors of interest that may explain a non-therapeutic INR. For example, "Did you consume any alcohol for the past one week?"

All the above processes typically happened in the morning hours from 07:00 to 11:30 AM. The afternoons were usually reserved for tracing the INR results, dosage adjustments, and calling the patients. The tracing of INR results was carried out by the pharmacist and nurses. Dosage adjustment using a dosage adjustment algorithm was strictly carried out by the pharmacist. In the historical control group, dosage adjustment was purely based on the latest INR result. Dosage adjustment in the intervention group was based on the latest INR results and a clinical judgement of the factors (from patient interviews) that could have affected the patient's latest INR results. The nurses assisted the pharmacist in calling the patients. During these calls, three instructions were provided to the patients: 1) asked that the patient recorded their INR results in their INR book, 2) confirmed their new warfarin dosage, and 3) scheduled their next follow-up date and any relevant counselling. The demographic data and data about the INRs were used to answer research questions 1 and 2 of this study. In the final two months of the study, the pharmacist carried out point-of-care INR testing using the CoaguChek® XS INR meter on 89 patients. These 89 patients also had their INRs checked by the NIP laboratory. This data was used to answer the third and last research questions of this study.

***The pharmacist's interventions*:** The pharmacist in the current study made up to 10 different intervention types during the study period. To begin with, the pharmacist interviewed each patient who came to the clinic. The interviews provided information that the pharmacist used to ensure more targeted and individualized interventions unique to the patients. This differed from the standard process at the clinic where dose adjustment decisions were based solely on the INR results. Warfarin training was

carried out for all patients visiting the warfarin outpatient clinic for the first time (new patients). Together with the clinical pharmacist, training was also provided to the nurses at the clinic. The clinical pharmacist was stationed at the hospital's (WCH) pharmacy department.

Warfarin dosage adjustment was carried out by the pharmacist. Once the dosage adjustment process was completed, the pharmacist and the nurses would telephonically communicate to the patients, their new warfarin dosage and their follow-up date. Patients with therapeutic INRs did not have their warfarin dosages changed and this was telephonically communicated as such. These patients would have longer intervals (on average a month) between visits to the clinic.

When clinically assessed to be appropriate, the pharmacist recommended stopping warfarin therapy. One of the common reasons that the pharmacist recommended stopping warfarin therapy was that the patients were being managed for a much longer period than recommended in the warfarin guideline for that specific condition regardless of the initial symptoms subsiding. Another intervention was switching patients from warfarin to another anticoagulation medicine such as dabigatran.

Patients in whom new thromboembolic events (new DVT or new PE, or a new stroke) were suspected, the pharmacist and the nurses observed that these patients' INR results were mostly subtherapeutic regardless of the numerous warfarin dosage increments. The pharmacist recommended such patients to see their medical officers from (at the wards where their warfarin therapy was initiated). A note was made in their health passport for the medical officers to consider putting the patient back on a treatment course of warfarin in combination with a low molecular weight heparin in the attempt to have their INRs therapeutic and thereafter possibly have a stable dosage of warfarin for their maintenance phase. The pharmacist also motivated for an onsite (at the clinic)

medical officer (MO). It was proposed that the MO would attend to the medical needs of patients at the clinic in the morning hours (08:00 to 12:00) of the warfarin clinic day. The motivation was communicated to the WCH cardiac consultant and IHK's internal medicine consultant. Another motivation was for the hospital to procure warfarin in a different strength other than the 5 mg tablets. The pharmacist, through the chief pharmacist at WCH, motivated for warfarin 1 mg tablets.

Another crucial role of the pharmacist was their involvement in handling queries from medical officers regarding warfarin. Finally, some patients had difficulty getting the time off from work to show up for their follow-up at the clinic. In these patients, the pharmacist wrote letters to their employer explaining the need for the patient to adhere to their recommended follow-up dates.

3.5 Research instruments.

The research instruments used were: a detailed data collection tool (Appendix III), a dose adjustment algorithm (Appendix IV), and the CoaguChek® XS INR meter. The data collection tool used (Appendix III) was adapted from the information/data collection system used by a free clinic in the United States of America (Birmingham Free Clinic, Pittsburgh, Pennsylvania). This tool was slightly modified to fit the purpose of this study (72). The modifications were such that the tool's dosage adjustment section, specifically table 2, included the patient's point-of-care INR and haemoglobin result. Due to the modifications made, the tool underwent extensive review by research supervisors ensuring face validity. The data collection tool was piloted in the first three patients who gave consent to be part of the study. It was clear that the dosage adjustment section of the tool was not user friendly. In addition, the

cardiac clinic's INR book had a better structure of capturing the previous weekly dosage and the recommended dosage for warfarin. Consequently, the INR book was used to capture details about the dosage adjustments instead of the data collection tool. Nonetheless, the data collection tool was used to collect patient demographic information (Patient Demographics Page) and information related to the warfarin maintenance treatment of the patient (Patient Assessment Page). These data were collected by interviewing the patients while at the clinic. Later in the day, when the INR results for that specific day were available, dosage adjustment was carried out based on the dose adjustment algorithm (Appendix IV) and factors that may have affected the patients' INR results. This algorithm is also used at the Birmingham Free Clinic (72). The internal validity of the study was improved by piloting the data collection tool.

3.6 Data analysis.

Statistical analyses were performed using IBM SPSS for Windows versions 27.0 and 28.0 (SPSS Inc, Chicago, Illinois). With the exception of the bivariate analysis for the binary logistic regression, statistical significance was set at a $p \leq 0.05$. The data analysis is described on the basis of the main objective and research questions.

3.6.1 Patient demographics in the intervention group.

Frequencies and percentages were used to summarize categorical demographic/clinical data such as pharmacist interventions and warfarin indications. Measures of central tendency (mean and median) and dispersion (standard deviation and interquartile range) were used to summarize continuous demographic/clinical data such as age, %TTR, and duration of warfarin treatment. The Kolmogorov-Smirnov

(KS) test and distribution histograms were used to determine the normality of continuous variables. The continuous variables were summarized using means and standard deviations if the KS test and distribution histograms showed a normal distribution. The continuous variable was summarized using median and interquartile ranges when the KS test and distribution histograms showed statistically significant deviation from the normal distribution.

3.6.2 Pharmacist and quality of anticoagulation control in the intervention group.

At the end of the study period, % individual Time in Therapeutic Range (%iTTR) for each patient was calculated using the Rosendaal method (12). %iTTR was calculated based on target INR ranges and expanded INR ranges adjusted with a tolerance of 0.4 units. The tolerance of 0.4 units was decided upon since it was within the tolerance range reported in the American College of Chest Physicians' evidence-based clinical practice guidelines (4). The mean or median %TTR was obtained by calculating the mean or median %TTR from all %iTTR. The mean or median %TTR calculated based on target INR ranges was designated "target %TTR" and the mean or median %TTR calculated based on the expanded INR ranges was designated "expanded %TTR."

3.6.3 Factors affecting the quality of anticoagulation control.

Binary logistic regression was used to examine the probability of achieving good anticoagulation control based on: age, sex, an indication of DVT, AF, or MVR, whether the patient was a new (attended the warfarin clinic and followed up for less than a month during the time of data collection or started on warfarin maintenance therapy during the intervention period) or an old patient (attended the warfarin clinic

and followed up for more than a month before the beginning of the intervention period) whether they had a therapeutic or non-therapeutic baseline INR result (the first INR result obtained from the patient at the warfarin clinic of WCH), adherence to their warfarin dosage (defined for the purposes of this study that the patient followed the warfarin dosage recommendations from the clinic more than 50% of the intervention study period), adherence to their follow-up dates (assessed to be adherent to follow up dates if the patient came to the clinic on the specified follow-up date or within seven days from the specified follow-up date), a co-diagnosis of HIV, HF, or hypertension, co-treatment with HAART, co-treatment with perindopril containing chronic regimens, and duration of warfarin therapy. A preliminary analysis was carried out to test for the assumptions required to undertake a binary logistic regression. The assumptions were:

1. the predictors should not be paired or have been measured twice,
2. the predictors should not have been highly correlated,
3. there should have been no outliers with continuous predictors,
4. the continuous variables should not have been linearly related to their log odds, and
5. the outcome should have been measured as a binary variable (73,74).

A Spearman's correlation was used to assess variables with a high correlation ($r \geq 0.7$) (75) and testing for outliers involved running a simple linear regression between the continuous variables (age and duration of treatment) and the outcome of anticoagulation (classified as good or poor anticoagulation control, i.e. %TTR $\geq$ 65% or < 65%).

A binary logistic regression sample run was carried out to assess whether the aforementioned independent variables were linearly related to their log odds.

Furthermore, to assess whether the two continuous variables, i.e. age and duration of warfarin therapy were independently and statistically significantly influencing the outcome of good quality of anticoagulation control, a univariate logistic regression was carried out. Before running the final binary logistic regression, a bivariate analysis between the categorical factors and the outcome of anticoagulation was carried out to determine the statistically significant factors (76). A p value of <0.25 was used to select the studied factors that would be included in the final binary regression model (76). A chi-squared test was used to undertake this analysis. Since the results of the chi-square test were expressed in a 2x2 contingency table and the degree of freedom was 1, the effect size of dependence was assessed using the Phi (φ) value. The effect size of the agreement was assessed as per the Phi value as follows: ≤0.10 = small effect size, 0.30 = medium effect size, and ≥0.50 = large effect size (77). Knowing that the outcome was measured as a binary variable, which was: good anticoagulation control = 1, and poor anticoagulation control = 0, a binary logistic regression was carried out. To avoid overcrowding the final model with variables, the event per variable (EPV) of 10 approach was used. The EPV of 10 is an objective method of determining the number of factors to include in the model in order for statistically sound conclusions to be made (78). To obtain this: first, the number of patients in the outcomes of interest (good anticoagulation control and poor anticoagulation control) is determined. Second, the outcome with the least number of patients is divided by 10. Third and lastly, the result of the division is the total number of variables to include in the final model. The binary regression model was run using the forward stepwise (likelihood ratio) method of covariate selection. A 0.1 alpha level was used to evaluate covariate significance and assessed as confounding covariate when there was a change in the model fit estimate greater than of 20% as compared to the model without the covariate.

3.6.4 Comparing the quality of anticoagulation control in the intervention group to the control group.

Firstly, there was need to find out if there were any paired cases of patients between the two groups. With the primary dataset from the control study made available, it was established that 22 patients were part of both the control and the intervention study. Henceforth, separate statistical analyses were carried out to compare the quality of anticoagulation control in the paired patient cases and the un-paired cases of patients. A descriptive comparison based on their demographics and then comparisons based on inferential statistics were carried out. The Mann-Whitney U test was used to determine if the median age distribution of the unpaired patient cases in the intervention group was statistically similar to the control group. The assumptions which were followed for a Mann-Whitney U test were:

1. the dependent variable (%TTR) was measured as a continuous variable,
2. the independent variable (age) came from two independent groups (the intervention group and the control group), and
3. age distribution in the intervention group and the control group was not normally distributed.

A Pearson's chi-square test was used to assess the proportion of sex distributions in the unpaired cases between the intervention and the control group. The Kolmogorov-Smirnov (KS) test was used to assess the normality of %TTR amongst unpaired cases in the intervention and the control group. To test the study hypothesis in the unpaired cases of patients, a Mann-Whitney U test was used to compare the median %TTR achieved from the intervention group to the median %TTR from the control group. In addition, the Shapiro-Wilk (SW) test was used to assess the normality of the paired

differences in %TTR amongst paired cases of patients. To test the study hypothesis in the paired cases of patients, a paired sample t-test was used to compare the mean %TTR achieved from the intervention group to the mean %TTR achieved in the control group. The following assumptions for carrying out a paired sample t-test were tested and not violated:

1. the dependent variable was continuous (%TTR),
2. we had dependent observations since the same patients who were part of the control group were also part of the intervention group,
3. While the control group included all records during the study period, patients in the intervention group were randomly selected,
4. the difference in the %TTR in the paired cases was normally distributed, and
5. we did not detect any outliers in the paired cases of the patients.

3.6.5 CoaguChek® XS INRs versus ACL NIP INRs.

The sensitivity and specificity of the CoaguChek® XS INR meter were assessed by comparing paired INR results obtained from the POC device and NIP's ACL INR analyzer in each patient. The comparison was carried out by Spearman's correlation analysis, a Bland – Altman plot, and a Cohen Kappa analysis of the paired INR values. Interpretation of Spearman's coefficient was based on the following scale: 0.00-0.19=very weak, 0.20-0.39=weak, 0.40-0.59=moderate, 0.60-0.79=strong, and 0.80-1.00=very strong (79). To determine the presence of proportional bias between the two methods, a simple linear regression was carried out before the Bland-Altman plots were constructed. Clinical concordance, sensitivity, and specificity were all obtained from the Cohen Kappa analysis. The following interpretation of the Kappa value was used: values ≤ 0= no agreement, 0.01–0.20= none to slight, 0.21–0.40= fair, 0.41–

0.60= moderate, 0.61–0.80= substantial, and 0.81–1.00= almost perfect agreement (80).

4. RESEARCH ETHICS.

The study protocol was approved by the Human Research Ethics Committee (HREC) of UNAM (Appendix III). Since the study was carried out in patients attending the warfarin clinic at a state hospital, permission to conduct the study was sought and obtained from the Ministry of Health and Social Services' directorate of research (Appendix IV). Only data from patients who gave informed written consent were used in the study. Patients were free to withdraw their informed written consent at any point in time during the intervention period without any consequences on their further treatment. To ensure anonymity, patients were de-identified by allocating them study identification numbers. The intervention study was carried out on the ethical principles of maximized beneficence and non-maleficence. Patients were treated fairly and with the utmost respect. The data collected from the patients were kept under lock and key and any electronic files were password protected. The paper records were shredded, and all electronic data related to the study was erased after two years.

5. RESULTS.

5.1 Patient demographics and clinical characteristics in the intervention group.

The intervention study sought consent from 124 patients to participate in the study. A response rate of 100% was achieved. For analysis, nine patients (7%) were excluded as they only had two INR readings. Consequently, the study patients consisted of 73 (63.5%) females and 42 (36.5%) males (N = 115). The average age was 45 ± 17.2 years. The youngest patient was 18 years and the oldest was 96 years old. The top three most frequent clinical indications for warfarin were: DVT (n=57, 49.6%), MVR (n=16, 13.9%), and PE (n=15, 13.0%). Only 12 (10.0%) of the patients were being managed with warfarin for atrial fibrillation (AF). Patients who were managed for DVT or PE were on average treated for a duration of 12 ± 14 months. The longest treatment duration amongst all patients was 55 months (4.6 years). Most of the patients (72%) missed at least one of their scheduled follow-up dates. However, the majority of the patients (76.5%) were assessed to be adherent to their warfarin dosage based on the definition of adherence set a priori. Table 3 below illustrates these results.

Table 3: General demographics and clinical characteristics in the intervention group.

