Development of Pharmacist-managed Warfarin Therapy at Mahosot Hospital, Lao PDR

Vanlounni Sibounheuang

A Thesis Submitted in Partial Fulfillment of Requirements for
degree of Master of Pharmacy in Clinical Pharmacy
September 2019

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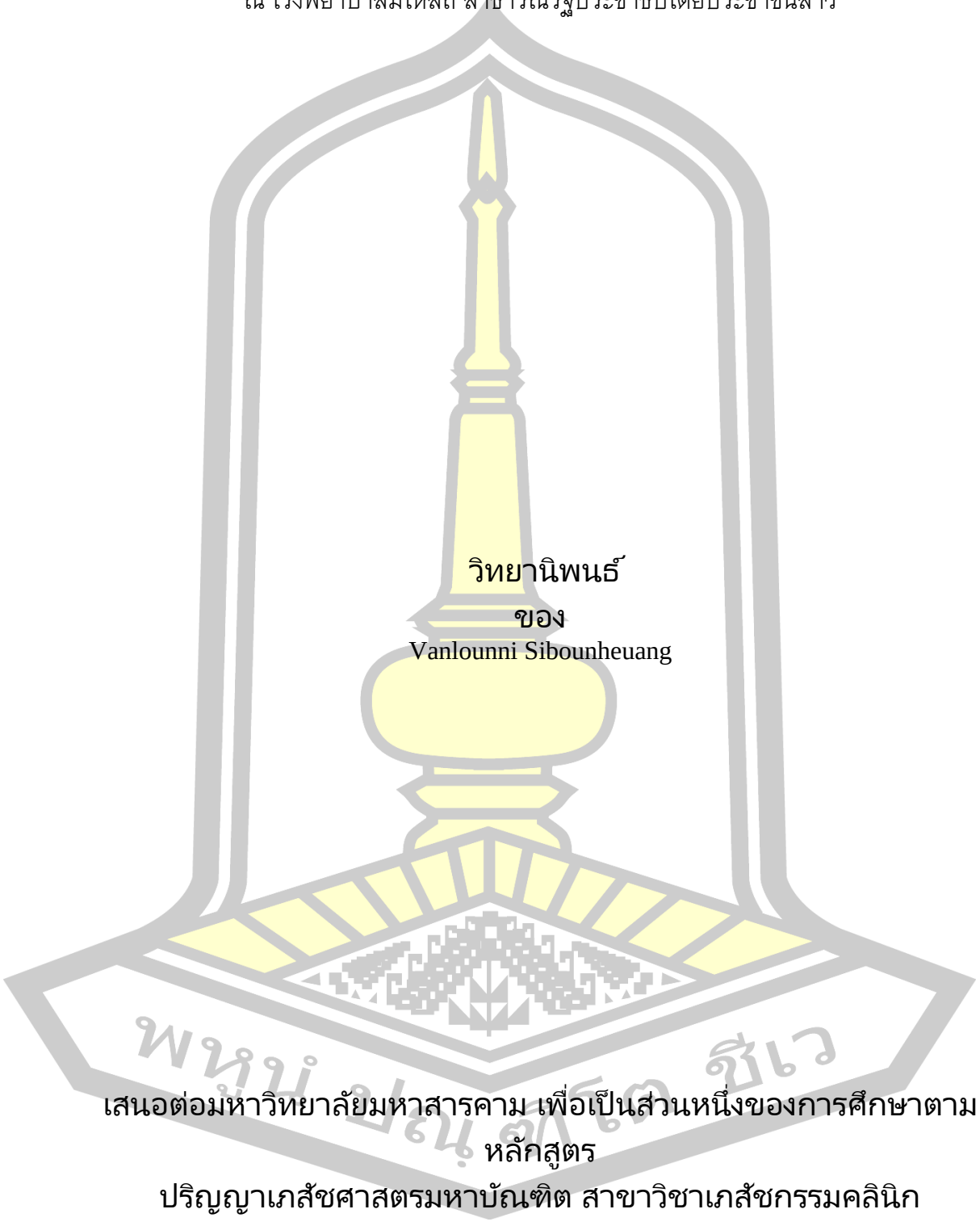

วิทยานิพนธ์
ของ
Vanlounni Sibounheuang

เสนอต่อมหาวิทยาลัยมหาสารคาม เพื่อเป็นส่วนหนึ่งของการศึกษาตามหลักสูตร
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กันยายน 2562

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The examining committee has unanimously approved this Thesis, submitted by Ms. Vanlounni Sibounheuang , as a partial fulfillment of the requirements for the Master of Pharmacy Clinical Pharmacy at Mahasarakham University

Examining Committee

.....Chairman
(Asst. Prof. Juntip Kanjanasilp , Ph.D.)

.....Advisor
(Wanarat Anusornsangiam , Ph.D.)

.....Co-advisor
(Asst. Prof. Pattarin Kittiboonyakun , Ph.D.)

.....Committee
(Asst. Prof. Peeraya Sriphong , Ph.D.)

.....External Committee
(Assoc. Prof. Verawan Uchaipichat , Ph.D.)

Mahasarakham University has granted approval to accept this Thesis as a partial fulfillment of the requirements for the Master of Pharmacy Clinical Pharmacy

.....
(Asst. Prof. Chanuttha Ploylearmsang , Ph.D.)
Dean of The Faculty of Pharmacy

.....
(Asst. Prof. Krit Chaimoon , Ph.D.)
Dean of Graduate School

TITLE Development of Pharmacist-managed Warfarin Therapy at Mahosot Hospital, Lao PDR

AUTHOR Vanlounni Sibounheuang

ADVISORS Wanarat Anusornsangiam , Ph.D.
Assistant Professor Pattarin Kittiboonyakun , Ph.D.

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ABSTRACT

The objective of this study was to develop pharmacist-managed warfarin therapy at Mahosot Hospital. The study was a mixed-method research including qualitative interviews and experimental study. The duration of the study was carried out between January and May 2019. Descriptive statistics and a content analysis were used for qualitative interviews. A student t-test, a Mann-Whitney U test, a repeated-measure ANOVA test, a Chi-squared test, a Fisher's exact test and a Cochran's test were implemented for statistical analysis. Measuring clinical outcomes as efficacy outcomes were: 1) time in therapeutic range (TTR) 2) INR 3) knowledge scores 4) DRPs (sub-therapeutic dosage, over dosage, and drug interactions) 5) thromboembolism events 6) patient adherences, and safety outcome was: 1) adverse drug reactions (major bleeding or minor bleeding). Qualitative interviews were face-to-face and focus group interviews. The face-to-face interviews was based on 9 healthcare professionals: 3 doctors, 3 nurses, and 3 pharmacists. The major themes emerged from the interviews consisted of healthcare professionals' experiences of current practice problems with warfarin therapy, healthcare professionals' perspectives on ways to improve services, and healthcare professionals' educations and training. The focus group interview was interviewed 8 healthcare professionals included 2 doctors, 3 nurses, and 3 pharmacists. The major themes were the collaborations among healthcare professionals, expectations of pharmacists' roles by healthcare professionals, and development of training program for healthcare professionals. The results from the qualitative interviews were used to develop the intervention of RCT study, called "pharmacist-managed warfarin therapy". The study was compared between 36 patients from the intervention group and 36 patients from the control group (usual care). Patients' mean age was 53.1 ± 14.6 and 50.8 ± 14.0 years old of the intervention and control group. There was 63.3 ± 35.5 % of time in therapeutic range (TTR) in the intervention group which higher than 45.3 ± 39.9 % of TTR in the control group, with statistically significant difference (p-value = 0.046). The percentage of patients' INR value in therapeutic range in the intervention group was higher than the percentage of patient in the control group (73.7 % with 61.7 %, respectively). There was statistically significant difference of patients' knowledge score between the intervention and control group at third visit (13.2 ± 1.4 and 7.0 ± 3.6, p-value = 0.013). Twenty DRPs found in 16 patients in the intervention group at

baseline visit. The most type of DRPs from 4 visits were sub-therapeutic dosage. Doctors and patients accepted drug-related problems (DRPs) and solved the problem at baseline to third visits 60.0 %, 33.3 %, 25.0 % and 16.7 % of DRPs in the intervention group. No events of thromboembolism and major bleeding were found. Patients' adherence were assessed by the Morisky, Green, and Levine (MGL) questionnaire 4-items scale. The highest adherence was 100.0 % and the lowest was 69.4 %. Mean percentage of pill count in the intervention group was 87.3 ± 16.9 % higher than 81.8 ± 15.7 % of patient in the control group, with no significant difference. Minor bleeding events were presented as bruising, nose bleeding, gum bleeding, and bleeding in stool. Almost 6 cases in 6 patients presented a minor bleeding in the intervention group and 9 cases in 9 patients in the control group.

Conclusion: Time in therapeutic range in the intervention group was statistically significant higher than in the control group. Pharmacist-managed warfarin therapy was developed by healthcare professionals could use it in the future when anticoagulant clinic is establishing.

Keyword : Warfarin, Pharmacist, Management, Lao PDR

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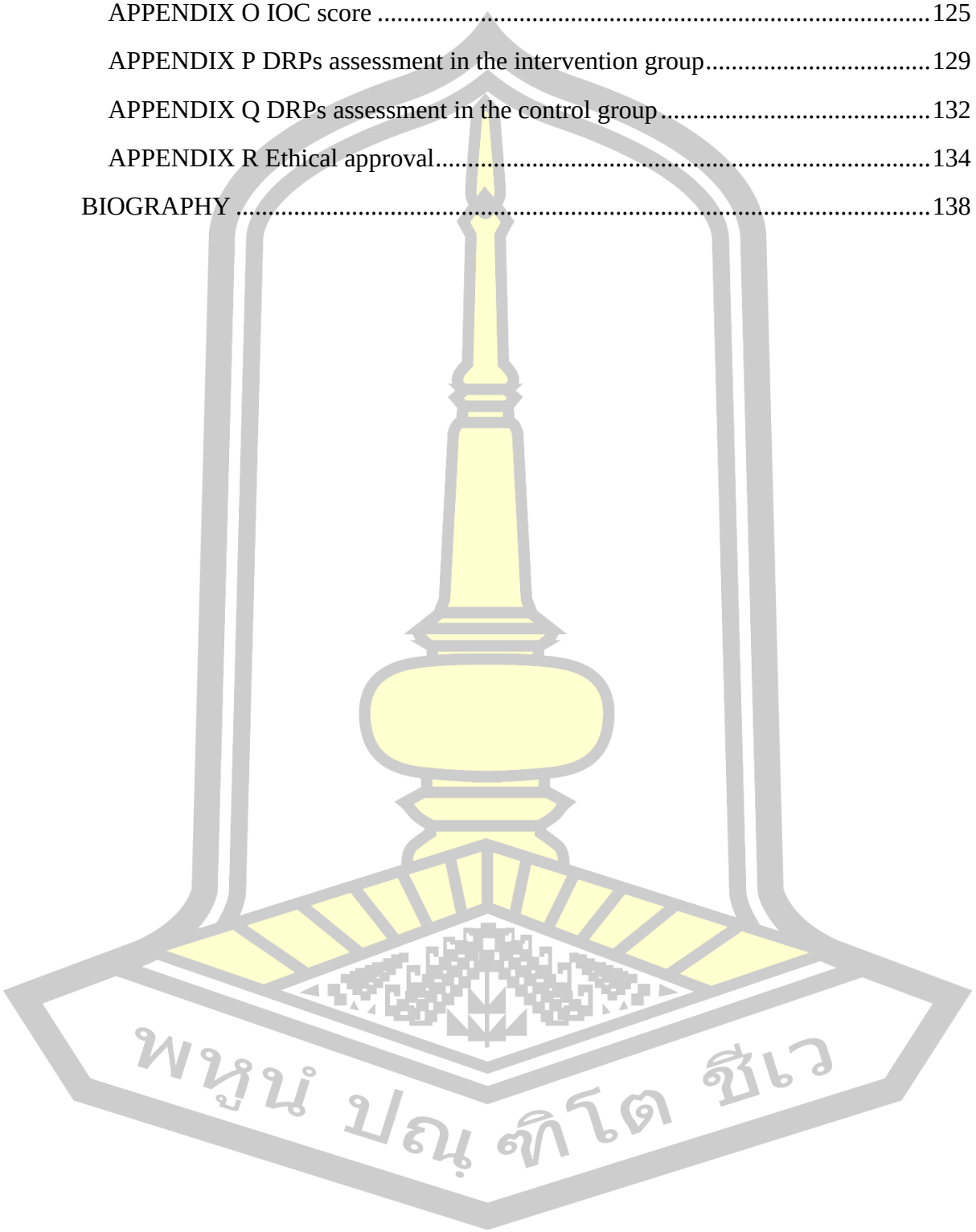