Demographics	N (%)	Mean (SD)
Sex		
Male	42 (36.5)	
Female	73 (63.5)	
Age (years)		44.8 (±17.2)
Clinical Indications		
DVT	57 (49.6)	
MVR	16 (13.9)	
PE	15 (13.0)	
AF	12 (10.4)	
AVR	5 (4.3)	
MVR/AVR	5 (4.3)	
STROKE	2 (1.7)	
AORTIC CLOT	1 (0.9)	
STROKE + DVT	1 (0.9)	
DVT + PE	1 (0.9)	
Treatment Duration (months)		
DVT and PE		12.3 (±14.1)
Adherence to follow-up dates		
Missed Follow-up	83 (72.2)	
Did Not Miss Follow-up	32 (27.8)	
Adherence to warfarin dosage		
Adherence	88 (76.5)	
Non-adherence	26 (22.6)	
Undetermined	1 (0.9)	

DVT: Deep Vein Thrombosis, MVR: Mitral Valve Replacement, PE: Pulmonary Embolism, AF: Atrial Fibrillation, AVR: Aortic Valve Replacement, DVR: Double Valve Replacement.

5.2 The profile of chronic comorbid conditions in the intervention group.

More than half of the participants had chronic disease (n=69, 60%). Cardiovascular diseases (CVD), (n=46, 67.0%) and infectious diseases, (n=17, 25.0%) constituted the top two most common chronic disease classifications (N = 69). Table 4 below shows the results.

Table 4: The profile of chronic comorbid conditions in the intervention group.

Disease	N (%)
CVD	
HTN	21 (30.4)
RHD	18 (26.1)
HF	7 (10.1)
Infectious disease	
HIV+	15 (21.7)
TB	2 (2.9)
Respiratory disease	
Asthma	2 (2.9)
Metabolic disease	
DM + Hypercholesterolemia	1 (1.4)
CNS disease	
Epilepsy	1 (1.4)
Other	
Osteoarthritis	1 (1.4)
Nephrotic Syndrome	1 (1.4)

CVD: Cardiovascular Disease, HTN: Hypertension, RHD, Rheumatic Heart Disease, HF: Heart Failure, HIV+: Human Immunodeficiency Virus positive, TB: Tuberculosis, DM: Diabetes Mellitus, CNS: Central Nervous System disorder.

5.1.1 *The profile of chronic co-treatment in the intervention group.*

Almost three-quarters (n=50, 72%) of the 69 patients with chronic diseases were being managed with chronic medication with known clinically significant drug interactions with warfarin. Cotrimoxazole (sulphamethoxazole + trimethoprim) (n=15, 30%) was the most common anti-infective known to clinically potentiate the effect of warfarin in the study. On the other hand, furosemide (n=15, 30%) was the most common cardiovascular medicine to potentially inhibit the effect of warfarin in the study patients. The results are shown in table 5 below.

Table 5: The profile of chronic co-treatment in the intervention group.

Medicine	N (%)
Cardiovascular medicines	
Increase Warfarin Activity	
Amiodarone	1 (2.1)
Aspirin	5 (10.6)
Simvastatin	4 (8.5)
Propranolol	1 (2.1)
Decrease Warfarin Activity	
Furosemide	15 (31.9)
Anti-infective medicines	
Increase Warfarin Activity	
Cotrimoxazole	15 (31.9)
Isoniazid	4 (8.5)
Decrease Warfarin Activity	
Rifampicin	2 (4.3)
Analgesics, Anti-inflammatory, immunologic	
Increase Warfarin Activity	
Paracetamol	1 (2.1)
Celecoxib	1 (2.1)

5.3 The pharmacist interventions in the intervention group.

The pharmacist carried out 10 different interventions types during the study period. These included interviewing patients, carrying out dosage adjustments, and educating new patients on their warfarin therapy. The pharmacist was also involved in educating the nurses and worked hand in hand with a hospital clinical pharmacist to manage the patients. Table 6 below gives a summary of the interventions that the pharmacist carried out during the intervention period.

Table 6: The pharmacist interventions in the intervention group.

Intervention	No. of Patients (Description)	Outcome(s)
1. Interviewing patients	All	
2. Dosage adjustment	279	Improved iTTR
3. Recommend stopping warfarin therapy	11 (2 were pregnant in their first trimester)	Doctors stopped warfarin use in 5 patients (2 pregnant), and 2 patients booked for Doppler ultrasound. 4 patients with status unknown
4. Motivation for an onsite physician during clinic days	Through the WCH cardiac consultant and the IHK internal medicine consultant.	Both attempts not successful. Physicians already understaffed.
5. Motivation for additional strengths of warfarin tablets beyond 5mg	Once through the chief pharmacist of WCH	Ongoing
6. Recommend switching therapy	2 patients (one switched to dabigatran and the other to aspirin)	Successful
7. Training and counseling of patients	55 (New patients offered warfarin 'training') Patient counseling was carried out in ALL patients on their visits	Successful
8. Training of onsite nurses	2: (onsite nurses) 1: (Final year clinical pharmacy candidate)	Successful
9. Handling queries from doctors	1: From dermatology (skin biopsy while on warfarin)	Successful
10. Writing letters to patient employers	1	Successful

5.4 Pharmacist and quality of anticoagulation control in the intervention group.

The Kolmogorov-Smirnov (KS) test of normality showed that the target %TTR and expanded %TTR were not normally distributed (p<0.05). The median target %TTR

was 42% (IQR: 18-64%) and the median expanded %TTR was 75% (IQR: 54-90%). Good anticoagulation control was defined as %TTR ≥ 65%. The median target %TTR obtained was below 65%, however, the median expanded %TTR was greater than 65%. Table: 7 below illustrates the results.

Table 7: Quality of anticoagulation control in the intervention group.

Variable	n	Median (IQR)
Target %TTR	115	42% (18-64)
Expanded %TTR	115	75% (54-90)

5.5 Adverse effects of warfarin in the intervention group.

Undesirable treatment outcomes were observed in 24 of the 115 patients (21%). Amongst these patients, bleeding events (n=13, 54%) were more commonly reported than new thromboembolic events (n=11, 46%).

5.6 Factors affecting the quality of anticoagulation control in the intervention group.

5.6.1 Independent continuous variable versus anticoagulation control.

Before carrying out the final binary logistic regression, a univariate logistic regression was carried out between the continuous variables (age and duration of warfarin therapy) and the outcome of anticoagulation control. At an adjusted $p<0.25$, none of the two variables were statistically significant. Table 8 below shows the results.

Table 8: Continuous variables versus anticoagulation control.

Predictor	B	S.E.	Wald	*df*	*p*	OR	95% C.I. for OR	
							Lower	Upper
Age	-.008	.014	.384	1	.535	.992	.965	1.018
Treat-duration	-.003	.011	.055	1	.815	.997	.976	1.019

5.6.2 Categorical variables versus anticoagulation control.

Before carrying out the final binary logistic regression, a bivariate analysis was carried out between categorical variables and the outcome of anticoagulation control (assessed as good or poor anticoagulation). At an adjusted $p<0.25$, the following six categorical variables were assessed to be statistically significant and were moved into the multi-variate regression: 1. Mitral valve replacement (p=0.23), 2. HIV (p=0.23), 3. Heart failure (p=0.20), 4. Being on a perindopril containing chronic regimen (p=0.22), 5. Baseline INR (p=0.008), and 6. Warfarin dosage adherence (p=0.04). By conventional levels of statistical significance, only baseline INR and warfarin dosage adherence had $p<0.05$. Specifics of the results are detailed below.

There were more female patients (60%) than male patients (40%) who achieved good anticoagulation control. Similarly, there were more female patients (65%) than male patients (35%) who achieved poor anticoagulation control. A chi-squared test of dependence showed that gender had a small (Phi = 0.04) and statistically non-significant influence on the outcome of good anticoagulation control, χ^2 (1, N = 115) =0.21, p =0.65.

Good anticoagulation control was achieved more in patients with a DVT diagnosis (53%) than those in whom DVT was not the indication for warfarin therapy (47%). Though there was a small difference in the percentage distribution of the outcomes, the opposite trend was observed with poor anticoagulation control. Patients with an indication for warfarin other than DVT had a higher chance (54%) than patients on

warfarin for DVT (46%) to achieve poor anticoagulation control. A chi-squared test of dependence showed that DVT, as an indication for warfarin therapy, had a small (Phi = 0.07) and statistically non-significant influence on the outcome of good anticoagulation control, χ^2 (1, N = 115) =0.49, p =0.48.

A smaller percentage (13%) of patients with a diagnosis of atrial fibrillation compared to those without atrial fibrillation (87%) achieved good anticoagulation control. Similarly, a smaller percentage (9%) of patients with a diagnosis of atrial fibrillation compared to those without atrial fibrillation (91%) achieved poor anticoagulation control. A chi-squared test of dependence also showed that a diagnosis of atrial fibrillation had a small (Phi = 0.06) and statistically non-significant influence on the outcome of good anticoagulation control, χ^2 (1, N = 115) =0.37, p =0.54.

A smaller percentage (7%) compared to those who had no MVR (93%) had good anticoagulation control. A similar trend was observed with poor anticoagulation control. A smaller percentage (15%) of patients compared to those who had no MVR (85%) had bad anticoagulation control. A chi-squared test of dependence also showed that having an MVR had a small to medium (Phi = 0.11) and statistically significant influence on the outcome of good anticoagulation control, χ^2 (1, N = 115) =1.46, p <0.25.

Good anticoagulation control was associated with patients who had their HIV status unknown, (assumed to be HIV negative) (93%) compared to those who were HIV positive (7%). Similarly, poor anticoagulation control was associated with patients who had their HIV status unknown, (assumed to be HIV negative) (85%) compared to those who were HIV positive (15%). A chi-squared test of dependence showed that HIV status had a small to medium (Phi = 0.11) and statistically significant influence on the outcome of good anticoagulation control, χ^2 (1, N = 115) =1.46, p <0.25.

Only 30% of patients with a co-diagnosis of heart failure compared to 70% of patients without a co-diagnosis of heart failure had good quality of anticoagulation control. Similarly, only 19% of patients with a co-diagnosis of heart failure compared to 81% of patients without a co-diagnosis of heart failure had poor anticoagulation control. A chi-squared test of dependence showed that having a co-diagnosis of heart failure had a small to medium (Phi = 0.12) but a statistically significant influence on the outcome of good anticoagulation control, χ^2 (1, N = 115) =1.63, p <0.25.

Only 17% of patients with a co-diagnosis of hypertension compared to 83% of patients without a co-diagnosis of hypertension had good quality of anticoagulation control. Similarly, only 13% of patients with a co-diagnosis of hypertension compared to 87% of patients without a co-diagnosis of hypertension had poor anticoagulation control. A co-diagnosis of hypertension had a small (Phi = 0.05) and statistically non-significant influence on the outcome of good anticoagulation control, χ^2 (1, N = 115) =0.26, p =0.61.

Fewer (17%) of patients on HAART compared to patients not on HAART (83%) achieved good anticoagulation control. A similar trend was observed with poor anticoagulation control. A lesser percentage (15%) of patients on HAART compared to patients not on HAART (85%) achieved poor anticoagulation control. A chi-squared test of dependence showed that co-medicating with HAART had a small (Phi = 0.02) and statistically non-significant influence on the outcome of good anticoagulation control, χ^2 (1, N = 115) =0.03, p =0.86.

Patients who were on perindopril-containing chronic medicines had a lower percentage (27%) than those who were not on perindopril-containing chronic medicines (73%) in achieving good anticoagulation control. Similarly, patients who were on perindopril-containing chronic medicines had a lower percentage (16%)

compared to those who were not on perindopril-containing chronic medicines (84%). A chi-squared test of dependence showed co-medicating with perindopril-containing chronic medicines had a small to medium (Phi = 0.11) and statistically significant influence on the outcome of good anticoagulation control, χ^2 (1, N = 115) =1.5, p <0.25.

Good anticoagulation control was also assessed for dependence based on the patient's baseline INR. 53% of patients with a therapeutic baseline INR compared to 47% with a non-therapeutic baseline INR achieved good anticoagulation control. Fewer patients (29%) with therapeutic baseline INR compared to patients with non-therapeutic baseline INR (71%) achieved poor anticoagulation control. A chi-squared test of dependence showed that having a therapeutic baseline INR had a small to medium (Phi = 0.22) and statistically significant influence on the outcome of good anticoagulation control, χ^2 (1, N = 115) =5.5, p<0.25.

Furthermore, adherence to follow-up dates and warfarin dosage adherence were assessed. Fewer patients (33%) who were assessed to be adherent to their follow up date compared to patients who were assessed to not be adherent to their follow up date (67%) had good anticoagulation control. However, even fewer patients (26%) who were assessed to be adherent to their follow-up date compared to patients who were assessed to not be adherent to their follow up date (74%) had poor anticoagulation control. A chi-squared test of dependence showed that adherence to follow-up dates had a small (Phi = 0.07) and statistically non-significant influence on the outcome of good anticoagulation control, χ^2 (1, N = 115) =0.61, p =0.43.

Most (90%) of patients who were adherent to their warfarin dosage compared to 10% who did not adhere to their dosage achieved good anticoagulation control. Similarly, 72% of the patients were adherent to their warfarin dosage compared to 28% of

patients who were not adherent to their warfarin dosage achieved poor anticoagulation control. A chi-squared test of dependence showed that being adherent to warfarin dosage had a small to medium (Phi = 0.19) but statistically significant influence on the outcome of good anticoagulation control, χ^2 (1, N = 115) = 4.1, p<0.25.

With respect to patient status. Patients who were new to the clinic had a lesser percentage (17%) compared to patients well known to the clinic (83%) in achieving good anticoagulation control. A similar trend was observed with poor anticoagulation control. New patients had a lesser percentage (20%) compared to the old patients (80%) in achieving poor anticoagulation control. A chi-squared test of dependence showed that patient status had a small (Phi = 0.04) and statistically non-significant influence on the outcome of good anticoagulation control, χ^2 (1, N = 115) =0.16, p =0.70. Table 9 below outlines these results.

Table 9: Categorical variables vs anticoagulation control.