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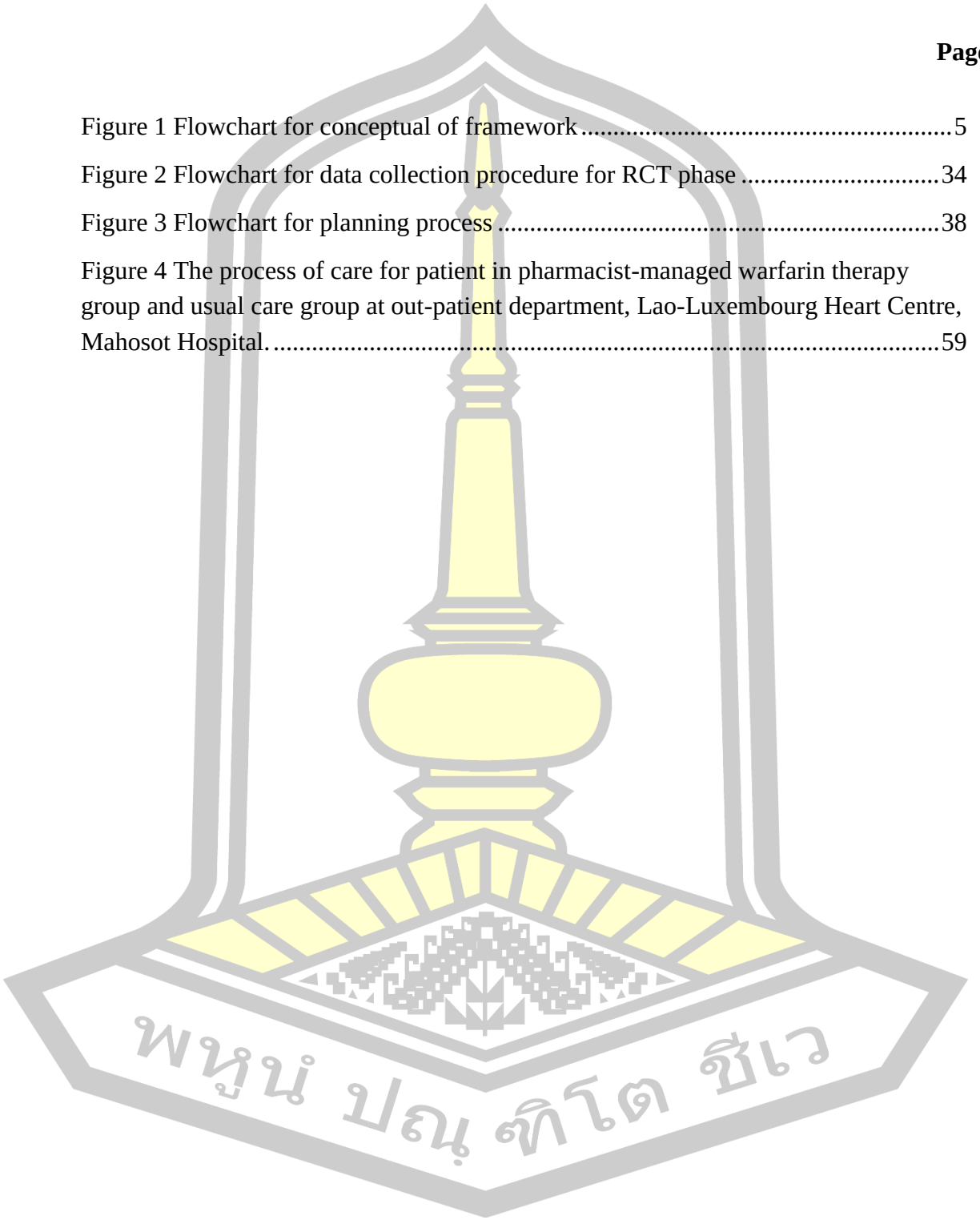


CHAPTER I

INTRODUCTION

1.1 Background and rationale of the study

Warfarin remains the most widely available anticoagulant in supply chain and is the one of oral anticoagulants (OACs) in the World Health Organization (WHO)'s model list of essential medicines (1, 2). Indications of warfarin are treating blood clots such as deep vein thrombosis (DVT), pulmonary embolism (PE) and preventing stroke in patients with atrial fibrillation (AF), valvular heart disease, artificial heart valves, and mechanical valve replacement (MVR) (3).

Among those patients with many difference diseases, AF is one of the most condition they had in common. In 2010 (4) numbers of patients with AF were estimated globally. There were significant regional variations in populations of 33.5 million (20.9 million males and 12.6 million females) and mortality increased to 2 folds in both males and females. Patients with AF face a strongly elevated risk of blood clots which leads to stroke. Stroke has already reached epidemic proportions. One in 6 peoples worldwide will have a stroke in their lifetime. Fifty million peoples worldwide suffer a stroke each year and 5.8 million peoples die from it (5). In 2016 (6) the number of patients who presented to emergency department with atrial fibrillation or atrial flutter as a primary or secondary diagnosis in 47 countries around the world. Southeast Asia was the third highest number of strokes occurred in patients 88 of 1331 (7%). Patients with AF or poor managed warfarin therapy have significant development of stroke.

The prevention of stroke and systemic embolism in AF patients were established by warfarin therapy but it could possibly lead to bleeding more than that the use of inadequate or excessive amount of warfarin could lead to death (7). Warfarin has a narrow therapeutic window and associate to drug-drug and drug-food interactions, and rely on international normalized ratio (INR) test. Hence, doctors and pharmacists need to adjust warfarin doses by INR result. Patients need to recognize and understand the INR results to make a discussion with doctors and pharmacists when the INR result is off the target range. The target INR range for most indications of warfarin therapy is 2.5 (range 2 to 3) (3). Therefore, the American College of Chest Physicians (ACCP) recommended the warfarin therapy with a target INR of 3.0 (range 2.5 to 3.5) for MVR (8).

Many patients were treated by heart valve operations and used warfarin therapy after the operations. According to the American Heart Association, about 5 million Americans are diagnosed with heart valve disease each year. A long-term administration of warfarin be necessary following valve replacement surgery, because prosthetic valves are associated with a higher risk of blood clots. Warfarin depends on the type of valve, mechanical or biological and on the presence or not of thromboembolic risk factors, for example AF. A mitral mechanical valve replacement lifelong oral anticoagulation with warfarin. For biological valve prosthesis, in patients without thromboembolic risk oral anticoagulation, warfarin with INR = 2.5 is used

during at least 3 months and for as long as 6 months following surgery. Patients with thromboembolic risk are treated with warfarin as long as the risk remains present (9).

More studies showed that patients getting better therapeutic outcomes when pharmacist-managed warfarin therapy is provided. Pharmacist-managed warfarin therapy consists of providing education, assess patients' adherence, reviewing medications, comorbidities, nutrition and drug interactions, and screening for side effects of thromboembolism or bleeding, adjusting warfarin dose, INR test scheduled. The study on comparing of pharmacist-managed warfarin therapy to usual care showed that patients in pharmacist-managed warfarin therapy group achieved better clinical outcomes on warfarin control by having higher percentages of time within the therapeutic range (TTR), improvement of patients' knowledge, significant reduction of bleeding complication and lower risk of minor hemorrhage (10-12).

Lao People's Democratic Republic (Lao PDR) is low middle incomes country, located in Southeast Asia. By 2017, life expectancy of male and female were 65.4 and 68.6 years old, respectively (13). Stroke was the third leading cause of death, after coronary heart disease and infectious diseases. In 2017, according to WHO ranking of mortality by stroke, Lao PDR was 37 (mortality rate: 9.99 %; n = 4273) in the world. Increasing to 45 in 2011(mortality rate: 9.01 %; n = 3762). Indonesia was not just number 1 in ASEAN (but also in the world). Following by Myanmar, Philippines and Lao PDR. The best ranking of mortality by stroke in ASEAN was Singapore. As stated in The Laos National Essential Medicines List (LNEML), heparin, enoxaparin, warfarin and dicoumarol were only 4 anticoagulations listed (14). In 2018, warfarin is an only OAC drug used in Lao PDR and Mahosot Hospital. Mahosot Hospital is tertiary teaching hospital with 450 beds located in Vientiane capital city, Lao PDR. The central cardiology center also located in Mahosot Hospital. According to warfarin dispensed in the central cardiology center, there was increasing from 2015 to 2016 and 2016 to 2017 by 38.09 % and 38.61 %, respectively (15). In the central cardiology center, warfarin is provided by usual care-doctors prescribe warfarin and adjust warfarin dose on each visit, nurses provide basic knowledge on warfarin and concerns of food interaction, pharmacists dispense warfarin but not acknowledge/counsel patients on warfarin. Since 2002, Mahosot Hospital has started the heart valve replacement operations. Nowadays, patients with MVR still needed follow ups and keep taking warfarin from there.

A cross-sectional descriptive study on patient using warfarin therapy at out-patient department, Lao-Luxembourg Heart Centre, Mahosot Hospital was conducted between September 2017 and January 2018. The study of 272 patients had reported outcome indicator of warfarin using (INR) met its goal in 48.16 %, 25.36 % of patient had INR over therapeutic range, 89.33 % of patients took warfarin with others medication e.g., acetaminophen, simvastatin, aspirin, omeprazole (16). An individual interview to investigates the patients' views on pharmacists' interventions was conducted between February and March 2018 with 10 of warfarin's patients at out-patient department, Lao-Luxembourg Heart Centre, Mahosot Hospital. The report showed that the patient likewise needed more information on the role and relative importance of warfarin therapy because they have never known about that (17).

To help patients recognize the signs and symptoms of bleeding or clotting from warfarin use, good knowledge on warfarin must be provided. Healthcare professional including doctors, nurses and pharmacists should work together in order

to monitor, rehabilitate and prevent the incidence of bleeding or clotting and unnecessary use warfarin. There were evidences proved that when warfarin was managed by pharmacists, patients produced better clinical outcome (18).

Currently, the usual care in Mahosot Hospital are not effective on policy maker to support patients who take warfarin. Especially, when pharmacist-managed warfarin therapy needed. This study aims to establish and develop pharmacist-managed warfarin therapy at Mahosot Hospital, Lao PDR.

1.2 Aim of the study

1.2.1 Aim of the study

To develop pharmacist-managed warfarin therapy at Mahosot Hospital.

1.2.2 Specific purposes:

1.2.2.1 To investigate the views of healthcare professionals including doctors, nurses and pharmacists on pharmacists' roles and processes of care for patients with warfarin therapy.

1.2.2.2 To explore views of healthcare professionals including doctors, nurses, and pharmacists on pharmacist-managed warfarin therapy developed by researcher.

1.2.2.3 To conduct a randomized controlled trial (RCT) for evaluating the effect of pharmacist-managed warfarin therapy on patients' clinical outcomes.

1.3 The scope of the study

This study was conducted at out-patient department, Lao Luxembourg heart center, Mahosot Hospital, Lao PDR. There are 2 phases including the qualitative study and RCT study. Population will be required to be healthcare professionals and patients with warfarin therapy. The duration of the study will be January to May, 2019.

1.4 Definition of specific terms

1.4.1 Pharmacist-managed warfarin therapy is defined as a process of care for patients with warfarin therapy, in collaborating with doctors, nurses and pharmacists, developed by researcher.

1.4.2 Usual care is defined as a routine process of care for out-patients using warfarin at Mahosot Hospital. The process including:

- Doctors prescribe warfarin and duration of therapy, adjust warfarin dose in each visit.
- Nurses educate patients or health care providers.
- Pharmacists dispense warfarin.