Predictor	Category	Poor anticoagulation n	Poor anticoagulation %	Good anticoagulation n	Good anticoagulation %	X^2	Phi
Sex	Male	30	35	12	40	0.21,	-
	Female	55	65	18	60	*P*=0.65	0.04
DVT	Yes	39	46	16	53	0.49,	0.07
	No	46	54	14	47	*P*=0.48	
AF	Yes	8	9	4	13	0.37	0.06
	No	77	91	26	87	*P*=0.54	
MVR	Yes	13	15	2	7	1.46	-
	No	72	85	28	93	*P*=0.23	0.11
HIV	Yes	13	15	2	7	1.46	-
	No	72	85	28	93	*P*=0.23	0.11
HF	Yes	16	19	9	30	1.63	0.12
	No	69	81	21	70	*P*=0.2	
HTN	Yes	11	13	5	17	0.26	0.05
	No	74	87	25	83	*P*=0.61	
HAART	Yes	13	15	5	17	0.03	0.02
	No	72	85	25	83	*P*=0.86	
Perind-R	Yes	14	16	8	27	1.5	0.11
	No	71	84	22	73	*P*=0.22	
Base-INR	Therap	25	29	16	53	5.5	
	Non-Therap	60	71	14	47	*P*=0.008	0.22
Follow-up	Adherent	22	26	10	33	0.61	-
	Non-adherent	63	74	20	67	*P*=0.43	0.07
Dosage	Adherent	61	72	27	90	4.1	
	Non-adherent	24	28	3	10	*P*=0.04	0.19
Patient	New	17	20	5	17	0.16	-
	Old	68	80	25	83	*P*=0.7	0.04

Note: DVT: Deep Vein Thrombosis, AF: Atrial Fibrillation, MVR: Mitral Valve Replacement, HIV: Human Immunodeficiency Virus, HF: Heart failure, HTN: Hypertension, HAART: Highly Active Antiretroviral Therapy, Perind-R: Perindopril containing regimen, and Base-INR: Baseline INR.

5.7 Binary logistic regression models.

5.7.1 The regression model as per the events per variable of 10.

A Spearman's correlation was used to assess variables with a high correlation ($r \geq 0.7$).

Patient status and duration of treatment had the highest correlation coefficient of 0.68.

This correlation was less than 0.7, therefore, none of the variables of interest were highly correlated. A test for outliers involved running a simple linear regression between the continuous variables (age, duration of treatment, and the number of co-medicines) and the outcome of anticoagulation (classified as good or poor anticoagulation control, i.e. %TTR ≥ 65% or < 65%). The test results showed that there were two outliers: cases 21 and 45. Nonetheless, these two outliers were included in the final model since there was no compelling reason for their exclusion.

As stated above, 25 of 115 patients achieved good anticoagulation control (TTR ≥ 65%) which makes it the outcome with the least number of patients. Dividing 25 by 10 gives 2.5 which meant that the final model needed to have a maximum of 2 factors. However, the bivariate analysis showed that six factors had a statistically significant influence on the quality of anticoagulation control. These factors were: MVR, HIV status, a co-diagnosis of heart failure, being on a perindopril containing chronic regimen, baseline INR, and warfarin dosage adherence. A forward stepwise (likelihood ratio) approach was employed to objectively select two factors out of the six to be included in the model.

The resultant regression model was statistically significant, χ^2 (2, n = 115) = 8.31, p <0.001, suggesting that it could adequately distinguish between those with poor and good anticoagulation control. In assessing the goodness-of-fit, the omnibus test of coefficients suggested that the model was statistically significant, p<0.01. In addition, the Hosmer and Lemeshow test showed a p >0.05 suggesting that the proposed model was a good fit. Therefore, it could adequately describe the outcome of good anticoagulation control. As per the Nagelkerke pseudo R square, the probability of the predictors predicting good anticoagulation control was 13%. Consequently, the sensitivity also known as the true positive rate of the model was 0% while the

specificity, which is the true negative rate of the model was 100%. It appeared that the model seemed to correctly classify poor anticoagulation control more than good anticoagulation control. An inspection of the standardized residual values in the case-wise list table revealed two outliers from the preliminary tests of assumptions. These cases were not removed from the model as there was no compelling reason to do so.

Out of the six studied predictors, only the baseline INR class and warfarin dosage adherence were statistically significant. A non-therapeutic baseline INR and poor warfarin dosage adherence were associated with 66% and 82% lower chance of achieving good quality of anticoagulation control respectively. Table 10 below shows the results of the model.

Table 10: Predictors of the quality of anticoagulation control in the intervention group (EPV=10).

							95% C.I. for OR	
Predictor	**B**	**S.E.**	**Wald**	***df***	***p***	**OR**	**Lower**	**Upper**
Baseline INR Class (0)	-1.094	.483	5.137	1	.023	.335	.130	.862
Dosage Adherence (0)	-1.731	.794	4.752	1	.029	.177	.037	.840
Constant	.352	.374	.887	1	.346	.703		

Note: ***Baseline INR Class*** *(1: Therapeutic baseline INR, 0: Non-therapeutic);* ***Dosage adherence*** *(1: Adherent, 0: Non-adherent).*

5.8 Comparing the quality of anticoagulation control in the intervention group to the control group.

5.8.1 The characteristics of INRs and quality of anticoagulation control in the intervention and the control group.

In the historical control group, patients whose target INR range was 2.0 – 3.0 had an average INR of 2.4 (n=165). In the intervention group, the average INR in the 2.0 – 3.0 target INR range in the intervention group was somewhat lower 2.06 (n=93), but

still in range. For a target INR range of 2.5 – 3.5, the control and intervention group had an average INR of 2.5 (n=50) and 2.3 (n=22) respectively. At the time of recruitment, therapeutic baseline INRs were observed in 54 (25%) patients in the control group while the intervention group recorded 41 (36%) of the patients. Only 22 of the 215 patients (10%) in the control group compared to 25 of 115 patients (22%) in the intervention group had TTR ≥65%.

The control group reported the quality of anticoagulation in terms of target %TTR. The comparison of the quality of anticoagulation between the two groups was based on the target %TTR and not the expanded %TTR. The median %TTR values in the control and intervention group were 25% (IQR: 10%-45%) and 42% (IQR: 18%-64%), respectively. The results showed a 17% improvement in the quality of anticoagulation control in the intervention group. Further comparison of the quality of anticoagulation had to be made on the basis of paired and unpaired patient cases.

Table 11: The characteristics of INRs and the quality of anticoagulation control in the control and intervention groups.

Characteristics/Outcome	Control Group n=215	Intervention Group n=115
INR value, mean (*n*).		
2.0 – 3.0	2.4 (165)	2.1 (93)
2.5 – 3.5	2.5 (50)	2.3 (22)
Baseline INR, n (%).		
Therapeutic	54 (25.1)	41 (35.7)
Non-therapeutic	161 (74.9)	74 (64.3)
Target %TTR median, (IQR)	25 (10-45)	42 (18-64)

5.8.2 A comparison of the demographics and clinical characteristics: unpaired patients.

We compared the demographic characteristics in the unpaired cases between the intervention and the control group. This comparison was based on: age distribution,

sex distribution, and warfarin indication. The Kolmogorov-Smirnov (KS) test showed that the age distribution in both groups was not normally distributed ($p<0.05$). Therefore, the Mann-Whitney U test was used to compare the difference in the median age between the two groups. The results showed a statistically significant difference in the median age of the two groups (control group: 46 (10-85) and intervention group: 42 (18-96)), though the clinical significance of this difference is unknown. In terms of sex distribution, however, a chi-square analysis showed no statistically significant difference between the two groups. In addition, the two groups had the same top three indications for warfarin therapy namely: DVT, MVR, and PE. Without withstanding the statistically significant difference in the median age, the rest of the demographics between the groups were similar and therefore the two groups were quite comparable.

Table 12: Unpaired patients: a comparison of their demographics and clinical characteristics.

Characteristic	**Control**	**Intervention**	**Mann-Whitney, (*p-value*)**	**Pearson Chi-square, (*p-value*)**
Sample size (No. of patients	192	94		
Age, years: median (range)	46 (10-85)	42 (18-96)	7611 (<0.001)	
Sex, n (%)				
Male	68 (31.6)	42 (36.5)		0.64
Female	147 (68.4)	73 (63.5)		(0.42)
Indication, n (%)				
DVT	62 (37.6)	57 (49.6)		
MVR	40 (18.6)	16 (13.9)		
PE	44 (26.7)	15 (13.0)		
AF	29 (17.6)	12 (10.4)		
AVR	9 (5.5)	5 (4.3)		
DVR	8 (3.7)	5 (4.3)		

DVT: Deep Vein Thrombosis, MVR: Mitral Valve Replacement, PE: Pulmonary Embolism, AF: Atrial Fibrillation, AVR: Aortic Valve Replacement, DVR: Double Valve Replacement.

5.8.3 A comparison of the quality of anticoagulation control in unpaired patients.

The Kolmogorov-Smirnov (KS) test showed that data on percentage time in the therapeutic range in both groups were not normally distributed ($p<0.05$). Therefore, the Mann-Whitney U-test was used to compare the median target %TTR obtained from the intervention group [42% (IQR: 18.5% – 63%)] to the median target %TTR obtained in the control group [24% (IQR: 9.50% - 45%)]. The results showed that there was a statistically significant improvement in the median target %TTR in the intervention compared to the control group [18% improvement, $p<0.05$]. Figure 5 below is a bar graph representing the quality of anticoagulation control between the groups in comparison to the target TTR of 65%

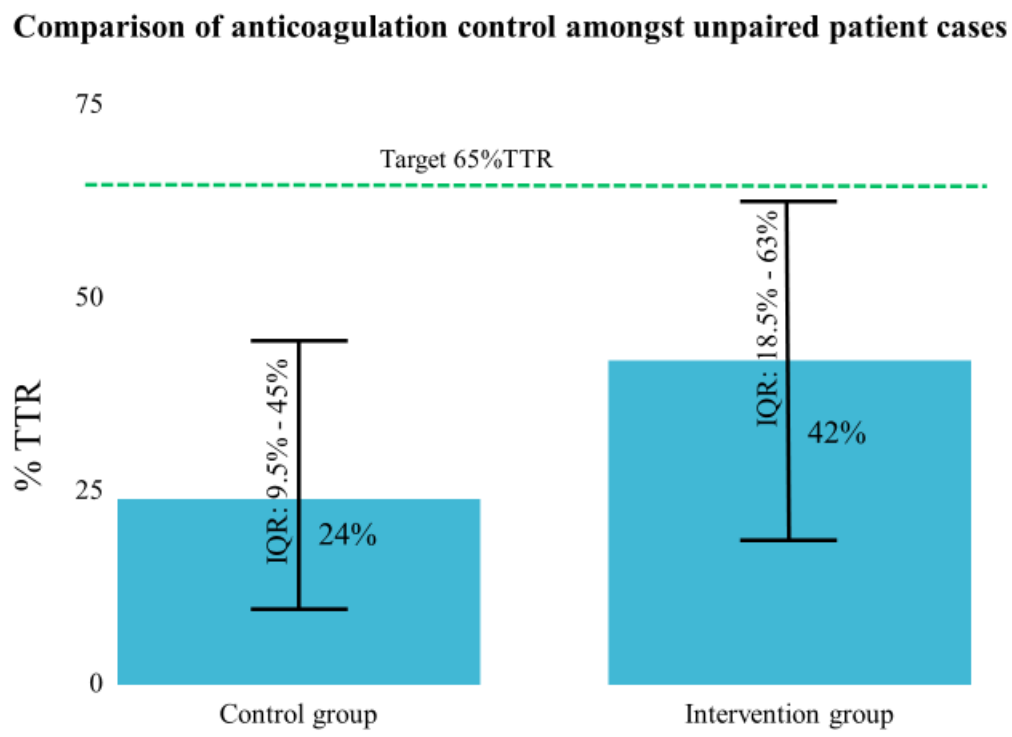

Figure 5. The quality of anticoagulation control in the unpaired patient cases.

5.8.4 A comparison of the quality of anticoagulation control in the paired patient cases.

An assumption was made that certain patient demographics such as gender in the paired cases have not changed over the two years from 2019 (control study) to 2021 (data collection for the intervention study). We also assumed that a four-year age difference between the two groups might not affect anticoagulation control to a large extent. The Shapiro-Wilk (SW) test on the paired differences of the percentage of individual Time in the Therapeutic Range (%iTTR) showed that the paired differences were normally distributed (p=0.60). A paired sample t-test was therefore used to compare the difference in the mean target %TTR obtained in the intervention group (39.7 ±28.8%) and the control group (29.4% ±24.9%). The results showed a 10.4% improvement in the mean target %TTR in the intervention group from the control group, though the change was not statistically significant (p=0.22). Figure 6 below is a graphical representation of the results.

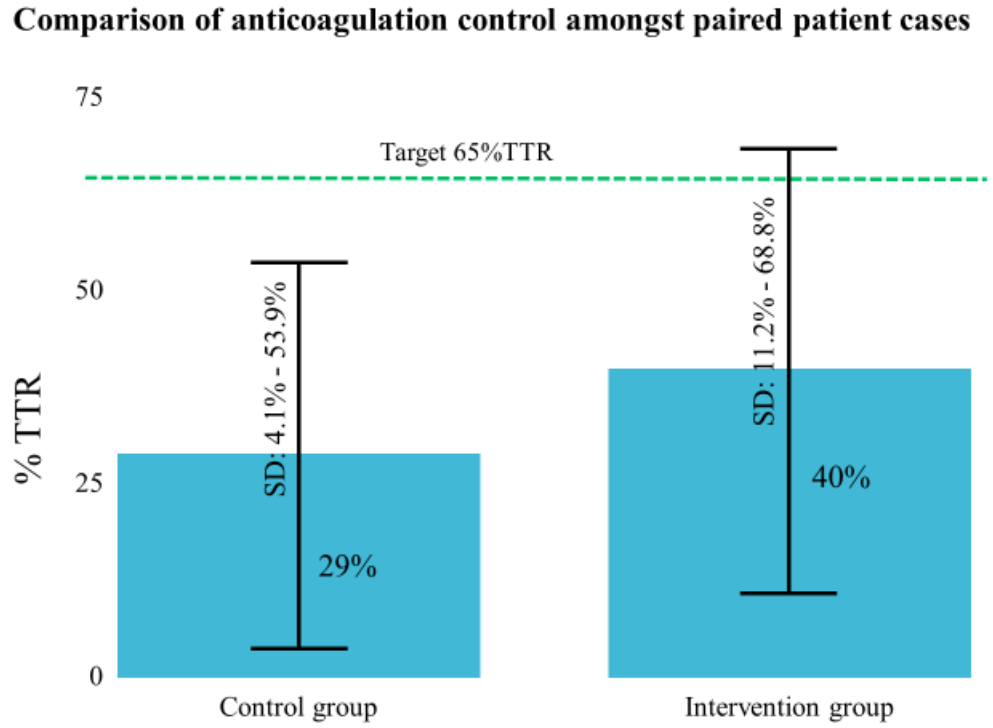

Figure 6. The quality of anticoagulation control in the paired patient cases.

5.9 COAGUCHEK® XS INRs versus ACL NIP INRs.

5.9.1 Correlation analysis.

Spearman's correlation analysis revealed that INR results from the CoaguChek® XS meter were positively and highly correlated to the Namibia Institute of Pathology (NIP) results (*Spearman's r*: 0.97, $p<0.001$, N=22). The scatterplot is shown in figure 7 below.