1.4.3 Clinical outcomes are defined as efficacy and safety of warfarin use including:

1.4.3.1 Efficacy outcomes:

- Time within the therapeutic range (TTR) is calculated by Rosendaal method by using 3 INR results for one patient (19). TTR was calculated measured by the percentage of the day that patient had INR within therapeutic range. The study used INR results of the first, second and third visit for both groups.

$$\text{Percentages of TTR} = \frac{\text{Number of day with INR in therapeutic range}}{\text{Total number of days}} \; x \; 100$$

- INR in exact therapeutic range is the real INR result from the test in each visit. Most INR in exact therapeutic range is 2-3 or 2.5-3.5 for MVR

- INR in expanded therapeutic range is INR in exact therapeutic range ± 0.2.

- Knowledge scores are measured by questionnaires modified from Lakshmi et al. (2013) study on impact of clinical pharmacist's interventions in the optimal use of oral anticoagulants in stroke patients. The question will have translated to Lao language by researcher and validated by supervisor. The questionnaire containing 15 items including 8 items of warfarin's knowledge and 7 items of patient's behavior (20).

- Drug-related problems (DRPs) are modified from Hepler and Strand's criteria (21). The focus categories of DRPs are to be identified actual or potential DRPs as following 3 items:

Sub-therapeutic dosage is assessing of doctor's prescription (looking for patient's INR below therapeutic range for each visit).

Over dosage is assessing of doctor's prescription (looking for patient's INR over therapeutic range for each visit).

Drug interactions are drug-drug, drug-food, drug-herb and drug-alcohol (22) interaction which can increase or decrease warfarin effect. For drug-drug interactions were investigated only significant level 1 and 2 that cited by Drug Interaction Facts 2015 (23). For drug-food and drug-herb were used reference from the study of warfarin and its interactions with foods, herbs and other dietary supplements (24).

- Thromboembolism events were defined as patient who was diagnosis to thromboembolism events by a doctor.

- Patient adherences assessment was used the Morisky, Green, and Levine (MGL) 4 item scale (25) and pill count.

Scoring the MGL scale is defined as Yes and No. Yes = 1, No = 0. Zero is good medication adherence, score 1 to 4 is non-adherence.

Pill count assessment tool was presented by mean ± SD.

$$\text{Pill count} = \frac{\text{Number of medication that patient taken in one visit x 100}}{\text{Total number of medication order in one visit}}$$

1.4.3.2 Safety outcomes were defined as adverse drug reactions (ADRs) from warfarin therapy including major bleeding and minor bleeding.

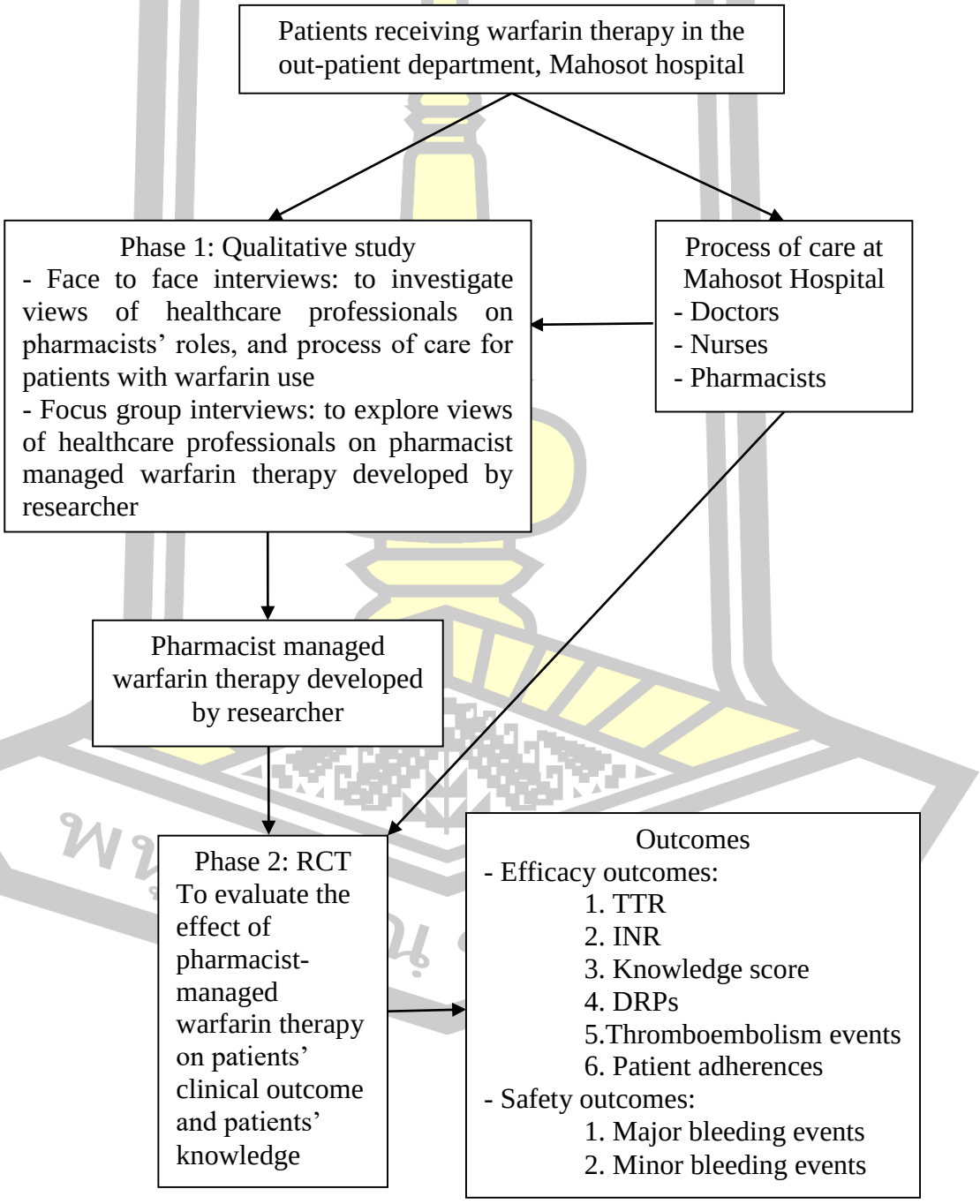
- Major bleeding events were defined as a fatal bleeding, and/or symptomatic bleeding in a critical area or organ, such as intracranial bleed, intraspinal

bleed, intraocular bleed, retroperitoneal bleed. Major bleeding was detected by diagnosis from doctors.

- Minor bleeding events were defined as a symptom of bruising, hematoma, nosebleeds, gum bleeding, bleeding in urine, or bleeding in stool. Minor bleeding was detected by doctor diagnosis or researcher assessment from patient's clinical symptoms.

1.5 Conceptual of framework

Figure 1 Flowchart for conceptual of framework



1.6 Hypothesis

This study is used non-directional hypothesis: patients in intervention group has different percentage of TTR compared with patients in control group.

H_0 is null hypothesis, H_0: $\mu_1=\mu_2$

H_a is alternative hypothesis, H_a: $\mu_1 \neq \mu_2$ or $\mu_1-\mu_2=0$

μ_1 is percentage of TTR for intervention group

μ_2 is percentage of TTR for control group

1.7 Expected outcome and benefits

1.7.1 To gain a pharmaceutical care model to be used in clinical practice at Mahosot Hospital as well as to enhance pharmacists' roles.

1.7.2 To be a model for develop pharmaceutical care in other diseases/medications.

1.7.3 To reduce rate of hospitalization in patients using warfarin.

CHAPTER II

LITERATURE REVIEW

2.1 Introduction of warfarin

Warfarin is the most widely prescribed oral anticoagulant agent in the world and has been used as an oral anticoagulant in clinical practice since 1954. It is anticoagulant agents which treats or prevent thrombosis. Commonly Indications of warfarin is to treat blood clotting such as deep vein thrombosis (DVT) and pulmonary embolism (PE) and prevent stroke in patients with atrial fibrillation (AF), valvular heart disease or artificial heart valves (3, 26, 27).

2.2 Pharmacodynamics and pharmacokinetics of warfarin

Warfarin is a vitamin K antagonists (VKAs), produce an anticoagulant effect by interfering with the cyclic conversion of vitamin K to its reduced form call vitamin K hydroquinone. Warfarin inhibits the regeneration of vitamin K hydroquinone from vitamin K epoxide by inhibiting the vitamin K epoxide reductase (VKOR) enzyme in the vitamin K cycle. Vitamin K hydroquinone is an essential co-factor for the post ribosomal activation (γ-carboxylation) of coagulation factors II, VII, IX and X without them, they are unable to bind calcium and become active in the coagulation cascade.

Warfarin is given orally and is rapidly absorbed from the gastrointestinal tract. Although, the maximum plasma concentration of warfarin is reached within 90 minutes in adults. The anticoagulant effect takes several days to develop the onset of action of warfarin, therefore being dependent on the half-lives of the relevant coagulation factors. The half-life of warfarin is approximately 40 hours and its anticoagulant effect lasts for 4 to 5 days. Warfarin is given as a once daily dose, usually during the evening.

Warfarin is 97% bound to albumin and is distributed in the plasma compartment. It is only the remaining 3% of unbound warfarin that is pharmacologically active and can be eliminated. Changes in the unbound fraction of warfarin may occur due to competition for protein binding sites with other drugs and has a major effect on its' elimination and on warfarin dose requirements. Commercially available warfarin is a 50:50 racemic mixtures of R and S enantiomers with the S enantiomer being three times more potent than the R enantiomer in its inhibitory effect on the VKOR enzyme. There are several different cytochrome P450 enzymes that contribute the metabolism of warfarin. The main enzyme responsible for the metabolism of the S enantiomer of warfarin is cytochrome P450 CYP2C9. The R enantiomer of warfarin is metabolized primarily by CYP1A2, with CYP3A4 and CYP2C19 providing a lesser contribution (27).

2.3 Warfarin dosage

Initial dosing of warfarin use must be individualized. Considering patients with hepatic function, cardiac function, age, body weight, nutritional status, comorbidities, concurrent therapy, concomitant medications, risk of bleeding in addition to prior dose response and the clinical situation. A formal bleeding risk assessment is recommended for all patients with warfarin therapy used by HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly e.g. age > 65, frailty, etc., drugs/alcohol concomitantly) , start 2 to 5 mg once daily for healthy individuals, 10 mg daily, adjust dose according to INR results, usual maintenance dose ranges from 2 to 10 mg daily but individual patients may require initial and maintenance doses outside these general guidelines .

Lower initial doses e.g., 5mg daily is recommended for patients with confirmed heparin induced thrombocytopenia (HIT) once platelet recovery has occurred. Some may be required for patient with hepatic impairment, poor nutrition, congestive heart failure (CHF), elderly, high risk of bleeding, or patients who are debilitated, or those with reduced function genomic variants of the catabolic enzymes CYP2C9 (*2 or *3 alleles) or VKORC1.

Higher initial doses may be reasonable in selected patients (e.g. receiving enzyme inducing agent and with low risk of bleeding). Overlapping a parenteral anticoagulant and warfarin therapy by at least 5 days is necessary in treatment of DVT or PE even if the INR is therapeutic earlier. Although an elevation in INR (due to factor VII depletion) may be seen early (within the first 24 to 48 hours) in warfarin therapy, it does not represent adequate anticoagulation. Factors II and X must also be depleted which takes considerably longer.

In conclusion, initial doses for the usual adult dose of warfarin is 5 mg per day for 2 to 4 days, followed by maintenance dose 2 to 10 mg per day as indicated by measurements of the INR. The typical maintenance dose of warfarin for most patients will be between 25 and 55 mg per week. In DVT or VTE, warfarin therapy is continued for a minimum of 3 months but should be given longer depending on the underlying etiology of the DTV or VTE and the patient’s risk factors. In AF, warfarin therapy is continued for long-life threatening. For MVR, warfarin use is up to doctor and valve machine. The American college of chest physicians (ACCP) recommends against the use of routine pharmacogenomics testing to guide dosing. Following with CYP2C9 and VKORC1 results doctors can informal to adjust warfarin dose for maintenance dose (as shown in Table 1) (28).

Table 1 Range of expected therapeutic maintenance dose based on CYP2C9 and VKORC1

VKORC1	CYP2C9					
	*1/*1	*1/*2	*1/*3	*2/*2	*2/*3	*3/*3
GG	5-7 mg	5-7 mg	3-4 mg	3-4 mg	3-4 mg	0.5-2 mg
AG	5-7 mg	3-4 mg	3-4 mg	3-4 mg	0.5-2 mg	0.5-2 mg
AA	3-4 mg	3-4 mg	0.5-2 mg	0.5-2 mg	0.5-2 mg	mg

2.4 Warfarin monitoring

Warfarin is monitored by INR which is a means of standardizing results obtained from different laboratories that may use different thromboplastin reagents and equipment. The INR is maintained within a desired therapeutic range, dependent upon the clinical indication for warfarin, by regular monitoring and adjustment of the dose of warfarin. The majority of patients receiving warfarin regularly attend an anticoagulant clinic, in the hospital or their general practice surgery, for monitoring of their INR.

The INR should be monitored at least every 2 to 3 days during the first week of therapy. This is usually continued for up to seven days to allow stabilization of the warfarin dose. Checking the INR too soon can lead to inappropriate dose adjustments and unstable anticoagulation status. Once a stable response to therapy is achieved, INR monitoring is performed less frequently, weekly for the first 1 to 2 weeks, then every 2 weeks, and every 4 to 6 weeks thereafter if the warfarin dose and the patients' health status are stable. Warfarin dose is adjusted if necessary by a trained healthcare professional, usually a clinical pharmacists or an anticoagulant nurse's practitioner, doctors. The warfarin adjust dose is depending on routine care in each hospital based on guideline of anticoagulant therapy.

Furthermore, warfarin monitoring use patients' TTR is defined as the duration of time in which the patient's INR values were within a desired range. TTR is the indicator to tell that patient was having efficacy of warfarin therapy. A recent European consensus document recommends that the average time in the therapeutic range should be > 68 % for optimal efficacy and safety outcomes while on warfarin and this is also recommended in the European Guidelines (29). In the National Institute for Health and Care Excellence guidelines, the percentage of time within the therapeutic range > 65 % is recommended for patients with AF who are on warfarin anticoagulation therapy (30).

Three common methodologies to calculate TTR were compared within the same cohort of patients by Schmitt (2003). There are 3 methods, first is the fraction of INR in range, second is the cross-section of the files methodology and last one is the Rosendaal linear interpolation method. There was no statistically significant difference between the first two means ($p < 0.15$), but there was between the Rosendaal method and each of the others ($p < 0.01$ for each). When the same analysis was performed for 3 and 6 month intervals the results were unchanged (31). Since

1993 to previously, Rosendaal method is the most common method in clinical studies. Which incorporates both the frequency of INR measurement and the actual values to interpolate daily INR values and define the percentage of time in range for each patient (19). Percent TTR was calculated using [(number of day with INR in therapeutic range/total number of days) x 100].

Nonetheless, to manage the elevated INR in maintenance therapy, doctors or other health care professional must follow the protocol of their hospital. There are several difference ways based on anticoagulant guideline on management of warfarin therapy. For example, this is the management of evaluated INR from Thai guideline (as shown in Table 2) (32).

Table 2 INR management

INR range 2-3	**Management of elevated INR**	**INR range 2.5-3.5**
INR less than 1.5	Consider extra dose, increase weekly dose by 10-20%. Monitor INR in frequently or repeat INR in 1 weeks	INR less than 2
INR 1.5-1.9	Consider extra dose, increase weekly dose by 5-10%. Monitor INR in frequently or repeat INR in 2-4 weeks	INR 2-2.4
INR 2-3	Continue same dose. Frequently repeat INR in 4 weeks	INR 2.5-3.5
INR 3.1-3.9	Consider reduce dose, decrease weekly dose by 5-10%. Monitor INR in frequently or repeat INR in 2-4 weeks	INR 3.6-4.5
INR 4-4.9	Hold next dose and monitor frequently or repeat INR in 2-4 weeks, when INR approaches desired range, resume dosing with a lower dose (decrease dose by 10 %)	INR 4.6-5.5
INR 5-8.9	Hold 1-2 dose and monitor frequently, when INR approaches desired range, resume dosing with a lower dose (decrease dose by 20 %). In case that there is risk of bleeding, add oral vitamin K 1-2.5 mg. In case of emergency surgery add oral vitamin K 2.5-5 mg	INR 5.6-8.9
INR >9 with no evidence of bleeding	Hold and monitor frequently, add oral vitamin K 2.5-5 mg when INR approaches desired range, resume dosing with a lower dose (decrease dose by 20 %). After 24-48 with high INR, repeat vitamin K 1.5-2 mg.	INR >9 with no evidence of bleeding
Major bleeding with any INR	Vitamin K 10 mg iv plus fresh frozen plasma (FFP), repeat vitamin K every 12 hours if needed	Major bleeding with any INR

2.5 Drug related problems of warfarin therapy

In 1990, Hepler and Strand were defined definition of DRPs as an event or circumstance involving a patient's drug treatment that actually or potentially interferes with the achievement of an optimal outcome. They were introduced several categories of DRPs. In the classification, the DRPs were classified as follows:

1. Untreated indications
2. Improper drug selection
3. Sub-therapeutic dosage
4. Failure to receive drugs
5. Over dosage
6. Adverse reactions
7. Drug interactions
8. Drug use without indication

As warfarin has a narrow therapeutic window and a deviation from the desired target INR range, it can cause a reduction in efficacy or an adverse event. Patients monitoring on warfarin therapy is important to prevent the DRPs. DRPs are also existing of ADR warfarin therapy, which major on bleeding and minor bleeding that cause by warfarin. Healthcare professional must play roles to improve patients' knowledge on warfarin use, to provide safe and effective outcomes. Practices must be complete by multiple healthcare professional such as doctors, nurses and pharmacists, laboratory staffs, etc.

The major complications associated with warfarin are clotting. Due to warfarin under dosing detected by an INR, meaning that it is below the target range and classified as sub-therapeutic dosage of DRPs, carrying a risk of thromboembolism. Blood clots developing in vein called DVT usually occurs in a deep leg vein, a large vein that runs through the muscles of the calf and the thigh. It can cause pain and swelling in the leg and may lead to PE. In some cases, there may be no symptoms of DVT. If symptoms do occur, patients can face: pain, swelling and tenderness in one of legs (usually calf), a heavy ache in the affected area, warm skin in the area of the clot, red skin, particularly at the back of leg below the knee, DVT usually (although not always) affects one leg. The pain may be worse when patient bend their foot upward or towards the knee.

Whereas, warfarin over dosing with an INR above target range can cause hemorrhage. It may occur at virtually any site risk, depending on multiple variables- the intensity of anticoagulation and patient susceptibility. Incidence of warfarin related to bleeding, appears highest during the first few weeks of therapy. The annual incidence of major bleeding ranges from 1% to 10% depending on the quality of warfarin therapy management. Instability and wide fluctuations in the INR are also associated with higher bleeding risk. Bleeding in the gastrointestinal tract is most common. However, intracranial hemorrhage (ICH) is one of the most serious complications because it often causes severe disability and death. Patients have to carefully observe their symptoms, unusual headache or a headache that more severe than usual is a sign that patient must go see doctors or healthcare providers immediately. Moreover, severe headache, confusion, weakness or numbness, coughing up large amounts of bright red blood, vomiting blood, not stop bleeding,

bright red blood in stool, fall or injury to the head are the experiences of bleeding that patient have to follow their signs with health care provider in the hospital (33).

Piazza et al. (2011) reported a five-year retrospective study at Brigham and Women's Hospital, USA to determine clinical characteristics, types, root causes, and outcomes of anticoagulant associated with adverse drug events (ADEs). Anticoagulant drugs are among the most common medications that cause ADEs in hospitalized patients. Characteristic of ADE in patients receiving anticoagulant is ADR 30.5 %, medication error 48.8 % and potentially preventable ADE 69.5 %. Anticoagulant associated with ADE is warfarin 20.7 %, less than Unfractionated heparin 58.3 %, and more than LMWH 9.5 %, Fondaparinux 0.7 %. Type of medication error is missed dose 24.5%, wrong rate or frequency 23.2 %, medication not discontinued when order 9.6 %, extra dose 8.1 %, wrong dose 7.1 %, wrong time of administration 5.3 %, etc. (34).

In addition, the major was defining of the International Society of Thrombosis and Hemostasis (ISTH) which include a fatal bleeding, and/or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome, and/or bleeding causing a fall in hemoglobin level of 20 g/L (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells (35). Minor bleeding is not meeting the criteria for major bleeding are including bruising, nosebleeds, gum bleeding, hematuria, or rectal bleeding not requiring further action.

Saokaew et al. (2010) studied a systematic review and meta-analysis of 5 RCTs and 19 non-RCTs. The result were 4 % (14 case) of the minor bleeding and 1 % (5 cases) of major bleeding in patients with pharmacist-managed warfarin therapy (12). Hou et al. (2017) studied a systematic review and meta-analysis of 8 RCT and 9 observational studies, reported that the corresponding risk of minor bleeding was 415 per 1000 cases for patients in group of pharmacist managed warfarin therapy. Also major bleeding was 28 per 1000 cases (11).

One important thing in DRP is drug interaction. In 2011, Bungard and colleagues developed the practice tool for drug interactions involving with warfarin. It was an originally developed by a single practitioner working in an anticoagulation management service. The aim of the practice tool was to assist clinicians in providing proactive patient care in management of interactions between warfarin and other drugs (36) .

2.6 Nutritional factors and drug interaction on warfarin therapy

The factor of INR elevation is vitamin K intake and drug interaction (drug-drug, drug-herb, drug-food) (37, 38). Any substances or conditions are potentially dangerous if it alters the uptake or metabolism of the warfarin or vitamin K, synthesis, function, or clearance of any factor or cell involved in hemostasis or fibrinolysis.

Changes in the usual intake of vitamin K may cause variable anticoagulation effects of warfarin. Several sources of vitamin K, difference food contained vitamin K in micrograms are provided at (as shown in Table 3). Patients education with vitamin K intake should be noted for all warfarin therapy. To prevent the INR elevation, patient must have the same amount of vitamin K daily. Intake recommendations for vitamin K are provided in the dietary reference intakes by the food and nutrition board at the institute of medicine of the national academies. The values vary by age and gender such as: the adequate intakes for people above 19 years is 120 mcg in male and 90 mcg in female, pregnancy and lactation (39).

One case of a man who began to drink 50 oz (1.47 L) of grapefruit juice per day attributes a greater than twofold increase in INR to grapefruit juice (40). Mango has been associated with an increased INR in 13 patients. There is one case report of an interaction between warfarin and papaya in a patient using papaya extract containing papain as a weight-loss aid. Moreover, herbals that may increase the risk of bleeding in person's taking warfarin are containing ginkgo, fish oil, aloe gel, garlic, onion, ginger, ginseng, vitamin E, omega 3 fatty acids, alcohol, etc. (24).

In a huge out-patient warfarin clinic, the most common factors associated with a transient elevation of the INR (warfarin overdosing), were a new medication known of potentiating warfarin (e.g. acetaminophen), advanced malignancy, recent diarrheal illness, decreased oral intake, and taking more warfarin than prescribed. The clinically warfarin drug interaction significant level 1 and 2 was reported in (as shown in Table 4).