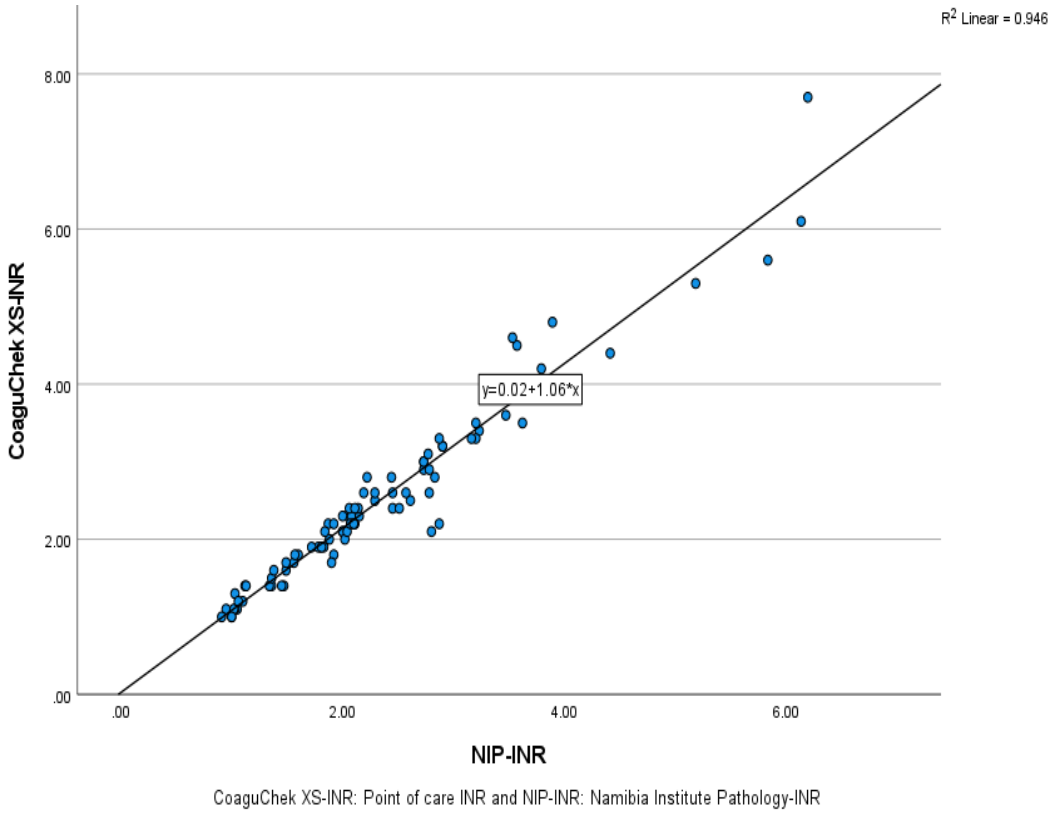

Figure 7. Scatter plot graph showing the correlation between the INR values obtained by the CoaguChek® XS INR meter and NIP ACL INR meter.

5.9.2 The Bland-Altman plot including the outliers.

Before carrying out the Bland-Altman analysis, a simple linear regression between the differences in the paired INR values and mean INR values was performed. It suggested the presence of proportional bias between the two methods (p<0.05). The proportional bias was noted to have a positive direction. Ideally, the presence of proportional bias means that the agreement between INR values obtained from the CoaguChek® XS INR meter and NIP's ACL should not have been assessed using the Bland-Altman method. However, the Bland-Altman plot, which excludes the outliers and with no presence of proportional bias, showed similar results to the Bland-Altman plot including outliers. The Bland-Altman plot inclusive of outliers showed that the mean INR difference between the CoaguChek® XS INR meter and the NIP's ACL INR

meter was - 0.15 (± 0.27, N=89). In other words, the plot showed a mean bias between the two methods of 0.15. The limits of agreement were between -0.68 and 0.38, a range in which 95% of the differences in paired INR values between the two methods fell. Five INR differences were plotted outside the aforementioned limits of agreement. The first INR difference outside the limits of agreement was plotted at a mean INR of about 2.5. A negative trend seems to be evident as shown by the regression line ($y = 5.94 - (0.09 * X)$). The Bland-Altman plot essentially showed that the difference in the paired INR values between the two methods increased with the increase in mean paired INR values meaning that the higher the INR the more likely there was a discrepancy. Figure 8 below illustrates the results of the Bland-Altman plot.

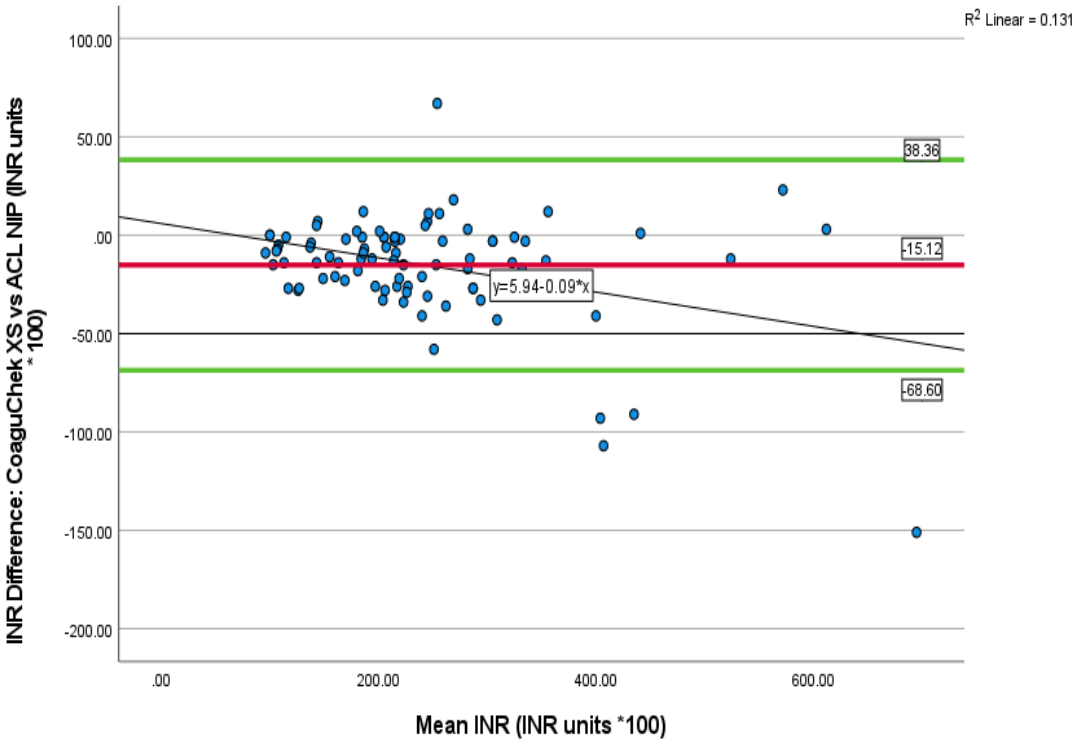

Figure 8. Bland Altman Plot (Tukey Mean-Difference) illustrating the difference in the CoaguChek® XS and ACL NIP INR values within the limits of agreement.

Note: The line that corresponds to an INR difference (Y-axis) of 0.00 is the line of equality, the red line shows the mean difference, the green line below the red line is the lower limit of agreement ***(***$LL = mean\ difference\ - (1.96\ \times$

$standard\ deviation$), ***and the green line above the red line shows the upper limit of agreement (*** $UL = mean\ difference\ +\ (1.96\ \times standard\ deviation)$**.**

5.9.3 *The Bland-Altman plot excluding the outliers.*

The therapeutic INR ranges for the different indications of warfarin in the study, 2-3 or 2.5-3.5, have an INR difference of 1 unit. It was therefore clinically justified that an INR difference between the CoaguChek® XS and ACL NIP INR reading greater than 1 unit should be considered an outlier. This criterion yielded two outliers, one with the difference of 1.51 (CoaguChek® XS: 7.70 and ACL NIP: 6.19) and the other with the difference of 1.07 (CoaguChek® XS: 4.60 and ACL NIP: 3.53). Without the two paired readings mentioned above, a simple linear regression test was run to assess for the presence of proportional bias. The coefficient table showed no presence of proportional bias (p value = 0.286) and therefore, a Bland-Altman plot on the data could be carried out. The plot showed that the mean INR difference between the CoaguChek® XS INR meter and the NIP's ACL INR meter was -0.14 (± 0.22, N=87). In other words, the plot showed a mean bias between the two methods of -0.14. The limits of agreement were between -0.58 and 0.30, a range in which 95% of the differences in paired INR values between the two methods fell. Four INR differences were plotted outside the aforementioned limits of agreement. The first INR difference outside the limits of agreement was plotted at a mean INR of about 2.5. A negative trend seems to be evident as shown by the regression line ($y = -7.98 - (0.03 * X)$). The plot essentially showed that the difference in the paired INR values between the two methods increased with the increase in mean paired INR values. Figure 9 below illustrates the results of the Bland-Altman plot.

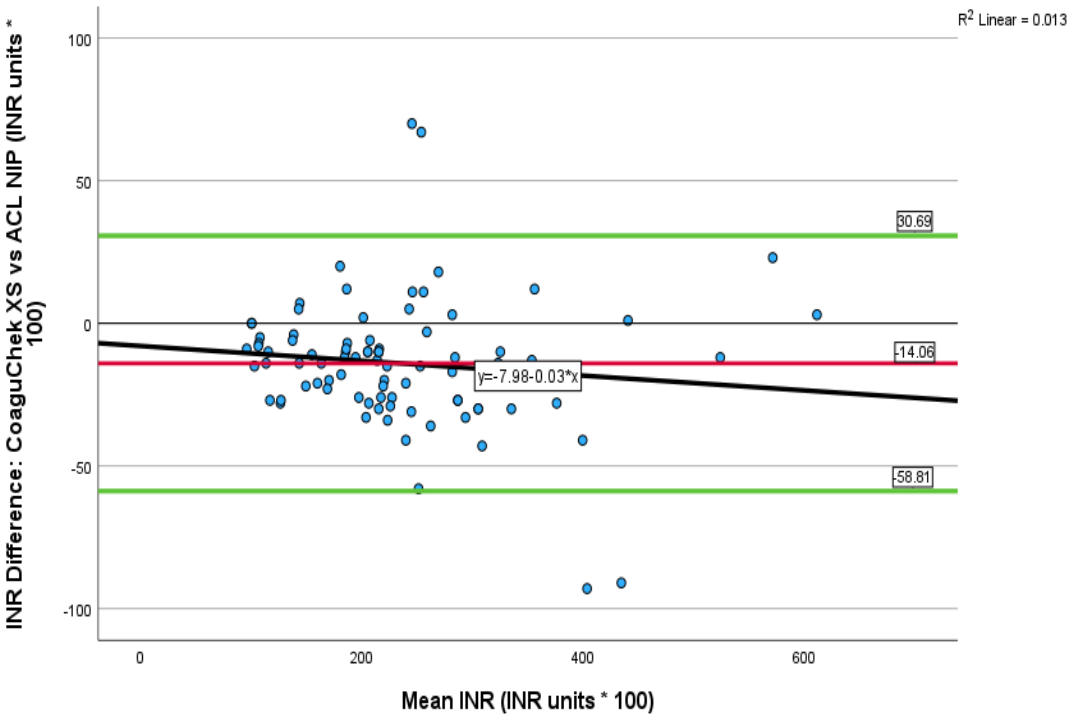

Figure 9. Bland Altman Plot (Tukey Mean-Difference) illustrating the difference in the CoaguChek® XS and NIP ACL INR values within the limits of agreement without outliers.

Note: The line that corresponds to an INR difference (Y-axis) of 0.00 is the line of equality, the red line shows the mean difference, the green line below the red line is the lower limit of agreement ($LL = mean\ difference\ - (1.96\ \times standard\ deviation)$***, and the green line above the red line shows the upper limit of agreement (*** $UL = mean\ difference\ +\ (1.96\ \times standard\ deviation)$***.***

5.9.4 Cohen Kappa analysis.

The agreement of INR measurements between the CoaguChek® XS and NIP's ACL INR meter was further assessed on the basis of three categories, i.e. subtherapeutic, therapeutic, and supratherapeutic using Cohen Kappa analysis. The results showed a statistically significant and an almost perfect clinical agreement between CoaguChek® INR and NIP INR of 83.8%, p<0.05.

In comparison to Namibia Institute of Pathology Automated Coagulation (NIP's ACL) INR analyser, the sensitivity of the CoaguChek® XS INR meter in accurately detecting therapeutic INRs was assessed to be 94.4%. The point of care device had a specificity of 82.5% in correctly detecting sub-therapeutic INR values and 100% for

correctly detecting supra-therapeutic INR values. Table 13 below shows the results of the analysis.

Table 13: Sensitivity (%) and specificity (%) of the CoaguChek® XS INR meter.

		NIP ACL INR Class		
		Sub-therapeutic	*Therapeutic*	*Supra-therapeutic*
Coagu Chek® XS INR Class	*Sub-therapeutic*	82.5	0	0
	Therapeutic	17.4	94.4	0
	Supra-therapeutic	0	5.6	100

6. DISCUSSION.

6.1 Outcomes of the intervention study.

The Windhoek Central Hospital warfarin outpatient clinic attends to more than 200 patients a year. The pharmacist's interventions were targeted to all patients who attended the warfarin-outpatient clinic from January 20th, 2021 to July 28th, 2021 as the interventions were aligned with high-quality warfarin management. However, only a total of 124 patients whom the pharmacist asked to give consent gave their informed consent to take part in the formal study. Of the participants, the majority were women (63.5%). The average age was 45 years (range 18-96). The primary indication for warfarin was venous thromboembolism: DVT (49.6%) and PE (13%). Other important indications included valve replacements: MVR (13.9%), AVR (4.3%), and atrial fibrillation (10%). These indications for warfarin were similar to those reported in the control study [8].

The response rate was 100% which was excellent. Several studies have previously reported response rates ranging from 87% up to 100% ((7–9,81,82). However, a much lower response rate of 70% was reported by Noor et al. (2021) ((54). This was a retrospective cohort study which aimed to assess and compare a pharmacist-led anticoagulation clinic to that of a haematologist. The lower response rate in this study was attributed to a several patients having "shifted to higher INR ranges" or that there were on warfarin therapy for less than six months or that they had inactive patient records. Having more restrictive inclusion criteria limited their ability to include all patients. The current study had wider inclusion criteria leading to few patients being excluded.

Only the data from patients who had more than 2 INR readings (N = 115) during the intervention period was used for analysis. When classifying the INR values as per the

target INR range of 2.0-3.0 or 2.5-3.5, it was found that 81% of the INR values belonged to the 2.0-3.0 target INR range. This is explained by the fact that the 2.0-3.0 INR range is the target INR range for two of the most common indications for warfarin in the study were VTE (DVT and PE).