Table 3 Vitamin K content of selected foods

Very high (> 200 mcg)	**High (100 - 200 mcg)**	**Medium (50 - 100 mcg)**	**Low (<50 mcg)**	
Brussels-sprouts	Basil	Apple green	Apple red	Eggs
Collard greens	Broccoli	Asparagus	Avocado	Fruit (varies)
Coriander	Chive	Cabbage	Beans	Lettuce
Kale	Coleslaw	Cauliflower	Carrot	Iceberg
Parsley	Cucumber	Mayonnaise	Celery	Meats
Spinach	Green onion	Pistachios	Cereal	Fish
Black tea	Scallion	Squash-summer	Coffee	Peanuts
Green tea	Lettuce		Corn	Potato
Watercress	Mustard-greens		Dairy-products	Rice
	Soybean oil			Tomato

Table 4 Clinically warfarin drug interactions significant level 1 and 2

Increase warfarin effect (Increase INR)			**Decrease warfarin effect**	**Increase bleeding risk**
Acetaminophen	Fluconazole	Norfloxacin	Carbamazepine	Aspirin
Clarithromycin	Fluorouracil	Ofloxacin	Cholestyramine	Clopidogrel
Chloramphe-nicol	Gemfibrozil	Piroxicam	Dicloxacillin	Dipyridamole
Cimetidine	Itraconazole	Quinidine	Propylthiouracil	LMWHs[1]
Ciprofloxacin	Levothyro-xine	Simvastatin	Phenobarbital	NSAIDs[2]
Danazol	Lovastatin	Sulfamethoxa-zole	Phenytoin	UFH[3]
Doxycycline	Metronida-zole	Sulfinpyrazone	Primidome	
Erythromycin	Micronazole	Vitamin-E	Rifampin	
Fenofibrate			Secobarbital	
			Vitamin K	

1 LMWHs is low-molecular-weight heparin
2 NSAIDs is nonsteroidal anti-inflammatory drugs
3 UFH is unfractionated heparin

2.7 Education for warfarin patients

After starting warfarin therapy, patients were counselled on warfarin therapy and its importance, details of the indication for therapy, duration for treatment, common ADRs and management, importance of patient compliance, dose titration, dietary modifications, and the need for INR monitoring by health care provider (doctors, nurses, pharmacists) difference in each hospital (32, 41, 42).

2.7.1 Patients have to know that warfarin is an anticoagulant. “Anti” means against and coagulant refers to blood clotting. Warfarin help reducing clots from forming in blood. Warfarin is also available by the brand name of Coumadin, Befarin or Jantoven (depend on each country).

2.7.2 The reason of taking warfarin are Because the body may make clots that patients don’t need. Clotting is a normal body function but if the body clots too quickly, serious medical problems may occur. A clot can move from heart to brain and cause stroke. Therefore, warfarin is used to treat and prevent many types of blood clots including: DVT (a blood clot generally with in the leg or arm), PE (a blood clot in the lung), stroke associates with an irregular, rapid heartbeat called AF and also heart valve replacement.

2.7.3 Duration for warfarin treatment will be determined by how long your doctor needed and up to the indication. Some conditions require patients to take warfarin lifelong. Some conditions may require only a short duration (3 to 12 months).

How much warfarin patient need to take? Doctor is a person who provides, determines how much warfarin patient needed. For each patient, dosage may be changed based on patients’ blood test results. It is common for changing dosage over time. Especially, when factors change. It is important to take a dose daily as prescribed by doctor to ensure optimal benefits of the medication.

2.7.4 The reason why patient needs to have a blood test is to help establish the dosage of warfarin. Doctors will take a finger tick blood sample to test INR. INR tests are very important to help doctor providing, determining how fast patients' blood is clotting and whether patients' dosage of warfarin should be changed. The INR is a standardized method for reporting blood coagulation.

2.7.5 If INR is above limit, patients are having too much warfarin effect and having a high risk of bleeding. If INR is below limit, patients are having too little warfarin effect and having a high risk of clotting. When patients start taking warfarin, they will generally have INR tests 2 to 3 times per week, then perhaps once every week. This will help doctor providing right dosage for patients. INR tests will be needed at periodic intervals throughout patients' course of therapy and helping their INR in the best range of medical condition (INR therapeutic range is 2 to 3 and 2.5 to 3.5 for MVR). INR should be tested at least monthly. When the dose is changed, the INR will generally be checked within 1 to 2 weeks. It is important to follow the recommended monitoring schedule.

2.7.6 Time of taking warfarin is depending on patients but it should be consistent by every day. Never skip or double doses unless recommend by doctor. On appointment days, the guideline prefers that patients have to wait for taking their dose until their appointment is done. If patient wants to bring their pill with them to their appointment, then they can take their dose right after the blood test. Do not take an extra tablet to catch up. If patient forgot to take a tablet, tell the healthcare provider immediately. Take the missed dose as soon as possible on the same day, but DO NOT take a double dose of warfarin by the next day to make up for the missed dose.
In case of surgery, dental works or some types of invasive procedures while being on warfarin, patient have to tell their doctor to manage warfarin therapy.

2.7.7 In general, foods containing vitamin K will only impact on warfarin therapy if patient eat multiple servings within a short period or have large quantities. in excess of the portion sizes are listed above (as shown in Table 3). Some foods that important to a healthy diet are high containing in vitamin K, like leafy, green vegetables. Eating a normal balance of dietary, maintaining a consistent amount of vitamin K. All food is acceptable. However, avoid drastic changing in dietary habits, eliminating all foods containing vitamin K from patients' diet is not necessary. Remember that it is more important that patients keep their diet consistent and notify their doctor, provider before making any major changes to their diet.

2.7.8 Patients have to know that herbal and vitamin supplements may interact warfarin. While herbals may be "natural" products but still have the potential of causing side effects and drug interactions. Some herbal products may have the potential of increasing or decreasing the effects of warfarin.

2.7.9 Warfarin interacts many drugs (as shown in Table 4), including prescription and nonprescription (over-the-counter) medications. For this reason, it is important for patient to notify their doctor, provider before starting, changing, or stopping any medication.

2.7.10 Patient have to carefully look for signs of bleeding. Tell their doctor provider immediately if they had bleeding, including minor and major bleed.

2.7.11 Patients can travel, but must telling their doctor, provider before they go. Patients may need to take an INR test before they leave, or doctor/health care provider may arrange for having one while be on their trip. Remember to keep

patients' eating habits and activity level as close to their everyday routine as possible. Also, make sure taking enough warfarin with them.

2.8 Literature reviews

2.8.1 Pharmaceutical care practice

Pharmaceutical care is a quality philosophy and working method for professionals within the medication chain. It is indispensable of helping for improving the good and safe use of medicines. Thus, realizing the full potential of medicines available on the market is to achieve the best possible outcome in patients. It contributes the prevention or reduction of inappropriate medicine use by promoting or medication related health literacy. The involvement and participation of patients in their medication, greater equality in healthcare, and the balanced sharing of responsibilities. These factors serve improvement of the quality of patients' life and their families and the cost-effective utilization of resources and to reduce inequalities in healthcare.

Pharmaceutical care is the responsible provision of drug therapy for the purpose of achieving definite outcomes, improving a quality of patient's life. These outcomes are (1) curing a disease, (2) elimination or reduction of a patients' symptomatology, (3) arresting or slowing down a disease process or (4) preventing a disease or symptomatology. Pharmaceutical care involves the process which thronging a pharmacist co-operates with a patient and other professionals in designing, implementing, and monitoring a therapeutic plan, producing specific therapeutic outcomes for the patient. This in turn, involves three major functions (43):

1. Identifying potential and actual drug-related problems.
2. Resolving actual drug-related problems.
3. Preventing drug-related problems.

2.8.2 Health care professional and patients' perspective on warfarin therapy

Stafford and colleagues (2011) explored the experiences of Australian patients and healthcare professionals of warfarin management in the post discharge period and identify the benefits and deficiencies of existing systems, informing the development of a model for a new collaborative post-discharge warfarin management service. The result shown all the healthcare professionals strongly believed that patients should receive comprehensive warfarin education, preferably from a pharmacist, prior to hospital discharge. However, hospital pharmacists described the logistical difficulties for their providing education when patients are discharged at short notice or out of normal business hours. Consumers generally expressed anxiety, confusion, concerning in warfarin, especially if the events leading up to their hospital admission and subsequent discharge unfolded quickly. Some reported that while they were receiving information in hospital, it was not everything they wanted to know. They felt like they were not fully aware of the required frequency of INR test and having little understanding of why they were taking warfarin. The importance of providing patients with simple written information to take home was highlighted by

the hospital based healthcare professionals. It was recognized that many patients do not retain all the information provided during their hospital stay, and within the current public healthcare system, there was limited access to services of offering patient follow-up or reinforcement of education after discharge. Participants believed that written information had to be concise. Large volumes may be discarded when patients return home or simply not be read (44).

2.8.3 Current research of pharmacist managed warfarin therapy

Zhou and colleagues (2016) reviewed the studies of 8 RCTs, comparing pharmacist led AMS with others. The results of the study indicated the INRs of patients in the pharmacist led AMS group achieved better anticoagulation control measured as percentage of time within the standard therapeutic range (MD: 3.66, 95% CI 2.20 – 5.11, P < 0.01). It was inconsistent with the study of Hou and colleagues (2017), 8 RCTs and 9 observational cohort studies were included to compare pharmacist led anticoagulant with others. The result of TTR were not significant from RCTs (MD: 1.25, 95% CI –2.82 – 5.32, p-value is 0.548). However, from overall results, they found that TTR control was significant better in pharmacist led management than others (MD: 8.03, 95% CI 2.19 – 13.88, P < 0.01). Similar to Manzoor and colleagues (2017), a systematic review of evaluating the quality of warfarin anticoagulant control in out-patient pharmacist managed anticoagulation services compare with routine care. The 3 RCTs and 22 non-RCT was included, overall the quality of anticoagulant control was better in the pharmacist group, comparing with routine group. As indicated by higher TTR in majority of the studies (N = 23 of 25, 92.00%) (10, 11, 45).

Effectiveness of pharmacist-managed warfarin therapy was greater than others model care, supported by the results of a systematic review and meta-analysis study of Manzoor and colleagues (2017). The 25 remaining studies consisted of 3 RCTs and 22 observational studies were included. The study reported the most common pharmacist activities including warfarin dose adjustment based on INR measurements interpreted by the pharmacist, medication interaction or drug interaction review and providing patient and/or health care provider education through clinic visits or telephone follow-up (45).

Lakshmi and colleagues (2013) (RCT study) assessed the anticoagulation knowledge of patients who are new to warfarin therapy. Using the questionnaire conducted by Winans et al., demonstrated that in-patient warfarin education programed by pharmacist care may empower patients to achieve a larger degree of initial warfarin knowledge than those educated by usual care. The intervention group patients were counselled on anticoagulation therapy and its importance, common ADRs and management, patient compliance, dose titration, dietary modifications, and the need for INR monitoring by a clinical pharmacist. Patient information booklets were also provided to all the patients in the intervention group. The patients were free to call the clinical pharmacists for clarification of any anticoagulation related issues between 8 am and 8 pm thorough an on call mobile allocated by the hospital administration for the AMS. The frequencies of INR monitoring and dose adjustments were based on the patients INR values. If the values were within therapeutic range, the frequency testing was once in every 2 weeks. The anticoagulation management

service was staffed by clinical pharmacists. It is a service established in order to monitor and manage oral and parenteral anticoagulants. Forty patients were included in each of the intervention and the control groups. In the intervention group, 73.45 % of the INR test results were within the therapeutic range, during the 6 months' data collection period. The corresponding data for the control group were 53.2 (P-value < 0.01) (20).

Bungard and colleagues (2012) (RCT study) used a standardized one-on-one educational session with an information package provided by the pharmacists (no report about information package). The study included total of 62 patients using warfarin therapy. With each INR drawn, patients were contacted by telephone by a pharmacist and an assessment was performed. Warfarin dosing instructions were given, and patients were scheduled for their next INR test. The primary outcome measured the mean percentage of time within the desired INR range after 6 months, compared between two groups, using both the actual range (INR 2.5 ± 0.5) and an expanded range (INR 2.5 ± 0.7). No significant difference was noted in outcomes of between two groups (73.5 ± 19.1 % vs 76.9 ± 24.5 % for the pharmacist group vs primary care groups, p=0.54) (46).

Verret and colleagues (2012) (RCT study) evaluated the impact of a pharmacist led warfarin patient self-management program on quality of life and anticoagulation control compared with management in physician led specialized anticoagulant clinic. The study included total of 114 patients using warfarin therapy. All patients attended a 3-hour educational lecture on anticoagulation provided by a pharmacist on day 1. During this didactic session, the patients received information on anticoagulation treatment and monitoring, as well as anticoagulation self-management. Patients completed a validated quality of life questionnaire at the beginning of the session, as well as the validated oral anticoagulation knowledge test. After 4 months of follow-up, a significant improvement in the self-management group was observed compared with the control group in four of the five quality of life topics ($p < 0.05$). Improvements in knowledge were observed in both groups after the training session and persisted after 4 months ($p < 0.05$ for all). The time spent in the therapeutic range (80.0 % in the self-management group vs 75 % in the control group, p-value 0.79) and in the extended therapeutic range ([target international normalized ratio ± 0.3] 93.2% in the self-management group vs 91.1 % in the control group, p-value 0.30) were similar between groups (47).