A closer look into the baseline INR values (the first INR result from each patient at the warfarin clinic) showed that only 36% of the study patients had a therapeutic INR result. Ideally, the warfarin outpatient clinic would be managing warfarin therapy in the maintenance phase of treatment for the majority of patients. For example, by the time a patient on warfarin therapy is referred to the clinic, they should have a therapeutic INR from wherever warfarin initiation took place. After that, the clinic takes over and maintains these therapeutic INRs for a defined treatment duration based on a well-defined diagnosis. The average treatment duration for DVT and PE, collectively referred to as VTE in the current study, was 12 months. This indicates that VTE patients were less likely to be treated as per the short treatment duration of 3 months but rather the longer and a limited period of 6 to 12 months (83). From the available data, it was not possible to determine whether each VTE was provoked or unprovoked making it difficult to determine the most appropriate duration of treatment. See Table 3 of the results section.

It was observed that one of the factors contributing to prolonged treatment durations is the unique challenge that the outpatient clinic finds itself in. The decision to stop warfarin therapy should be made by medical officers. However, patients attending the warfarin outpatient clinic do not have a dedicated team of medical officers strictly handling their anticoagulation therapy at the clinic. In addition, most of the patients were referred from the internal medicine and surgical units of Intermediate Hospital Katutura (IHK) – a neighbouring referral hospital in Windhoek. Since the majority of

patients were referred from inpatient services, most patients would not have long-term continuity with their initial prescriber leading to lack of clarity about duration of treatment. Each medical officer spends about 4-6 months on a particular ward after which they rotate to a different ward and a new team takes over. As a result, chances are high that different medical officers or medical interns attend to these patients when they require a medical assessment while on warfarin therapy. A lack of familiarity to patient's medical history coupled with deficiencies in the documentation of the clinical characterisation of the VTE diagnosis at the point of diagnosis makes it difficult for the different medical officers or medical interns attending to the patients to make certain clinical decisions such as stopping warfarin therapy. It is therefore likely that the average treatment duration in VTE patients could have been shorter than 12 months. This may have negative implications on the quality of life of patients (continued anticoagulation unnecessarily) and associated increase in cost of health care and risk of adverse events. Upon making these observations, the pharmacist engaged with the consultant of the internal medicine unit to find solutions. Unfortunately, the medical team responded that they were significantly understaffed and unable to commit a long-term clinician to the anticoagulation service. One potential solution was to ensure that duration of treatment is documented clearly in the health passport upon diagnosis. If the duration is adequately documented, the anticoagulation team would be able to appropriately discontinue anticoagulation therapy at the end of this time period.

When it comes to the patients' chronic diseases, cardiovascular (67%) and infectious diseases (25%) were the most common classification of chronic diseases observed (See Table 4 of the results section). This is not surprising as the majority of patients attending the warfarin clinic were referrals from the internal medicine department of

the Intermediate Hospital Katutura (IHK). Relatedly, it was expected to find that the most common class of chronic medicines taken by the patients were cardiovascular and anti-infective medicine. Most of patients with chronic diseases (76%) were being managed with at least one chronic medicine with known clinically significant drug interactions with warfarin (see Table 5 of the results section). Teklay et al. (2015) found similar results when studying drug-drug interactions among 133 patients on warfarin therapy (84). They reported a prevalence of 99.2% drug-drug interactions and 49.2% of these were graded moderate or even major (84). Similar to the findings of this study, most of these interactions involved cardiovascular medicines (such as spironolactone) and antibiotics. In the current study, furosemide and cotrimoxazole were the two most commonly prescribed chronic medicines. The results of a systematic review published by Holbrook et al. (2005) revealed that furosemide decreases warfarin activity while cotrimoxazole increases it (32). The mechanism of drug interaction between furosemide and warfarin has not been well elucidated. However, that of cotrimoxazole has been reported in literature. In general, all antibiotics affect the physiology of gut microbiome, an important source of vitamin K (85,86). A decrease in gut microbiome is associated with the initiation of antibiotics while an increase/recovery of gut microbiome is associated with stopping antibiotic therapy (87). A decrease in gut microbiome entails a decrease in vitamin K which may result in potentiating warfarin effects. The opposite is true whereby an increase in gut microbiome resulting in blunting the effects of warfarin. It is therefore prudent that close INR monitoring is ensured when initiating and stopping antibiotic therapy. Furthermore, cotrimoxazole has been shown to inhibit CYP2C9 isoenzyme further potentiating the effects of warfarin (88,89). That said, the majority of interacting medications in this study are chronic medications. Even antibiotics with interactions

in this study are predominantly used over long periods of time, rather than short courses. The benefit of warfarin (as opposed to DOACs) is that the dose can be adjusted to maintain a therapeutic INR. The largest risk with warfarin drug-drug interactions is when new medications are initiated and discontinued. In this study, they major risk is when tuberculosis treatment is initiated and when it is completed. These high-risk times require close management and anticipatory adjustments.

Last but not least, the clinical characteristics revealed that 72% of the study patients missed at least one of their scheduled follow-up dates. When patients are only provided enough warfarin to last until their next INR check, missed appointments result in missed warfarin doses. Further, infrequent follow-up has a negative effect on the prompt identification of non-therapeutic INR results (both subtherapeutic and supratherapeutic) and consequently the appropriate clinical decisions that needed to be taken. Further for VTE patients, missed doses and missed appointments may impact the time required to dissolve the thrombosis requiring longer duration of therapy. To maximize the time that the patients' INR results were therapeutic, the patients would need to be followed-up with more frequent checks for longer periods than usual. This might explain the need to treat VTE patients for extended periods. Nonetheless, the assessment of warfarin dosage adherence showed that 76.5% of the patients were adherent to their medication.

***The pharmacist's interventions*:** In the past two decades, there has been a paradigm shift in the scope of practice of pharmacists. A typical example is their growing involvement in anticoagulation clinics. The pharmacist in the current study made up to 10 different intervention types during the study period. These interventions are outlined in Table 6 of the results section. To begin with, the pharmacist interviewed

each patient who came to the clinic. The interviews provided information that the pharmacist used to ensure more targeted and individualized interventions unique to the patients. Warfarin training was carried out for all patients visiting the warfarin outpatient clinic for the first time (new patients). Together with the clinical pharmacist, training was also provided to the nurses at the clinic.

A total of 279 patients had their warfarin dosages adjusted by the pharmacist. Once the dosage adjustment process was completed, the pharmacist and the nurses would telephonically communicate to the patients, their new warfarin dosage and their follow-up date. Patients with therapeutic INRs did not have their warfarin dosages changed and this was telephonically communicated as such. These patients would have longer intervals (on average a month) between visits to the clinic.

Another intervention was that the pharmacist recommended stopping warfarin therapy in 11 patients. Two of these patients were pregnant in their first trimester and warfarin is contraindicated in pregnancy. Of the 11 patients, the medical officers stopped warfarin therapy in five (including the two pregnant patients). Two of the remaining 6 had a repeat Doppler ultrasound test booked to assess whether their VTE had fully dissolved. The outcome of the recommendation in the remaining 4 patients is unknown. One of the common reasons that the pharmacist recommended stopping warfarin therapy was that the patients were being managed for a much longer period than recommended in the warfarin guideline for that specific condition. It was observed by both the pharmacist and the nurses that the lack of a medical officer dedicated to the clinic could be contributing to warfarin therapy being utilized for longer than recommended. As the number of patients requiring anticoagulation service continues to increase and almost none of the patients' warfarin therapy is stopped, the clinic may reach their capacity. This could have a negative impact on the quality of

the anticoagulation service in the long run. Another intervention was in two patients: one with Alzheimer's disease who was struggling follow warfarin dosage adjustments from the clinic and had to be switched from warfarin to dabigatran 110 mg twice daily and the other with a bioprosthetic aortic valve who was able to be switched from warfarin to aspirin 150 mg daily. The indication for warfarin in the patient co-diagnosed with Alzheimer's disease was valvular atrial fibrillation. The patient was 79 years old with labile INRs, constantly reporting blood stains in his stool within a week of visiting the clinic. It was clear that the patient had difficult peripheral veins too. The NIP laboratory staff made a note in the patient's health passport that they were having difficulty obtaining a sufficient blood sample from the patient. After the pharmacist's intervention, the patient became the third to be put on dabigatran in the entire country. While newer data suggests that warfarin is preferred for valvular atrial fibrillation, the INVICTUS trial was not published at the time of this intervention (71). Further, warfarin was not going to be a reasonable intervention for this patient.

For patients in whom new thromboembolic events (new DVT or new PE, or a new stroke) were suspected, the pharmacist and the nurses observed that these patients' INR results were mostly subtherapeutic regardless of the numerous warfarin dosage increments. Therefore, the pharmacist recommended that the patients had to seek medical care. A note was made in their health passport for the medical officers to consider putting the patient back on a treatment course of warfarin in combination with a low molecular weight heparin in an attempt to have their INRs therapeutic and thereafter possibly have a stable dosage of warfarin. The pharmacist also motivated for an onsite medical officer (MO). We proposed that the MO would attend to the medical needs of patients at the clinic in the morning hours (08:00 to 12:00) of the warfarin clinic day. The motivation was communicated to the WCH cardiac consultant

and IHK's internal medicine consultant. Though the consultants appreciated the gravity of the challenge, the attempt failed due to the critical need for MOs in their respective wards. Another motivation was for the hospital to procure warfarin in a different strength other than the 5mg tablets. The pharmacist, through the chief pharmacist of WCH, motivated for warfarin 1mg tablets. This would cater for patients whose total weekly dosage of warfarin could not be adjusted by 5mg or 2.5 mg. Several patients in the clinic required less than 2.5 mg of warfarin daily, often secondary to interacting medications. Without a lower available strength, some were prescribed to take 2.5 mg on only a few days a week which may lead to more labile INRs.

Another crucial role of the pharmacist involved handling queries from medical officers regarding the use of warfarin. Last but not least, some patients had difficulty getting the time off from work to show up for their follow-up at the clinic. In one of the patients, the pharmacist had to write a letter to their employer explaining the need for the patient to adhere to their recommended follow-up dates.

Time in therapeutic range: The individual patient's INR values were analysed into %iTTR using the Rosendaal method. The Rosendaal method assumes linearity in the INR values from one patient's clinic visit to the next (12). %iTTR was calculated based on target INR ranges and expanded INR ranges adjusted with a tolerance or variance in the range of 0.4. For example, %iTTR calculated on 2-3 INR ranges adjusted with a tolerance of 0.4 units means that a patient's INR value is assessed to be therapeutic if it falls in the INR range of 1.6-3.4. In the current study, the mean and median %TTRs were calculated based on target INR ranges was designated "target %TTR" and the mean/median %TTR calculated based on the adjusted INR ranges was designated

"expanded %TTR." The literature review did not reveal on what basis a particular tolerance was chosen. In the current study, adjusted INR ranges using a tolerance of 0.4 units resulted in a median expanded %TTR of 75%. However, when the INR ranges were not adjusted by a tolerance of 0.4 units, a median target %TTR of 42% was obtained (see Table 7 of the results section). Using the > 65% TTR cut-off, it was concluded, based on the target %TTR, that anticoagulation control was still poor. In the current study, calculating the expanded %TTR was more pragmatic. This was due to the fact that the University of Pittsburgh's Warfarin Dose Algorithm used in the study gives warfarin dose recommendations based on adjusted INR ranges of 0.3-0.5 units and not target INR ranges (Appendix II). To add on, state hospitals only have one strength of warfarin tablets (5 mg). A patient whose INR value was 0.1 or 0.2 units below the lower value of the target range might have required an increase in the weekly warfarin dose of 1 mg. This increase was difficult to achieve when the patients only had warfarin 5 mg tablets and not any other smaller strength like the warfarin 1 mg tablets.

Adverse events: Undesirable treatment outcomes associated with warfarin were noted in 19.4% of the patients. This translated to almost one in five patients noted to have some adverse effect of warfarin. Haemorrhagic events were the most reported. These ranged from epistaxis, gum bleeds, and observing blood-stained stool or urine. This observation was not surprising since there are studies reporting that haemorrhagic events associated with warfarin therapy are more common than thromboembolic events. For instance, Sonuga et al. (2016) reported that the prevalence of haemorrhagic versus thrombotic events at Victoria district hospital in South Africa were 14% and 2.2%, respectively (27). However, the prevalence of haemorrhagic events is not always

more than that of thrombotic events. This outcome may be influenced by the severity of the haemorrhagic events reported. For example, Mohammed et al. (2022) reported the prevalence of major bleeding and recurrent VTE to be 6.4% and 8.2% in patients with provoked VTE (2). They also reported a similar trend in patients with unprovoked VTE where the prevalence of major bleeding and recurrent VTE was 2.4% and 22.3% respectively. Nonetheless, secondary outcomes of anticoagulation control were not compared in the two groups since the historical control group did not report these (11).

Factors contributing to poor control: A total of 14 possible factors which may have affected the quality of anticoagulation control were studied. These included: age, sex, patient status, DVT indication, AF indication, MVR indication, baseline INR, HIV comorbidity, HF comorbidity, HTN comorbidity, co-medicating with a perindopril-based regimen, adherence to warfarin dosage, adherence to follow-up dates, and then duration on warfarin therapy. Of all the studied factors, only the baseline INR and warfarin dosage adherence were predictors of good quality of anticoagulation control (see Table 10 of the results section). These two predictors are discussed in detail below. The current study showed that having a therapeutic baseline INR was a predictor of good quality of anticoagulation control. A closer look into the baseline INRs in the patients revealed that only 36% of the study patients had a therapeutic baseline INR result. Whether this is reflective of INR control in the different wards that these patients came from before being referred to the clinic is unknown. What was observed by the pharmacist and the nurses at the warfarin clinic is that upon discharge from the wards and referral to the warfarin clinic, the patients received a limited supply (for approximately 5 to 7 days) of warfarin tablets from the hospital pharmacy. The majority of these patients, who were classified as new patients, would show up to the

warfarin clinic at least a week later from the date of referral to the clinic. The motivation for showing up to the clinic is usually in the order of: first, they ran out of warfarin tablets and second, that they were referred to the clinic. Usually, they have a non-therapeutic INR by the time they come to their first appointment at the warfarin clinic. Similarly, to the findings of the bivariate analysis, the logistic regression model showed that patients who had a non-therapeutic baseline INR, regardless of the indication for warfarin, had a 78% less chance of achieving good anticoagulation control. There were no Cochrane reviews or any studies to compare these findings to. It is likely that patients on warfarin maintenance with a stable warfarin dose and stable INR as evidenced by a therapeutic baseline INR might have a better chance of achieving good anticoagulation control. Therefore, a possible explanation for why non-therapeutic baseline INRs were associated with a 78% less chance of achieving good anticoagulation control could be that the patients were not on stable warfarin dosages and stable INRs in the first place or that it is a marker for non-adherence overall. Perhaps the anticoagulation pharmacist needs to ensure that patients referred to the clinic have stable INRs and that they are on stable doses whilst on the wards before being referred for maintenance to the clinic. Further, warm handoffs (i.e. having the anticoagulation pharmacist visit the patient in the hospital to provide education and to explain the process of INR monitoring) may improve this high-risk transition of care. Once at the clinic, immediate management of unstable INRs is a challenge since both the pharmacist and the nurses do not have prescribing rights. Creating clear nurse and pharmacist managed protocols to allow for the clinic staff to restart LMWHs for patients with a high risk of thrombosis may improve management at the clinic.

In this study, patients were assessed to be adherent to their warfarin dosage if they said that they followed the warfarin dosage recommendations from the clinic on more than

50% of their visits to the clinic during the duration of data collection. In 2015, Lo-Ciganic et al. (90) reported that the cut-off adherence measures which were meant to assess the risk of all-cause hospitalization ranged from 46%-94%. They elucidated further on this by stating that these cut-offs may have been affected by the clinical profile of the patients and consequently by the complexity of their medications. In addition, a systematic review carried out three years later by Baumgartner et al. (91) also suggested that the level of adherence may not be standardized but rather dependent on disease states, medicines prescribed and dispensed, and patient characteristics. The 50% cut-off utilized in the current study falls within this previously reported range of cut-offs. However, it falls on the lower end of the range of cut-offs. Despite the findings from the two studies, a cut-off of ≥80% has been conventionally used to assess the level of adherence to medicines as good (≥80%) or poor (<80%) regardless of the clinical context (92). Therefore, conventionally, the cut-off of 50% may have overestimated the level of medication adherence posing as limitation in this study. Nonetheless, the current study showed that adherence to warfarin dosage was associated with good quality of anticoagulation control. However, the results also revealed that 76.5% of the patients were adherent to their warfarin dosage, nevertheless, the overall quality of anticoagulation control was still suboptimal (iTTR = 42%). In 2016, the results of a cross-sectional survey assessing adherence to warfarin therapy and its impact on the quality of anticoagulation were published (93). They used the Arabic version of the Morisky Medication Adherence Scale (MMAS-8) and defined good anticoagulation control as TTR≥75% and not ≥65%. They found that 46.4% (89/192) patients had high adherence to warfarin therapy. However, similar to the findings of this study, only 38.2% (34/89) of these patients had good anticoagulation control. The authors concluded that there was no

association between adherence to warfarin therapy and anticoagulation control. Contrary to the findings of this study, two recent studies have shown that poor adherence to warfarin therapy is associated with poor quality of anticoagulation control (94,95). A much closer observation into the patients provided a number of possible explanations for the finding. First, a patient can adhere to their warfarin dosage but they can miss doses if they run out of warfarin tablets. Patients will tell the pharmacist and nurses the correct warfarin dose as prescribed from their last visit but few will voluntarily inform them of running out of medicines. This aspect of warfarin management is discussed under the social determinants of health below. Second, was the observation that some patients had non-therapeutic INRs regardless of them being assessed to be adherent to their warfarin dosage. For example, there was one female patient with a co-diagnosis of tuberculosis (TB). They were on the continuation phase of TB treatment on rifampicin/isoniazid/ethambutol combination. Rifampicin is a potent inducer of the cytochrome P450 enzymes. It is known that CYP450 enzyme induction is a much slower process than CYP450 enzyme inhibition. However, the patient was already in the continuation phase of their TB treatment. This meant that they were on rifampicin for a minimum of two months, which was more than adequate time for rifampicin to induce CYP450 enzymes. Therefore, it was clear from the start that that patient needed a much higher total weekly dose than the average patient without TB and not on rifampicin-based treatment. At the time, the question that the pharmacist and the nurses could not answer was how high of the warfarin weekly dose did the patient require. It was decided to continue escalating her warfarin dose slowly (+2.5mg weekly increase). The warfarin dose was still being escalated when the study period came to an end and the patient had subtherapeutic INRs throughout her visits. Developing standard adjustments for common interacting medications would assist the

entire clinical team with improving empiric adjustments. The third and last possible explanation relates to discrepancies between self-reporting adherence and actual adherence to warfarin dosage. There was no objective measure of correlating and confirming the method of assessing adherence to warfarin dosage in the intervention study.

6.2 Contextual factors.

One limitation of the study was that data for all factors influencing anticoagulation control was not systematically collected and analysed. As shown in appendix five below, these factors were classified into dose-related, drug-related, disease-related, diet-related, and social determinants of health (SDOH). The data presented is based on 72 patients' self-reporting. The recording of the data was not linked to a specific patient. Therefore, a statistical analysis of the influence of these factors on the quality of anticoagulation control was not carried out.

Of the 72 patients, dose-related (39%) factors were the majority of identified factors. Firstly, half of these patients reported missing warfarin doses because they ran out of warfarin tablets. As stated earlier, a good number of patients in the current study were referrals from IHK's medical wards, and at the time of these reports, warfarin tablets were out of stock from IHK's pharmacy. The unavailability of warfarin tablets at the pharmacy where these patients would get their warfarin prescriptions filled at the time could have contributed to the patients missing their warfarin doses.

Secondly, seven patients reported that they were not following the warfarin dosage recommendations given by the pharmacist at the clinic. Upon further discussions with these patients, it was clear that they followed the warfarin dosage instructions provided by pharmacists at their respective hospital pharmacies where they filled their warfarin

prescriptions (Windhoek Central Hospital or Intermediate Hospital Katutura). Since the pharmacist-recommended warfarin dosage is communicated to the patients telephonically after the patient has picked up their supply of medicine, there is essentially no written proof of these warfarin dosage recommendations in the patient's health passport. The consequence of this comes into effect when the patients need to get their prescriptions renewed. At that point, the prescriber can put the patient on any warfarin dosage they see fit. The common observation made by these seven patients was that they did not inform their prescribers of the new warfarin dosage recommended by the pharmacist from the clinic. Usually, the prescriber will put the patient back on a standard dose of warfarin (5 mg daily) or the dose of warfarin on which the patient was discharged on. The pharmacist at the hospital pharmacy will supply a quantity of warfarin tablets and provide warfarin dosage instructions to the patients based on the written prescription. The patients will follow these dosage instructions which in most cases deviate from the recommended warfarin dosage by the warfarin outpatient clinic. For patients who insist to follow the warfarin dosage instructions from the warfarin outpatient clinic, chances were that they would run out of their warfarin supply before their next scheduled re-prescription. This is especially true when the prescriber's warfarin dosage, which the hospital pharmacists use as the basis of the quantity of warfarin tablets dispensed to the patients, is lower than the warfarin dosage recommended by the warfarin clinic. This too might have contributed to the patients missing their warfarin doses.

Lastly, two patients reported that they would forget to take their warfarin tablets. It was discovered that these patients would take their warfarin tablets in the morning hours before starting their day. With busy schedules, it is not uncommon, for a patient to forget to take their medicines in the morning hours. The two patients were advised

to start taking their warfarin tablets in the evening instead when they were more likely to be home.

Medication related factors: These factors contributed a small percentage (5.6%). First, two of the patients had a co-diagnosis of tuberculosis (TB). They were both in their continuation phase of TB treatment on the Rifampicin/Isoniazid/Ethambutol (RHE) combination. Rifampicin is a potent inducer of CYP450 enzymes which are involved in the biotransformation of warfarin. Assuming normal metabolism status of the patients, inducing these enzymes entails an increase in the plasma clearance of warfarin. Therefore, to maintain the therapeutic concentrations of warfarin, an increase in the weekly dose of warfarin may be warranted. The weekly dose of warfarin was slowly increased to a maximum of 20 mg. The consequence of this slow increase in the weekly dose was that it took longer to get these patients to a therapeutic INR. This essentially meant that the two patient's anticoagulation control was suboptimal for the majority of the study duration. More aggressive adjustment for known major drug-drug interactions would have been beneficial.

Secondly, two other patients reported using immune boosters and other herbal supplements or homemade remedies. This was highly anticipated since data collection took place during the COVID-19 pandemic. However, no further details were obtained about these factors to allow for a scientific assessment of the possible influence that these factors had on the quality of anticoagulation control.

Disease-related factors: These factors constituted a small percentage (12.5%) too. Firstly, four of these patients were diagnosed with COVID-19 infection. The national COVID-19 management protocol required at the time that the patients be admitted to

an isolated COVID-19 health facility. Management of their COVID-19 infection meant that their warfarin therapy had to be interrupted and they had to be started on subcutaneous injections of enoxaparin instead. As enoxaparin does not affect INR, INRs were noted to be mostly subtherapeutic during their admission period.

Secondly, two other patients had scheduled surgeries that required interruption of their warfarin therapy with enoxaparin bridging instead. Three more patients were classified to have difficult anticoagulation control due to specific disease states. One was a patient with end-stage renal failure, another with a diagnosis of schizophrenia, and the third had chronic diarrhoea. A reduction in renal function can lead to the accumulation of nitrogenous waste products and other products of cellular metabolism. These can alter the pharmacologic and/or physiologic effects of warfarin consequently affecting the dose-response relationship of the drug. As a result, this can make it difficult to attain good anticoagulation control.

For patients with schizophrenia, medication adherence can be a challenge, particularly if their schizophrenia symptoms are not well controlled (96). Poor adherence to warfarin therapy most likely resulted in suboptimal anticoagulation control in the patient, though medication interactions may have also contributed. Further, tobacco use is often higher amongst patients with schizophrenia as nicotine can help manage symptoms (97). Tobacco smoke can decrease INR (98).

Diarrhoea could be associated with a reduction in the absorption of warfarin from the gastrointestinal tract (99,100). A decreased absorption translates into a decreased bioavailability which essentially results in a decreased area under the curve of warfarin and the associated subtherapeutic effects thereafter. However, a case report from 1999 showed that diarrhoea may be associated with supratherapeutic INRs instead (101).

Whatever the case may be, it was clear that diarrhoea is associated with non-therapeutic INRs and therefore suboptimal anticoagulation control.

Diet related factors: These factors were noted in 21% of the patients in the present study. First, 73.3% of these patients admitted having eaten green leafy vegetables as part of their diet. At least half of these patients were from the Zambezi region and this was clinically significant because green leafy vegetables constitute a part of their staple food. As long as the consumption of green leafy vegetables is relatively constant, it should not have a clinically significant effect on their INR fluctuations (102). However, what was observed was the sporadic consumption of varying quantities of green leafy vegetables which were highly dependent on availability. Sporadic consumption of green leafy vegetables in varying quantities while on warfarin has been shown to induce clinically significant fluctuations in the patient's INR results (102). For example, the consumption of large quantities of green leafy vegetables highly correlates with subtherapeutic INRs whilst on warfarin therapy. Green leafy vegetables contain a high content of vitamin K which, in its reduced form, is required for the carboxylation of the glutamic residues of vitamin K-dependent clotting factors thereby promoting thrombosis (21). The higher the vitamin K content, the more the prothrombotic effects (essentially inhibiting the anticoagulation effect of warfarin), the shorter the prothrombin time (PT), and the lower the INR hence subtherapeutic INR.
Second, over a quarter of patients (27%) were noted to consume alcohol. Alcohol consumption has been shown to clinically interact with warfarin by increasing INR thereby increasing the risk of haemorrhagic events (103). This interaction is more prominent in the setting of concomitant hepatic disorder. It is also possible that chronic alcohol consumption may result in subtherapeutic INRs through the upregulation of

CYP450 enzymes (104). Further, patients who binge drink alcohol could be at risk of missing their warfarin doses resulting in subtherapeutic INRs.

Social determinants of health: These constituted the third largest (19%) classification of factors which could have affected the quality of anticoagulation control in the intervention study. Two patients had situations associated with social and cultural beliefs. The first was a female patient who had three consecutive subtherapeutic INRs. On her fourth visit to the clinic, the pharmacist interviewed the patient and discovered that she had abruptly stopped taking her warfarin tablets close to two months ago. She reported that the husband ordered her to stop taking warfarin tablets because they were affecting his manhood. Warfarin was the reason that they could not get pregnant. This may actually be true as warfarin can lead to miscarriages. The second patient believed that since warfarin is a blood thinner, the tablets were meant to make him weak. He believed that the blood in a man ought to be thicker than that of a woman. Interrupting warfarin therapy due to these beliefs could negatively influence the probability of attaining good anticoagulation control.

On the 14th of April, 2021, the pharmacist and the team received a similar query from several patients. The warfarin tablets looked different from the usual. The hospital pharmacy had ordered and received warfarin 5mg tablets from a different supplier. The patients were unsure whether the crème and smaller warfarin tablets from the latest supplier work the same as the maroon and bigger warfarin tablets from the usual supplier. It was possible that some of the patients may have not taken the new batch of warfarin tablets until they got clarity from the clinic that they worked the same. This concern may be been alleviated had the pharmacy team at the hospital explained the change to patients when they picked up their repeat prescription.

The second factor was associated with job security. Three patients reported difficulty adhering to their follow-up dates because it was difficult for them to get permission from their employer to do so. This might have been more difficult for the new patients since they were required to follow-up at the clinic more often than the patients who had consistently therapeutic INRs. Upon a request from one of the patients, the pharmacist wrote a letter to their employer explaining why it was crucial for the patient to adhere to their follow-up dates. While this was only self-reported by 3 patients, it is possible that many more patients were affected but did not volunteer such information to the team. Further, for some their employers would have allowed them to leave, but financially they were unable to take a day without pay. This could help explain how at least 72% of the study patients missed at least one of their scheduled follow-up dates. The lower the adherence to follow-up dates, the longer it took for the team (nurses and the pharmacist) to detect deranged INR results and the longer the patient remained with non-therapeutic INR results. Further, as refills were often tied to visits, delayed appointments also may have led to greater time without warfarin (or patients stretching their doses to last).

Third, six patients reported having difficulties travelling to either one of the anticoagulation clinics (WCH or Oshakati Intermediate Hospital). A good number of these patients work on farms in the outskirts of Windhoek. They reported financial challenges to enable them secure transport to and from the anticoagulation clinics. On top of this, they also have to strategize how to get their prescriptions renewed by the doctors and filled at a pharmacy while they are in Windhoek. It was observed that these patients had to cope using one of three ways: 1) The patient could make transport arrangements with the transport officer of the nearest local hospital or clinic. This would allow the patient to tag along on patient buses if they happen to be travelling to

Windhoek and back on that specific follow-up date. This method was mostly observed with patients coming from Gobabis – a small town, 200 kilometres, east of Windhoek. The method requires a number of logistics to be met and to satisfy all of them is always a challenge. As a consequence, these patients were most likely to miss their follow-up dates. 2) The patient could opt to get their bloods drawn for INR monitoring at their nearest clinic or hospital. The patient was then required to call the anticoagulation clinic and give their details, including the unique number of the sample provided to the patient wherever their bloods were drawn. The unique number of the sample was necessary for the warfarin clinic to trace the results from the laboratory. Since a good number of these clinics or hospitals do not have an onsite, designated laboratory, the blood samples, along with other samples had to be transported from the local hospital or clinic to the central NIP laboratory in Windhoek for testing. Depending on how the sample was handled during the entire process, there were usually two possible outcomes: either the blood sample would haemolyze or the unique sample number would not match the patient in question. Even in the best-case scenario where the anticoagulation clinic was able to trace and get the patient's INR results, it would take days before the patient gets to know their INR results and the changes they needed to make to their warfarin dosage. 3) The patient could just continue taking warfarin tablets daily, regardless of the dose, and then not worry about follow-up dates and INR checks. Figure 10 below better illustrates this method. This was a patient's medicine sachet containing warfarin tablets. As stated before, the hospital pharmacy only keeps one strength of warfarin tablets, the 5mg. The patient broke the tablets into four pieces believing that they are taking at least 1mg of warfarin a day and this dose will sustain their therapeutic INRs until they get the opportunity to visit the anticoagulation clinic.