Schilling and colleagues (2011) (RCT study) conduct the study to improve communication regarding anticoagulation, safety as patients transition from the inpatient to out-patient settings, and standardize anticoagulant dosing, monitoring, and patient education. The anticoagulation clinics were staffed by nurses and pharmacists who provide standardized management of warfarin for patients of all physicians within the health system and provide consistent high quality care. This study included 500 patients. Transition of care metric compliance occurred in 73 % more patients in the pharmacist group ($P < 0.01$). There was also a 32 % reduction in the composite safety endpoint in the pharmacist group (p-value 0.10). This finding was driven by a reduction in rate of INR ≥ 5 (p-value 0.07) (48).

Lalonde and colleagues (2008) study: Warfarin patients were initially followed up at the pharmacist management anticoagulant service. One hundred thirty-eight physicians and 250 patients participated. The pharmacist met them once to

review their medical history and discuss the objectives of treatment, possible adverse events, the need for frequent INR tests, and drug and food interactions. Warfarin was initiated according to an institution approved protocol, and follow-up was conducted by telephone. Laboratory results were available via a computer system. Once INR values and dosing regiments were well stabilized, patients were randomized to continue followed up at the pharmacist group or be transferred to their physician. Physician follow-up was not standardized. Physicians provided their usual type of follow-up and their patients may be temporarily transferred back to the PMAS if they become unstable or before a surgery or an invasive diagnostic procedure. Patient in pharmacist group and physician group were within the exact target range 77.3 % and 76.7 % of the time (95 % CI of the difference −4.9 % to 6.0 %) and within the extended range 93.0 % and 91.6 % of the time (95 % CI -2.1 % to 4.7 %), respectively. Pharmacist group, patients have seen their physician group less often (95% CI −3.1 to −0.1 visit per year). Number of INR tests, incidence of complications, and health related quality of life were similar in both groups (49).

Gupta and colleagues (2015), (non-RCT study) stated that the clinical pharmacist was responsible for warfarin dose adjustment, assessing the patient's understanding of anticoagulation therapy, adherence to therapy, adverse events, changes in diet, concomitant drug therapy, and comorbidities. Patient education on safety and effective use of warfarin was also provided. The percentage of INR results within the goal range (2.0 - 3.0) was greater among patients in the pharmacist-led group (n = 130) than the physician-led group (n = 96; 57.5 % vs 50.0 %, respectively; $P < 0.01$). The percentage of INR results < 1.5 (7.3 % vs 5.1 %) and > 3.5 (11.4 % vs 7.1 %) was also statistically significant in favor of the pharmacist-led AMS, with P values of 0.03 and <0.01, respectively (50).

Wilson and colleagues (2003), (RCT study) was determined whether anticoagulation clinics improve the quality of anticoagulant management compared with family physician–based monitoring. The study included 112 patients for anticoagulant clinic group and 109 patients for family physician group, follow for 3 months. The primary outcome was the proportion of time that patients receiving warfarin sodium had their INR within ± 0.2 units of the TTR (expanded therapeutic range). A 2-tailed p value of less than 0.05 was regarded as a statistically significant difference between the 2 groups. The result was shown the INR of patients managed by anticoagulation clinics was within the expanded therapeutic range 82 % (95 % confidence interval [CI] 78 % – 85 %) of the time versus 76 % (95 % CI 72 % – 80 %) of the time for patients in the family physician group (p-value 0.034). Moreover, the result of TTR for patient in anticoagulation clinics group had significant higher percentage in 63 % ± 4 versus 59 % ± 5 compared with the family physician group (51).

Previous studies summarized the details of pharmacist activities on warfarin therapy. A systematic review in 2017 (45) summarized 6 activities:

1. Dosage adjustment
2. Scheduled INR test appointment and follow-up visit
3. Education provision to patients
4. Assess compliance with regimen
5. Review medications, comorbidities, diet, and drug interactions

6. Screen for side effects, thromboembolism or bleeding events and recurrence

Furthermore, a systematic review and meta-analysis study in 2010 reported the summary of details of pharmacists' activities from 24 articles in 2 styles, in activities group and activities by items (12).

For the activities group are:

1. Dosage adjustment
2. Bridging assessment and next INR appointment or follow-up
3. Education role to patients

For activities by items are:

1. Determine indication and duration of therapy
2. Establish a therapeutic range and/or warfarin dosing/adjustment
3. Education of the patient and/or other healthcare provider
4. Assess compliance with regimen
5. Review medication, co-morbidities, diet or drug interaction
6. Screen for thromboembolism or bleeding events and recurrence
7. Schedule INR test interval or follow-up visit
8. Ordering/request INR test or point of care INR test
9. Prescribing warfarin

In addition, patient receiving pharmacist management on warfarin therapy reported significant impacts on their INR or TTR better than other health care management.

CHAPTER III

METHODOLOGY

This study was a mixed-method research including qualitative interviews and experimental study to develop pharmacist-managed warfarin therapy at Mahosot Hospital, as well as to assess its outcomes on patients using warfarin. There were two phases of this study:

Phase 1: Qualitative interviews

Two processes of phase 1 included face to face and focus group interviews:

- Face to face interviews were conducted to investigate views of healthcare professionals including doctors, nurses and pharmacists.
- Focus group interviews were undertaken to gain views of healthcare professionals involving in the provision of health care services for patients using warfarin and develop the practical intervention called pharmacist-managed warfarin therapy at Mahosot Hospital based on evidence-based intervention model.

Phase 2: A Randomized Controlled Trial Study

It was conducted to evaluate the effects of pharmacist-managed warfarin therapy on clinical outcomes at Mahosot Hospital.

3.1 Phase 1: Qualitative interviews

3.1.1 Research design

Qualitative interviews were conducted to develop a pharmacist-managed warfarin therapy as a practical intervention model. The interviews included a face to face and a focus group interviews.

3.1.2 Research setting

The interview was undertaken in the out-patient department at Lao Luxembourg heart center, Mahosot Hospital, Lao PDR. Healthcare service is normally from Monday to Friday. Health care team being in charge of providing care for patients using warfarin included 10 doctors, 10 nurses and 5 pharmacists. Each day, there are two doctors conducting diagnosis, prescribing and following-up patients with cardiovascular disease, two nurses providing the first screening and information, and three pharmacists dispensing drugs to patients.

3.1.3 Sample of study

3.1.3.1 The face to face interviews

- Inclusion criteria of participants were healthcare professionals having at least one year of work experience on patients using warfarin.

-The purposive sampling was used to recruit participants for the interviews. The participants were selected by the head of out-patient department.

- Nine healthcare professionals providing care for patients using warfarin from the out-patient department were selected including 3 doctors, 3 nurses and 3 pharmacists.

3.1.3.2 The focus group interviews

- Inclusion criteria of participants were healthcare professionals having at least one year of work experience on patients using warfarin.

- The convenience sampling was used to recruit doctors and nurses. Two cardiologists were included one was head of Heart Association of Lao, one was senior physician. Two senior nurses were recruited.

- The purposive sampling was used to recruit pharmacists. They were different persons from the face to face interviews. Three pharmacists were selected by the head of out-patient department.

3.1.4 Research tool

One interviews guide was made for face to face semi-structure interviews.

3.1.4.1 Face to face interviews:

The interview guide was created based on the purpose of the research. The main topic guides were as follows (see Appendix A):

Doctors' and nurses' interview guide:

Q1. Have you ever experienced the problems of patients taking warfarin? If yes. What is the problems?

Q2. Currently, how do patients with warfarin receive the usual care?

Q3. Apart from question, do you think patients taking warfarin should receive special care from other healthcare professional? And what or how should they receive?

Q4. From Q1. What would you like to improve? Who do you think that they would be able to contribute improvement?

Q5. What do you think if pharmacist-managed warfarin therapy is provided?

Q6. If all healthcare professional is involved in the care of patients taking warfarin, do you think the policy, the system, the manpower and the budget are sufficient or not?

Pharmacists' interview guide:

Question 1 to 6 were the same as doctors' and nurses' interview guide. Additional interview guide for pharmacists was:

Q7. Have you ever advised warfarin patients? What advices do you give?

Q8. Do you think the advices you give are sufficient or not? If no, what could be the best for you giving sufficient advises to patients?

3.1.4.2 Focus group interviews:

During the interview, researcher was presenting three main topics to interviewee:

- The process of care for patients using warfarin (see Appendix B).
- The pharmacists' roles for patients using warfarin (see Appendix C).
- The education tool by pharmacist for patient using warfarin (see Appendix D).

The interview guide was created base on the purpose of the research. To developing the practical intervention called pharmacist-managed warfarin therapy at Mahosot Hospital based on evidence-based intervention model. The main topic guides are established as follows:

Q1. What do you think about the process of care for patients using warfarin, is there any part of the proposed intervention should be improved?

Q2. What should be the roles of pharmacists involving in the practical process at out-patient department, Lao-Luxembourg Heart Center, Mahosot Hospital?

Q3. Would the counselling points of pharmacists educating patients cover all important issues and/or your concerns? Are there any points of pharmacy educations duplicate with doctors or nurses educating patients? Are there any points that should be removed or corrected?

Q4. Other recommendations?

3.1.5 Validation of interview guides

3.1.5.1 The interview guides for face to face and focus group interviews were validated by two research supervisors.

3.1.5.2 The interview guides were translated to Lao languages by a researcher.

3.1.5.3 An interview guides version Lao language were validated by two experts working in the health care field (one expert is working at Mahosot Hospital and one is working at the University of Health Science, Lao PDR).

3.1.6 Recording tool

- For face to face interviews, the participants' voice was recorded by using digital voice recording machine (SONY IC RECORDER ICD-MX20).
- Video record was used for focus group interview.

3.1.7 Data collection procedures

3.1.7.1 The researcher coordinate with the hospital to inform the purpose of the research and to confirm for the interview dates and times. The dates of an interview were arranged by head of Lao Luxembourg heart center in January 2019.

3.1.7.2 After that, the head of heart center selected the interviewees from the healthcare professionals, and allowed them to participate in the face to face interviews. The interviews were conducted in the out-patient department meeting room, Mahosot Hospital.

3.1.7.3 Face to face semi-structured interviews were processed as follow:

- Researcher described the purpose of the study and prepared inform consent form 1 to be signed by participant (see Appendix E). The participant information form 1 was given to all participants (see Appendix F).
- The face to face interviews lasted about 20 minutes per person.
- The interviews were conducted following upon the interview guides (see Appendix A).

3.1.7.4 Focus group interviews processed as follow:

- Researcher described the purpose of the study and prepared inform consent form to be signed by interviewee (see Appendix J). The participant information form was given to all participants (see Appendix K).
- The focus group interviews lasted about 4 hours in the morning.

- Intervention model developed by researcher and based on literature review of pharmacist-managed warfarin therapy (systematic review and meta-analysis) was proposed.

- A researcher presented the problems of pharmacist-managed warfarin therapy by healthcare professional views from the results of face to face interviews. Major themes derived from face-to-face semi-structure interview were explained.

- Researcher presented three main topics to interviewee: the process of care for patients using warfarin (see Appendix B), the pharmacists' roles for patients using warfarin (see Appendix C) and the education tool by pharmacist for patient using warfarin (see Appendix D).

- Moderator (researcher) of the focus group was lead, discuss, and summary key points of the interviews based on the main topic guide.

- Intervention model is to be developed. All comment and suggestion during the interviews were taken into amended draft.

- The amended draft had been approved by all same healthcare professionals.

- The pharmacist intervention model called "pharmacist-managed warfarin therapy" is finally developed and to be used for the experimental study.

3.1.7.5 The researcher was stressed that all information would be kept anonymous and that the audiotaped, videotaped interviews were secretly kept and only the research team can access by using password.

3.1.8 Data analysis

3.1.8.1 Descriptive statistics were used to present demographic data: information of participants. All were presented by number and percentage for both face to face and focus group interview data.

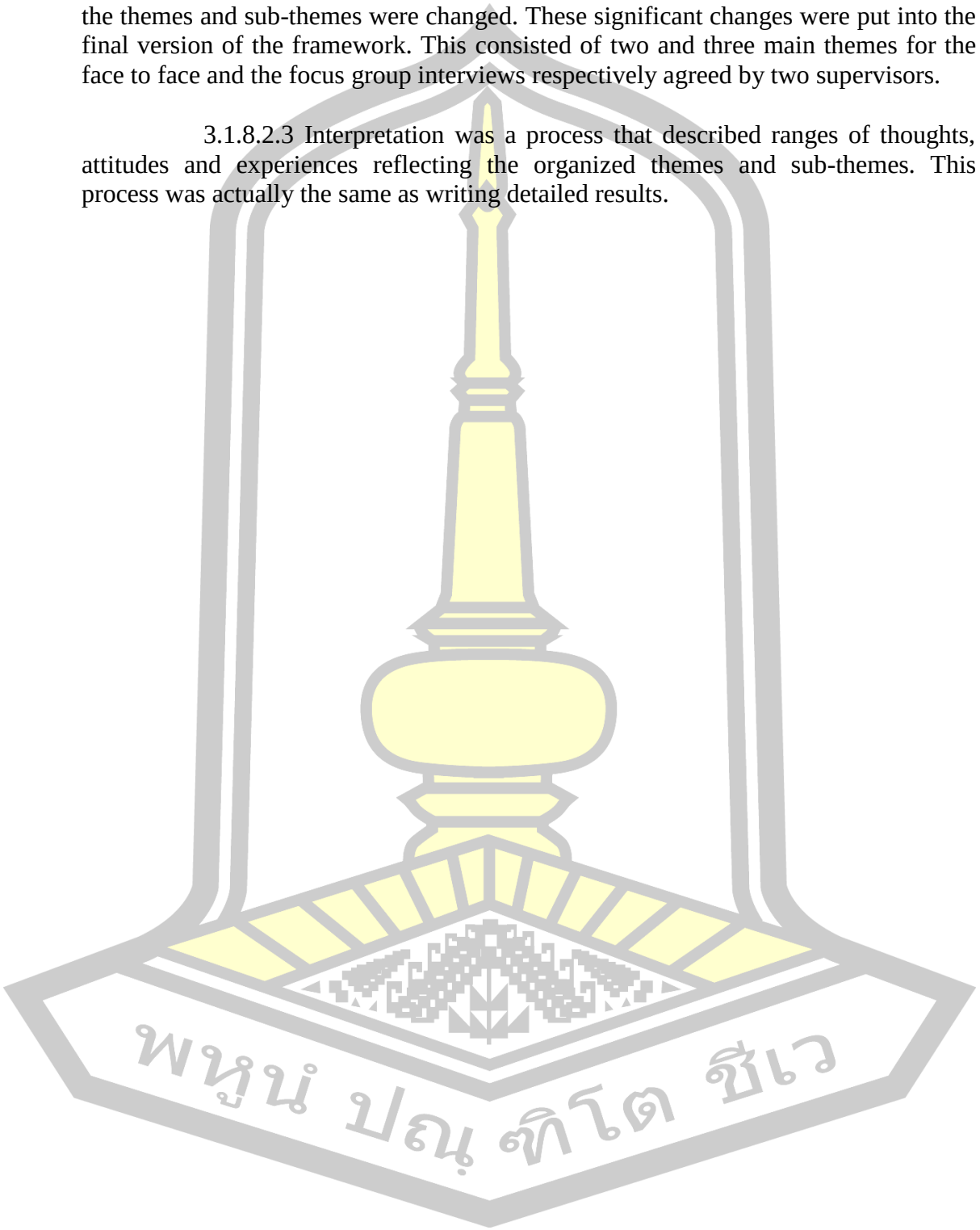
3.1.8.2 A content analysis (52) was used for both interviews, it consist of three key steps: familiarization, indexing and coding themes and sub-themes, and finally interpretation, as follows:

3.1.8.2.1 Familiarizing involved immersion in the data and gaining detailed information from the interviews. This was achieved through the process of listening to, and transcribing. All the tapes and then reading through the transcripts, which helped to identify emerging main themes. Transcribing verbatim was done after all interviews were finished. The researcher transcribed 9 interview tapes from face to face interviews and 8 interview tapes from focus group interviews. The transcribing process by the researcher was taken from one and a half to six hours per interview depending on the duration of the interviews.

3.1.8.2.2 Indexing and coding themes and sub-themes were identified through the transcripts. The final thematic framework was subsequently created in three stages. Different thematic frameworks were created based on themes identified from face-to-face and focus group interviews. Completed transcripts obtained by two supervisors. Secondly, it was amended after the validation process was carried out.

The result of thematic framework was then agreed by two supervisors. Consequently, some sub-themes were grouped together and reorganized and the names of some of the themes and sub-themes were changed. These significant changes were put into the final version of the framework. This consisted of two and three main themes for the face to face and the focus group interviews respectively agreed by two supervisors.

3.1.8.2.3 Interpretation was a process that described ranges of thoughts, attitudes and experiences reflecting the organized themes and sub-themes. This process was actually the same as writing detailed results.



3.2 Phase 2: A Randomized Controlled Trial (RCT) study

3.2.1 Research design

A randomized controlled trial using developed methods of treatment from phase 1, study of pharmacist-managed warfarin therapy to access efficacy and safety of the ways compare pharmacist-managed warfarin therapy (intervention group) with usual care (control group).

3.2.2 Research setting

This study was set in the out-patient department, Lao Luxembourg heart center, Mahosot Hospital, Lao PDR. This department is available on weekday, Monday to Friday. Patients who receive warfarin therapy is about 15 cases per day. The duration of the study is four months and it was carried out between February and May 2019.

3.2.3 Population and sample

Population of this study was patients who are receiving warfarin therapy. Sample was patients who are receiving warfarin therapy at the out-patient department, Lao Luxembourg heart center, Mahosot Hospital, Lao PDR during running of the research.

3.2.4 Inclusion criteria

Patients included in this study was met the following requirements:

3.2.4.1 Patient were required to be 18 years old or above.

3.2.4.2 Patient were being receiving warfarin for at least 1 month and were expected to continue warfarin for a minimum of 4 months.

3.2.4.3 Patient must have INR result for each visit.

3.2.4.4 Patient must be able to speak Lao language.

3.2.4.5 Patient were agreeable to be participant and had been willing to provide written informed consent form.

3.2.5 Exclusion criteria

Patients having the following conditions were excluded from this study:

3.2.5.1 Patient had active cancer.

3.2.5.2 Patient had a hearing impairment and does not have a caregiver.

3.2.6 Sample size estimation

Sample size estimation was used a calculation of comparing mean between two groups (53). The calculation was based on previously published data.

$$\text{n/group} = \frac{2\left(Z_{\alpha/2}+Z_{\beta}\right)^2\sigma^2}{(\mu_2-\mu_1)^2}$$

Wilson and colleagues (2003) conducted a randomized controlled trial to determine whether anticoagulation clinic improve the quality of anticoagulant management compared with family physician. A total of 218 patients was studied. The result of patient in the anticoagulation clinic (pharmacist group) had significant higher percentage TTR in standard 63 % ± 4 versus 59 % ± 5 compared to those in family physician group (51).

A confidence level of 95 %, α is 0.05. A power of 80 %, β is 0.20. μ1 and μ2 are the mean of the two groups.

n = number of sample size for each group

$\alpha = 0.05$, $Z_{\alpha/2} = 1.96$ (two-tailed)

$\beta = 0.20$, $Z_{\beta} = 0.84$

μ_1 = the percentage TTR in standard of the intervention group (pharmacist group) = 63

μ_2 = the percentage TTR in standard of the control group (usual care group) = 59

σ = standard deviation = 5.00

$$\text{n/group} = \frac{2\,(1.96+0.84)^2(5)^2}{(63-59)^2} = \frac{2\,(2.8)^2(25)}{(4)^2} = \frac{2\,(7.84)\,25}{16} = \frac{392}{16} = 24.5 \sim 25$$

Dropout rate 20 %, $n = \frac{(25)(20)}{100} = 5$ patients

Our study was conducted in at least 30 patients for each group.

The control group was patients who have been receiving warfarin therapy using usual care from the out-patient department, Lao Luxembourg heart center, Mahosot Hospital, Lao PDR.

The intervention group was patients who are receiving warfarin therapy using the usual care at the out-patient department, Lao Luxembourg heart center, Mahosot Hospital, Lao PDR, and are receiving intervention from pharmacist (researcher) using the new warfarin therapy, which it was developed during the first phase (phase 1: qualitative interview).

Patients from both groups was receiving warfarin therapy at out-patient department during February to May 2019, and who was selected using the inclusion and exclusion criteria.

3.2.7 Random sampling

To select patients for the control and intervention groups. The random sampling method was used to attain a randomization scheme of permuted blocks. The target sample size was 60 patients (30 in the control group and 30 in the intervention group), and the researcher plans to use blocks sizes of 4 as these are natural for this type and size of study (54).

3.2.7.1 To determine:

A was patient who receives usual care.

B was patient who receives usual care plus pharmacist-managed warfarin therapy.

3.2.7.2 To distribute the patient who was selected from the criteria for 60 patients then they were divided into:

A was patient who receives the usual care and is part of 30 patients.

B was patient who receives the usual care plus the pharmacist-managed warfarin therapy and is part of 30 patients.

3.2.7.3 To build the table of random sample model: block of size 4 have 6 models:

Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
A	B	A	B	A	B
A	B	B	A	B	A
B	A	A	B	B	A
B	A	B	A	A	B

3.2.7.4 To draw lots to decide what model was first to six orders like the table below:

Model 2	Model 6	Model 5	Model 3	Model 1	Model 4
B	B	A	A	A	B
B	A	B	B	A	A
A	A	B	A	B	B
A	B	A	B	B	A

3.2.7.5 To sort assign the random sample of intervention and control group participants. (This table was to show the random sample for 72 patients):

Model 2		Model 6		Model 5		Model 3		Model 1		Model 4	
1	B	5	B	9	A	13	A	17	A	21	B
2	B	6	A	10	B	14	B	18	A	22	A
3	A	7	A	11	B	15	A	19	B	23	B
4	A	8	B	12	A	16	B	20	B	24	A

Model 2		Model 6		Model 5		Model 3		Model 1		Model 4	
25	B	29	B	33	A	37	A	41	A	45	B
26	B	30	A	34	B	38	B	42	A	46	A
27	A	31	A	35	B	39	A	43	B	47	B
28	A	32	B	36	A	40	B	44	B	48	A
Model 2		Model 6		Model 5		Model 3		Model 1		Model 4	
49	B	53	B	57	A	61	A	65	A	69	B
50	B	54	A	58	B	62	B	66	A	70	A
51	A	55	A	59	B	63	A	67	B	71	B
52	A	56	B	60	A	64	B	68	B	72	A

3.2.8 Research outcomes

3.2.8.1 Efficacy:
- TTR
- INR
- Knowledge scores
- DRPs (sub-therapeutic dosage, over dosage, and drug interactions)
- Thromboembolism events
- Patient adherences

3.2.8.2 Safety:
- ADRs (major bleeding or minor bleeding)

3.2.9 Measurements and data collection tool

Measurements and data collection tool were developed by the researcher using the review of literature from a previous study and a result of interviews phase to be modified for the current research.

3.2.9.1. Patients' data collecting form (see Appendix G):

Part 1: General information: gender, age.

Part 2: Efficacy outcomes:

- Indication of warfarin therapy, therapeutic INR, and duration of warfarin therapy in past and future time.
- Patients' result for INR test: INR baseline (first visit which patient meet researcher) and INR for 3 visits (second visit, third visit and fourth visit).
- Comorbidities and medication use.
- Warfarin interaction note: drug-drug, drug-food, drug-herb.
- Thromboembolism event.

Part 3: Patients' adherences using Morisky, Green, and Levine (MGL) 4 item scale (25), and pill count.

Questions MGL	Yes	No
Do you ever forget to take your warfarin?		
Do you ever have problems remembering to take your warfarin?		
When you feel better, do you sometimes stop taking your warfarin?		
Sometimes if you feel worse when you take warfarin, do you stop taking it?		

Part 4: ADRs to assess major and minor bleeding.

3.2.9.2. Questionnaire for patients' knowledge assessment (see Appendix H):

- Knowledge assessment are measured by questionnaires modified from Lakshmi and colleagues (2013) study on impact of clinical pharmacist's interventions in the optimal use of oral anticoagulants in stroke patients. The questionnaire contains 15 items, 8 items of warfarin and 7 items of behavior (20).