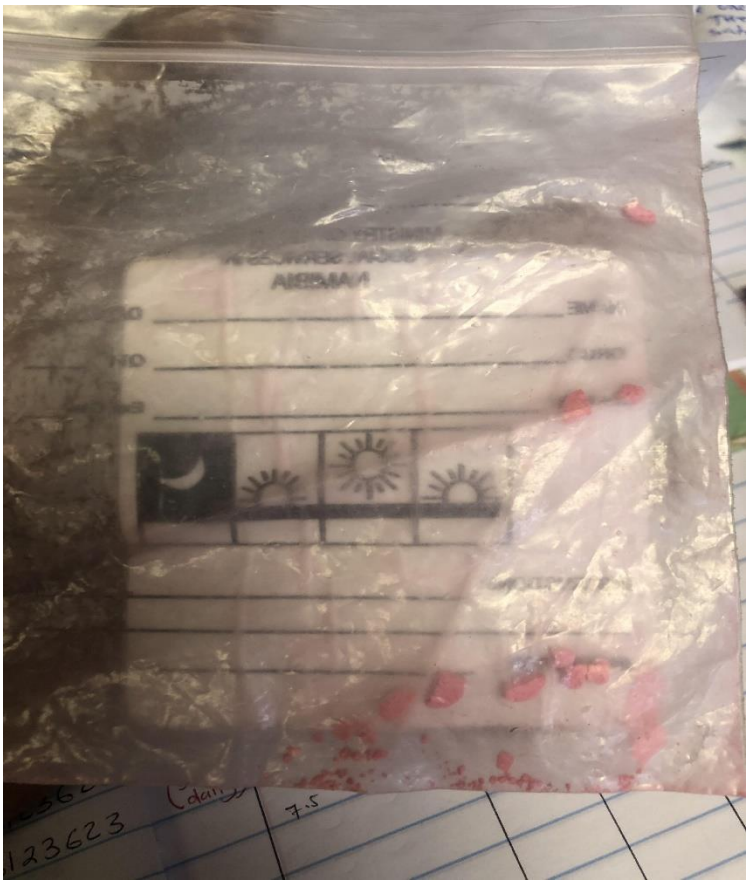

Figure 10. A sachet of warfarin tablet from one of the patients in the intervention group.

The fourth social determinant of health in the patients was language barrier. The majority of the patients in this study could either speak Oshiwambo, Afrikaans, and/or English. The pharmacist communicated with the patients in English and the nurses assisted with patients who only understood and spoke Oshiwambo and/or Afrikaans. However, two of the patients, both Angolan nationals, could only understand and speak Portuguese. Notes were written in their passports asking their relatives who were able to read the note to always accompany the patients when they came for follow-up. One patient continued to show up to the clinic but the other patient did not come back for the remainder of the study duration. In a multi-lingual and multi-ethnic country, patients have the right to receive health care services in the language they feel most comfortable. However, the implementation of diverse language services is difficult.

Electronic tools including Google Translate would be able to assist with common languages (for instance Portuguese or Afrikaans), however other languages in Namibia are not available through most interpretation applications requiring live interpreters.

Lastly, there was one patient in whom prior to visiting the anticoagulation clinic had their INR monitoring done by a private health practitioner. INR monitoring in that particular patient was poor. INR checks were done, at most, three or four times a year and their INRs were always non-therapeutic. This may highlight gaps in care for anticoagulation amongst the private health sector in Namibia too.

6.3 Anticoagulation control in the intervention group versus the historical control group.

The main objective of this study was to improve the quality of anticoagulation control in the intervention group and compare it to the historical control group (11). The control group reported the quality of anticoagulation control in terms of target %TTR. Therefore, the comparison between the two groups was based on the target %TTR and not the expanded %TTR. The results showed a 17% improvement in the quality of anticoagulation control in the intervention group. Back in 2012, Harriette and colleagues published their findings on how variation in dose adjustment practices could explain the differences in the quality of anticoagulation control reported from different settings. They reported a 20% improvement in reducing stroke, systemic embolism, and major haemorrhage among patients with a more than 10% improvement in TTR (105). Nonetheless, the hypothesis of the current study could not be tested based on these median %TTRs because the two groups had paired patient cases. Consequently, the comparison of the quality of anticoagulation between the intervention study and the control was made on the basis of both the paired patient

cases (smaller sample, but paired data) and the unpaired patient cases (larger sample). The discussion below begins with the unpaired patient cases.

First, the demographic characteristics in the unpaired cases between the intervention and the control group were compared. The results showed a statistically significant difference in the median age of the two groups, though the difference was likely not clinically meaningful. In terms of gender distribution, there no statistically significant difference between the two groups. In addition, the two groups had the same top three indications for warfarin therapy namely, i.e. DVT, MVR, and PE. On the basis of these results, the two groups were assessed to have similar demographics and therefore comparable. The results showed an 18% improvement in the median target %TTR in the intervention group compared to the control group.

With the exception of age, an assumption was made that the demographic characteristics amongst paired patient cases were similar over the 4 years from 2017 to 2021 and the two groups were therefore comparable. The majority of the patients were female with a comparable average age and similar indications (DVT and MVR) for warfarin therapy. Given that the control study was carried out in 2019 (11), it was expected that the indications for warfarin in these patients warranted prolonged or life-long warfarin therapy. MVR patients are typically managed with life-long warfarin therapy. However, with respect to DVT, this demographic finding reinforces the fact that DVT patient were being treated with warfarin therapy for a prolonged duration of therapy and not for 3-6 months. The comparison of the mean target %TTR showed that the pharmacist's involvement at the warfarin clinic resulted in a 10% improvement in the quality of anticoagulation control. More patients (22%) in the intervention group had a mean target %TTR $\geq$ 65% compared to the control group (10%).

Pharmacist integration in anticoagulation management: The literature review revealed that improvements in the quality of anticoagulation control with pharmacists involved anticoagulation services have been reported as early as the year 2005 (7). Since then, several studies have confirmed this finding (8–10,53–56,69,81,106,107). This improvement has been linked to better patient education and knowledge of warfarin anticoagulation achieved in patients under the care of pharmacists involved warfarin clinics. This subsequently improves patient adherence to warfarin therapy which is a known predictor of good INR control. In line with this, the pharmacist in the intervention group was actively involved in patient counselling throughout the follow-up period (see table 6). Although a structured assessment of adherence was not carried out in the intervention study, the demographics revealed that 72% of patients in the current study missed at least one of their scheduled follow-up dates regardless of the extensive counselling sessions offered by the pharmacist both face-to-face and telephonically. This may highlight structural issues, both in terms of SDOH and from the health care system. From 2005 to 2021, percentage improvement in the mean target TTR with pharmacist managed anticoagulation service ranged from 5% to 17%. The highest improvement in mean target %TTR of 17% was obtained from a study by Bungard et al. (2009) (8). This high improvement could be explained by the fact that Bungard and colleagues did not include INR values from the first 30 days of warfarin management in their data analysis. The first 30 days of warfarin management are usually characterised by labile INR values that are often non-therapeutic. INR values are expected to stabilize after 30 to 90 days from initiation of warfarin therapy (8). Exclusion of the potentially unstable INR results during the first month of warfarin treatment in the study by Bungard et al., very likely contributed to the relatively high

improvement in %TTR. The current study evaluated all the INR values despite the number of new patients started on warfarin therapy during the follow-up period.

A systematic review by Manzoor et al. (2017) showed that 23 out of the 25 studies included in the review concluded that pharmacist involved anticoagulation service improved overall quality of anticoagulation control (56). In the same year, another systematic review and meta-analysis by Hou et al. (2017) showed that pharmacist involved anticoagulation service had a positive impact on the treatment outcomes (reduced new thromboembolic and bleeding complications) (55). However, Hou et al. (2017) also reported that there was no statistically significant difference in %TTR achieved from pharmacist managed warfarin clinics when compared to standard of care. Similarly, two randomised control trials obtained a 5% (p=0.79) and 6.4% (p=0.20) improvement in %TTR between pharmacist managed and standard of care warfarin clinics were also not statistically significant (69,106). Despite the improvement in the median and mean target %TTR in the current study, the target %TTR of 65% was not reached. The extent to which pharmacists' involvement in anticoagulation services improve the quality of anticoagulation control vary from one study to another. Such variations are expected and can be explained by the wide range of factors which affect the quality of anticoagulation control. These factors could be patient-related and the context-related including the geographical locations where the study was carried out. A qualitative study by Tadesse et al. (2022) has expounded on facility-based factors such as unavailability of warfarin and high patient load that may affect the quality of anticoagulation control (108). Regardless, individual time in therapeutic ranges in Sub-Saharan Africa have been shown to be generally poor (3). For example, even under clinical trial conditions, the mean %TTR achieved ranged from 46% to 58% (14,22,29).

The current study reports an improvement in the quality of anticoagulation control at the warfarin clinic (see Figures 6 and 7 in the result section). More patients had %TTR ≥ 65 in the current study compared to the control group. However, the overall %TTR achieved indicates that the quality of anticoagulation control is still poor.

6.4 COAGUCHEK® XS INRs versus ACL NIP INRs.

Tadesse et al. (2022) indicated that one of the facility-specific factors affecting the quality of anticoagulation control is a high patient load (108). The number of patients requiring warfarin therapy will continue to increase with the overall positive shift in the prevalence of non-communicable diseases (NCDs) in the Southern African Development Community (SADC) (3). The clear solution to this is to recruit more qualified HCWs for the warfarin clinics. In a setting like Namibia, in which the availability of qualified health care professionals is still low, more immediate interventions such as health care worker-supervised patient self-management may need to be explored. In anticoagulation services, patient education coupled with the safe use of POC devices for INR monitoring and warfarin therapy adjustments is critical to introducing patient self-management which may inadvertently reduce the workload on healthcare workers.

The safe use of POC devices warrants an assessment of their accuracy and precision to measure INR values. For this analysis, a data set of paired INR values from 89 patients whose INR results were determined using both Roche's CoaguChek® XS INR meter and NIP's ACL INR analyser was used. The correlation analysis between Roche's CoaguChek® XS INR meter and NIP's ACL INR analyser revealed a very high positive correlation ($r = 0.973$, $p<0.001$) (see Figure 8 in the result section). The difference in the paired INR values from the two methods increased with an increase

in the mean paired INR values. The findings of this study are similar to those reported by other studies (17,57,60). Kalcik et al. (2017) found a Pearson's correlation coefficient of 0.966 (p<0.001; 95%CI: 0.95-0.97) between the Roche's CoaguChek® XS INR meter and the laboratory method (STAGO STAR) (17). Similar to this study's Bland-Altman results, Kalcik et al. (2017) and Donaldson et al. (2010) also found that the differences in the INR values from the CoaguChek® XS INR meter and STAGO STAR analyser increased as the mean INR values increased (17,60). Although their comparison did not include the CoaguChek® XS meter, this observation was described earlier in 2007 when the CoaguChek® - S and other POC devices were compared to the Innovin thromboplastin on a Sysmex CA1500 automated analyser (57).

In certain aspects, the findings from the Bland-Altman plot in this study were also different from other studies (see Figures 9 and 10 in the result section). The present study found a mean difference of 0.15 units which is well below the 0.5 cut-off that has been described (57). The limit of agreement in the study were -0.68 and 0.38 slightly narrower than those reported in other studies (0.16 to 0.56 and −0.41 to 0.86) (109,110). Most (95%) of the differences in paired INR values between the two methods fell within the limits of agreement; this is well above the differences in the paired INR values reported with earlier CoaguChek® S model 85% (111) and 88% (112). While it has been reported that the INR value differences increase with an increase in the mean INR values, the mean INR value of 2.5 (from the visual inspection of the Bland-Altman plot) is lower than the 3.6 and 4.5 reported in the literature (62,113). This difference could be explained by known factors that have been reported to influence the sensitivity, precision, and clinical use of POC devices. For example, the fibrinogen and haemoglobin status of patients can influence the INR results obtained from POC testing (64).

Moreover, Gardiner et al. (2005) explained that out of range INRs from POC devices were mostly due to the use and preparation of INR testing rather than the faulty instruments or test strips (113). A similar view was shared by Perry et al. (2010) stressing the need for adequate formal training on the use of POC devices (58). The current study did not test the patient's fibrinogen status and haemoglobin testing is not routinely carried out at the clinic. However, some of these explanations could apply to the study since the pharmacist who carried out the CoaguChek® INR testing did not get formal training on the use of the device. The relative inaccuracy of POC devices to measure INR at higher mean INR values led authors like Sharma et al. (2015) to recommend that laboratory INR testing should be done in patients with a INR result >4.0 from the POC device (114). What is important to note though was that almost 100% of the POC results matched with the overall assessment of INR control: subtherapeutic, therapeutic, and supratherapeutic.

As outlined in table 13 in the result section, the Cohen Kappa analysis between Roche's CoaguChek® XS INR meter and NIP's ACL INR analyzer gave a Kappa value of 0.838 (p<0.001). The kappa analysis is used to assess clinical concordance between two methods based on a grading system (k value of <0.4, poor; 0.4 – 0.75, fair to good; > 0.75, excellent) (17). The analysis found an excellent clinical concordance between the two methods. Furthermore, it also showed that the CoaguChek® XS INR meter had a sensitivity of 94.4% in correctly detecting therapeutic INR values. It also revealed a specificity of 82.5% and 100% in correctly detecting non-therapeutic INR values which were sub-therapeutic and supra-therapeutic respectively. Although most studies do not report on the sensitivity and specificity of POC devices, Elise et al. (2016), similarly reported a sensitivity and specificity of 91.7% and 99.2% respectively (115). The CoaguChek® XS INR meters

are, therefore, safe for use in selected patients attending the warfarin clinic. Their major drawback is that, without reimbursement, they can be costly for most patients and for health systems (15).

The future direction of research on this subject is the safe use of POC devices to facilitate supervised anticoagulation self-management and in emergency units. There has been a pattern from randomized controlled trials, systematic reviews and other studies showing that they are indeed safe for use in warfarin self-management (16,114,116–118). The need for warfarin self-management became more apparent during the COVID-19 pandemic as it reduced physical interactions between patients and healthcare workers. This inadvertently reduced patient exposure to high COVID–19 transmission zones such as clinics and hospital laboratories. Other than the possibility of reducing workload, POC testing offers more advantages in the management of patients on warfarin therapy. Among other advantages, POC testing allows for quicker availability of INR results and prompt clinical decisions can be made. These benefits could not be tested in the current study as decisions about warfarin adjustment had to wait until the laboratory result was released by NIP.

This study showed that Roche's CoaguChek® XS INR meter results had an excellent clinical agreement with the INR results from NIP's ACL analyser. With appropriate formal training of patients and HCWs, POC testing can be safely introduced at the Warfarin Outpatient Clinic of Windhoek Central Hospital. With reimbursement, applications of POC devices can be extended to supervised patient self-management on warfarin therapy.

6.5 Limitations.

The current study was not without limitations. The paired comparison of the mean % TTR achieved from the intervention and the control group was based on a small number of patients (n = 22). Ideally, the control and the intervention group should be identical with the only difference being that the intervention group is exposed to the interventions. The historical control group of the current study was not a true control group. Although statistical analyses were carried out to compare the demographic and clinical characteristics between the groups, there were some differences. These differences could have affected the outcomes of the study. For example, the intervention study was carried out during the COVID-19 pandemic, which may have contributed to the higher percentage of VTE patients. These patients faced unique challenges such as being hospitalized at COVID-19 isolation facilities where their warfarin therapy was interrupted. Such a challenge for instance did not affect the control group. The interventions in the study were carried out by one pharmacist early in their career. This might be a limitation as replication across different pharmacists was not established in this study. Further, the pharmacist's level of experience managing warfarin therapy may have underestimated the effect of the intervention. The study also did not assess the impact of other predictors of %iTTR like herbal medicines, BMI, COVID-19 infection, level of patient education, genetics, and social determinants of health. Highly anticipated factors relating to the use of herbal medicines and supplements in the setting of the COVID-19 pandemic were not studied. Data on the social determinants of health was not properly gathered therefore data analysis on the influence of these factors on quality of anticoagulation control was not performed.

INR results using the CoaguChek® XS -INR meter could not be obtained in all patients because it was too costly to procure the test strips. Demographic information on the 89 patients whose INR values were used in assessing the accuracy and precision of the CoaguChek® XS INR meter was poorly documented.

7. CONCLUSIONS.

The study showed that the introduction of a pharmacist, a detailed data collection tool, and a dosage adjustment algorithm at the warfarin clinic of Windhoek Central Hospital improved the quality of anticoagulation control at the clinic. While the overall time in therapeutic range increased by 18% (from 24% to 42%), the overall quality of anticoagulation control was still below the target (65%). A dedicated multidisciplinary team was required to continue improving the quality of anticoagulation control at the clinic. Various factors affected the quality of anticoagulation control. The statistically significant predictors of good anticoagulation control were patient adherence to warfarin dosage and the baseline INR result. The CoaguChek® XS INR meter was a safe alternative to NIP's ACL analyser for monitoring INR results and adjusting warfarin therapy.

8. RECOMMENDATIONS.

The warfarin outpatient clinic of Windhoek Central Hospital requires the services of pharmacists. There is need to set up a cardiac pharmacy near the clinic which will strictly serve the pharmaceutical needs of the growing number of cardiac patients receiving health care services at the clinic.

The influence of warfarin dosage adherence on the quality of anticoagulation control should be studied further using a standardized method of assessing warfarin dosage adherence. Furthermore, other factors need further study too. This may include but not limited to the use of herbal medicines, BMI, level of patient education, genetics, and social determinants of health.

Lastly, Roche's CoaguChek® XS INR monitoring can be safely carried out in selected patients.

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APPENDIX I: The UNAM- HREC ethical clearance certificate.

UNAM
UNIVERSITY OF NAMIBIA

ETHICAL CLEARANCE CERTIFICATE

Ethical Clearance Reference Number: H-G /571/2020 **Date: 7 July, 2020**

This Ethical Clearance Certificate is issued by the University of Namibia Research Ethics Committee (UREC) in accordance with the University of Namibia's Research Ethics Policy and Guidelines. Ethical approval is given in respect of undertakings contained in the Research Project outlined below. This Certificate is issued on the recommendations of the ethical evaluation done by the Faculty/Centre/Campus Research & Publications Committee sitting with the Postgraduate Studies Committee.

Title of Project: The Triad Intervention Into Warfin Monitoring Service at Windhoek Central Hospital

Researcher: MOSES MAKWIPURE THIKUKUTU

Student Number: 201404207

Supervisor(s): *Prof. R. Verbeeck (Main) Mr. B. Singu (Co)*

Campus: Hage Geingob Campus
Take note of the following:

(a) Any significant changes in the conditions or undertakings outlined in the approved Proposal must be communicated to the UREC. An application to make amendments may be necessary.
(b) Any breaches of ethical undertakings or practices that have an impact on ethical conduct of the research must be reported to the UREC.
(c) The Principal Researcher must report issues of ethical compliance to the UREC (through the Chairperson of the Faculty/Centre/Campus Research & Publications Committee) at the end of the Project or as may be requested by UREC.
(d) The UREC retains the right to:

(i) Withdraw or amend this Ethical Clearance if any unethical practices (as outlined in the Research Ethics Policy) have been detected or suspected,
(ii) Request for an ethical compliance report at any point during the course of the research;
(iii) Cognizance and the observation of Namibia's Research Science and Technology Act, 2004 which makes it compulsory for Non-Namibian based researchers to obtain the compulsory Research Permit from the National Commission on Research Science and Technology (NCRST), FIRST, BEFORE the research can commence.

UREC wishes you the best in your research.

Prof. Dr. J.E. de Villiers: HREC Chairperson

Ms. P. Claassen: HREC Secretary

APPENDIX II: The MoHSS approval to conduct the study.

REPUBLIC OF NAMIBIA

Ministry of Health and Social Services

Private Bag 13198
Windhoek
Namibia

Ministerial Building
Harvey Street
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Tel: 061 – 203 2507
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OFFICE OF THE EXECUTIVE DIRECTOR

Ref: 17/3/3MMT
Enquiries: Mr. A. Shipanga

Date: 10 September 2020

Mr. Moses M. Thikukutu
University of Namibia
Windhoek

Dear Mr. Thikukutu

Re: Triad intervention into the warfarin monitoring service at Windhoek Central Hospital.

1. Reference is made to your application to conduct the above-mentioned study.

2. The proposal has been evaluated and found to have merit.

3. **Kindly be informed that permission to conduct the study has been granted under the following conditions:**

3.1 The data to be collected must only be used for academic purpose;

3.2 No other data should be collected other than the data stated in the proposal;

3.3 Stipulated ethical considerations in the protocol related to the protection of Human Subjects should be observed and adhered to, any violation thereof will lead to termination of the study at any stage;

10/14252

3.4 A quarterly report to be submitted to the Ministry's Research Unit;

3.5 Preliminary findings to be submitted upon completion of the study;

3.6 Final report to be submitted upon completion of the study;

3.7 Separate permission should be sought from the Ministry for the publication of the findings.

4. All the cost implications that will result from this study will be the responsibility of the applicant and **not** of the MoHSS.

Yours sincerely,

BEN NANGOMBE
EXECUTIVE DIRECTOR

"Health for All"

APPENDIX III: Data collection tool.

Adopted and modified from *the University of Pittsburgh Anticoagulation Clinic Maintenance Phase Data Collection Tool*

Patient Demographics

Patient name: title ( )

D.O.B:

Date:

Warfarin indication:	
Target INR	
Duration of Treatment	

Chronic Disease and Treatment

What time of the day do you take warfarin?

Patient:
Contact number:

Physician:
Contact number

Patient Assessment

Since your last INR check, have you

	Yes	**No**	**If yes, please explain:**
Missed any dosses of warfarin?			
Taken any extra dose of warfarin?			
Experienced any changes in diet?			
Experienced nausea, vomiting, diarrhea, fever/cold or constipation?			
Consumed any alcohol?			

Since your last INR check, have you experienced any of the following signs or symptoms of bleeding?

	Yes	**No**	**If yes, please explain:**
Red or dark brown urine			
Red or black, tarry stool			
Vomiting or coughing up blood			
Unexplained bruising on body			
Severe headache or stomachache			
Frequent nosebleeds			
Frequent bleeding from gums			
Other (please specify):			

Since your last INR check, have you experienced any of the following signs or symptoms of blood clots

	Yes	**No**	**If yes, please explain:**
New shortness of breath or chest pain			
New pain, swelling, redness or heat in an extremity			
New visual changes or loss of sight			
Sudden weakness in any limb			
New dizziness or faintness			
New numbness or tingling			
Sudden onset of slurred speech			
Other (please specify):			

Dosage Adjustment

Table 1: Current weekly dose

Date:			**/ /20**			**/ /20**		
Day	**Dose**							
Mon								
Tue								
Wed								
Thu								
Fri								
Sat								
Sun								
Total								

Table 2: CoaguChek-INR vs NIP-INR

Tests	**/ /20**	**/ / 20**	**/ / 20**
POC-INR			
POC LAB			
HB			
Dose Adjustment			

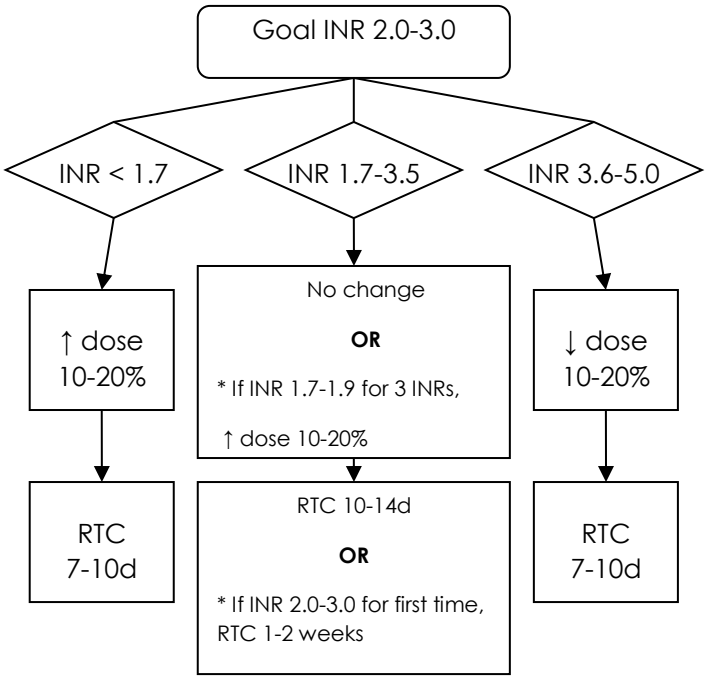
Table 3: Recommended weekly dose

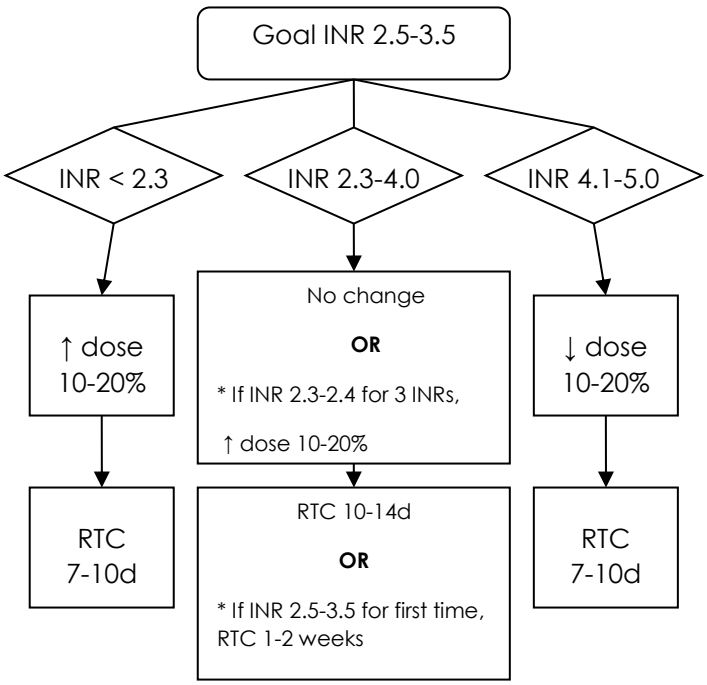
Date			**/ / 20**				**/ /20**				**/ / 20**			
Day	**Dose**													
	R	**A**												
Mon														
Tue														
Wed														
Thu														
Fri														
Sat														
Sun														

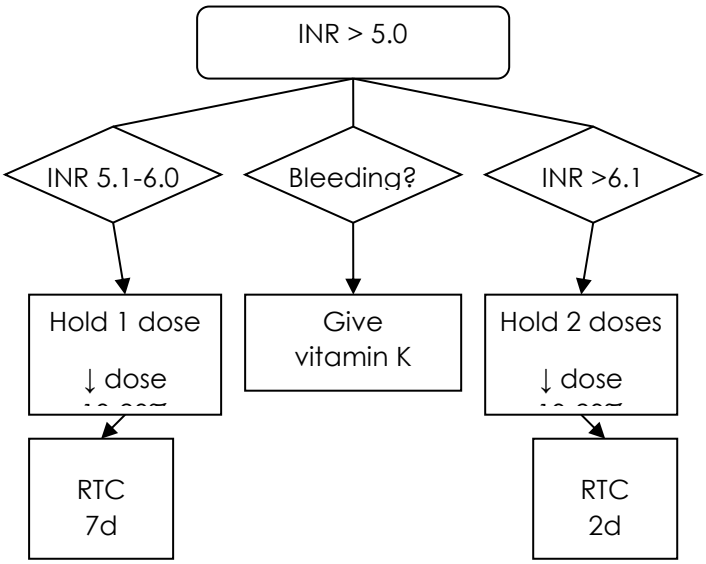
Key: **R:** Recommended and **A**, for Actual doses taken.

APPENDIX IV: Warfarin dosage adjustment.

Adapted from: *The University of Pittsburgh Anticoagulation Clinic Maintenance Phase Warfar*in *Dose Alteration Algorithm*






INR > 5.0
INR 5.1-6.0
Bleeding?
INR >6.1
Hold 1 dose
↓ dose
Give
vitamin K
Hold 2 doses
↓ dose
RTC
7d
RTC
2d

APPENDIX V: A frequency table of the classification of factors affecting INR values randomly noted from the intervention patients.

CLASSIFICATION	N
UNKNOWN	2
DOSE (Ran out of medicine (13), Not-from-clinic instructions (7), Forgot (2), inadequate adjustment (5), Warfarin unavailable (1))	28
DRUGS (Rifampicin (2) and other drug interactions: amiodarone/home-based remedies for COVID (2))	4
DISEASE (COVID (4), scheduled surgical procedures (2), renal failure (1), psych (1), diarrhoea (1))	9
DIET (Alcohol (4), green vegetables (11))	15
SOCIAL DETERMINANTS OF HEALTH (social & cultural beliefs (2), job security: difficult to adhere to follow-up dates (3), transport issues: patients stay out of town (6), language barrier (2), private patient: poor INR monitoring service (1)	14
TOTAL	**72**

In 72 patients, dose-related 28 (39%), Diet 15 (21%), and social determinants of health 14 (19%) detailed in table 10 above were the top 3 classifications of possible reasons noted, on a random basis, from patient self-reporting to affect INR control during the study period.