-The questions were translated to Lao language by researcher.

-The results were used to compare the baseline data of patients' knowledge and knowledge after intervention. Also, results were used to compare between two groups.

-The answer guides of questionnaire were created by researcher using reviews of literature to be used to give patient's knowledge score (see Appendix I).

3.2.9.3. DRPs assessment form (see Appendix I).

3.2.9.4. Informed consent form 2 (see Appendix J).

3.2.9.5. Participant information form 2 (see Appendix K).

3.2.9.6. Patient books from the hospital are used to write all information. Patients must carry them every time to follow-up (see Appendix L).

3.2.9.7. Answer guides for knowledge questionnaires (see Appendix M).

3.2.9.8. The education tool by pharmacist for patient using warfarin. (see Appendix N)

3.2.10 Quality of measurement instruments

3.2.10.1 To determine quality of measurement instruments, the properties (validity) need to be access based on standardized criteria.

3.2.10.2 Content validity demonstrates level of instrument accuracy in measuring what it was intended to measure and provides information on the representativeness.

3.2.10.3 The patients' data collecting form and questionnaire for patients' knowledge assessment was validated by two research supervisors.

3.2.10.4 It was translated to Lao languages by a researcher.

3.2.10.5 Lao language version form was validated by two experts working in the health care field (one expert is working at Mahosot Hospital and one is working at the University of Health and Sciences, Lao PDR).

3.2.10.6 Two supervisors were requested to evaluate each item by giving the item a rating of +1 = agreement, -1 = no agreement, or 0 = not assurance for each objective.

3.2.10.7 The formula to evaluate Item Objective Congruence (IOC). IOC scores were ≥ 0.5 on representativeness.

3.2.10.8 Cronbach's alpha was used for reliability. The experiment with 20 patients using warfarin therapy were used about a week for test reliability.

3.2.11 Data collection procedure

3.2.11.1 The researcher was contacted with Mahosot Hospital to confirm the dates (during February to May, 2019).

3.2.11.2 When research met patients for the first time, patients were guided by nurses. When patient walk in, researcher identified the patient who was participant in the study following the inclusion and exclusion criteria.

3.2.11.3 Researcher was asked for patients who met the inclusion and exclusion criteria to be a participant on the research during February to May 2019. Participant information forms were given to all participants (see Appendix K). All included patients had to sign an informed consent form (see Appendix J).

3.2.11.4 Patients were divided into two groups using a randomized table (permuted block). During baseline visit in February, researcher could invite 72 patients, 36 patients for each group.

3.2.11.5 A sticker was used to mark patients who is in trial. Patient individual codes were used to divide the control or intervention group.

Data collection procedure for patient in the pharmacist-managed warfarin therapy (intervention group):

- Patients were received usual care then following with the intervention led by researcher which was developed from phase 1.
- Each patient was met the researcher four times (take about 15 minutes for each visit).

First visit:

- Patients were asked for a patients' data.
- Patients were asked a question following the questionnaire for warfarin therapy to be patients' baseline knowledge.
- To give patients' intervention by researcher and to take individual short note for each patient.

Second, third and fourth visit:

- Patients were asked for a patients' data.
- Patients were asked a question following the questionnaire for warfarin therapy to assess patients' knowledge.

- To give patients' intervention by researcher and to take individual short note for each patient.

Data collection procedure for patient in the usual care (control group):

- Patients were received usual care then following to answer a questionnaire with preparing by a researcher.

- Each patient was met the researcher four times (take about 5 minutes for each visit).

First visit:

- Patients were asked for a patients' data.

- Patients were asked a question following the questionnaire for patients' knowledge assessment to be patients' baseline knowledge.

Second and third visit:

- Patients were asked for a patients' data.

Fourth visit:

- Patients were asked for a patients' data.

- Patients were asked a question following the questionnaire for patients' knowledge assessment to assess patients' knowledge.

3.2.11.6 In case of patients who do not come to follow were during the second visit, the researcher was called to ask for the reason. If patients were not available for a next visit, the patients were excluded from the study. A new case was randomly selected to compensate for patients who was cut.

3.2.11.7 In case of patients who do not come to follow-up during the third or fourth visit. That patients were cut from the study. A new case was not being randomly selected to compensate for patients who was cut.

3.2.11.8 Figure 2 was guide how the data collection procedure was being followed.

3.2.11.9 Table 5 was explained the workflow of the groups.

3.2.11.10 Outcomes measurement is in the table 6.

Figure 2 Flowchart for data collection procedure for RCT phase

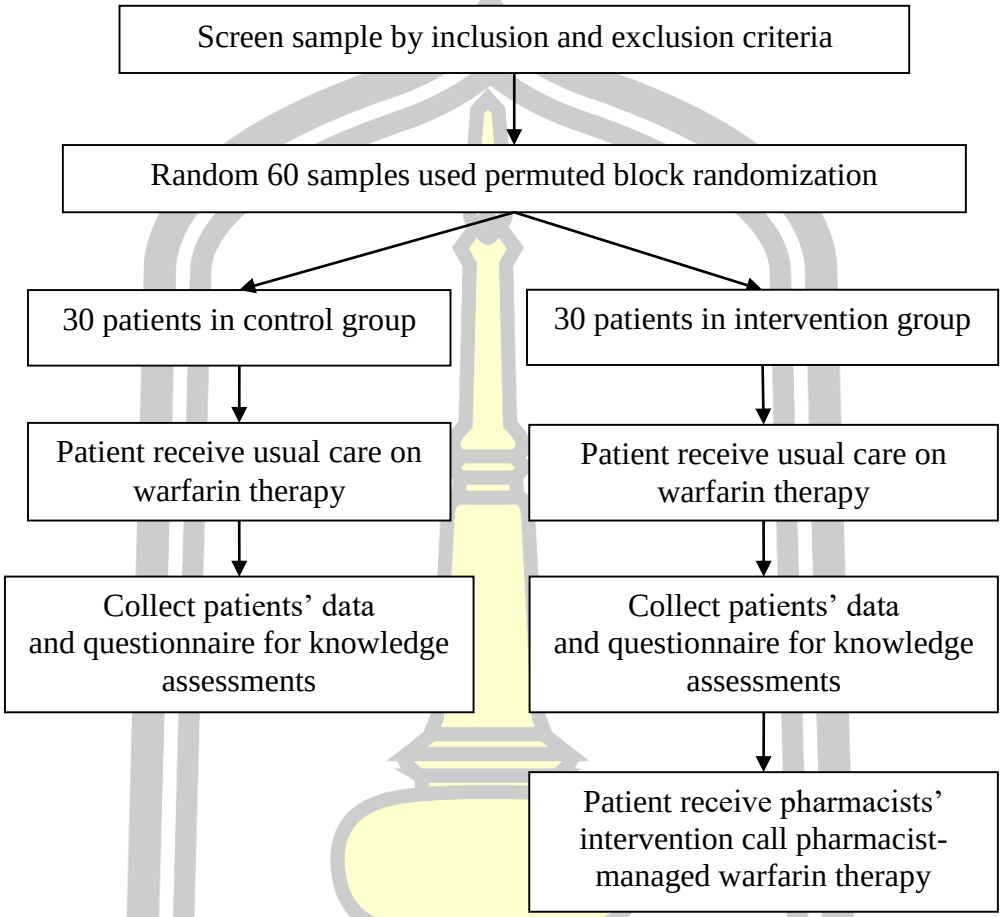


Table 5 The workflow of the groups

Timing	**Usual care (control group)**	**The pharmacist-managed warfarin therapy (intervention group)**
Month 0 (first visit)	- Receive usual care as following step: 1. Patient takes a blood test (INR test) at the laboratory room. 2. Patient registration, recipe the bill, a queue card. 3. A nurse was interviewed them about some patient characteristics. To measure blood pressure and record it in to the patient's book. 4. The doctor (cardiology specialist) was diagnosed, recommend to continues or change cardiovascular drugs including warfarin, provide a short counselling about the disease and the medication use to patient. So, the next follow up was up to the doctor appointment. - After meeting with doctor, patient was met the pharmacist (researcher) as following step: 1. Make an understanding to sign the informed-consent form. 2. Patient's data collection. 3. Ask a questionnaire for patients' knowledge assessment.	- Receive usual care. - After meeting with doctor, patient was met the pharmacist (researcher) as following step: 1. Make an understanding to sign the informed-consent form. 2. Patient's data collection. 3. Ask a questionnaire for patients' knowledge assessment. 4. Medication review: DRPs. 5. Patient adherence checking. 6. In case of any DRPs, notify doctor and record the change in DRPs assessment form. 7. Patient education about warfarin therapy (see Appendix N).
Month 1 (second visit)	- Receive the usual care. - Meet the researcher for patient's data collection.	- Receive usual care. - After meeting with doctor, patient was meet the pharmacist (researcher) as following step: 1. Patient's data collection. 2. Ask a questionnaire for patients' knowledge assessment. 3. Medication review: DRPs.

Table 5 (continued)

Timing	**Usual care (control group)**	**The pharmacist-managed warfarin therapy (intervention group)**
		4. Patient adherence checking. 5. In case of any DRPs, notify doctor and record the change in DRPs assessment form. 6. Patient education about warfarin therapy (see Appendix N).
Month 2 (third visit)	- Receive the usual care. - Meet the researcher for patient's data collecting.	- Receive usual care. - After meeting with doctor, patient was met the pharmacist (researcher) as following step: 1. Patient's data collecting. 2. Ask a questionnaire for patients' knowledge assessment. 3. Medication review: DRPs. 4. Patient adherence checking. 5. In case of any DRPs, notify doctor and record the change in DRPs assessment form. 6. Patient education about warfarin therapy (see Appendix N).
Month 3 (fourth visit)	- Receive usual care. - After meeting with doctor, patient was met the pharmacist (researcher) as following step: 1. Patient's data collecting. 2. Ask a questionnaire for patients' knowledge assessment. 3. Medication review: DRPs. 4. Patient adherence checking. 5. In case of any DRPs, notify doctor and record the change. Patient education about warfarin therapy.	- Receive usual care. - After meeting with doctor, patient was met the pharmacist (researcher) as following step: 1. Patient's data collecting. 2. Ask a questionnaire for patients' knowledge assessment. 3. Medication review: DRPs. 4. Patient adherence checking. 5. In case of any DRPs, notify doctor and record the change in DRPs assessment form. 6. Patient education about warfarin therapy (see Appendix N).

Table 6 Outcomes measurement

Control group	Intervention group
1. Efficacy outcome: - TTR - INR - Knowledge scores - DRPs - Thromboembolism events - Patients adherences 2. Safety outcome: - ADRs	1. Efficacy outcome: - TTR - INR - Knowledge scores - DRPs - Thromboembolism events - Patients adherences 2. Safety outcome: - ADRs

3.2.12 Data analysis

All data was used a computer program analyses, statistical analysis was performed using STATA software (version 14). A 95% confidence interval was used to analyze ($\alpha = 0.05$). Per-protocol analysis was performed.

3.2.11.1 To calculate TTR were used 3 INR results, the method previously proposed was used the Rosendaal method (55).

3.2.11.2 The value of the Kolmogorov-Smirnov test was used to test for normal distribution, if p-value was greater than 0.05, the data was a normal distribution.

3.2.11.3 Continuous variables were presented as mean ± SD when data is normal distribution. A student *t*-test for independent samples were used to compare the mean values between groups.

3.2.11.4 Continuous values were presented as median if the data significantly not normal distribution. A Mann-Whitney *U* test for independent samples were used to compare the median values between groups.

3.2.11.5 Patients' age, duration with warfarin therapy, and TTR results were presented by continuous variables.

3.2.11.6 For continuous variables, a repeated-measure ANOVA test was used to compare within group, for each visit.

3.2.11.7 Categorical variables were presented as numbers and percentages. Patients' gender, indication, therapeutic INR, result for INR test, comorbidities, medication used, food interaction with warfarin, herb interaction with warfarin, patient adherence, major and minor bleeding, patient knowledge were presented by categorical variables.

3.2.11.8 For categorical variables, a Chi-squared test were used to compare between group, with the Fisher's exact test being performed when the sample size is small.

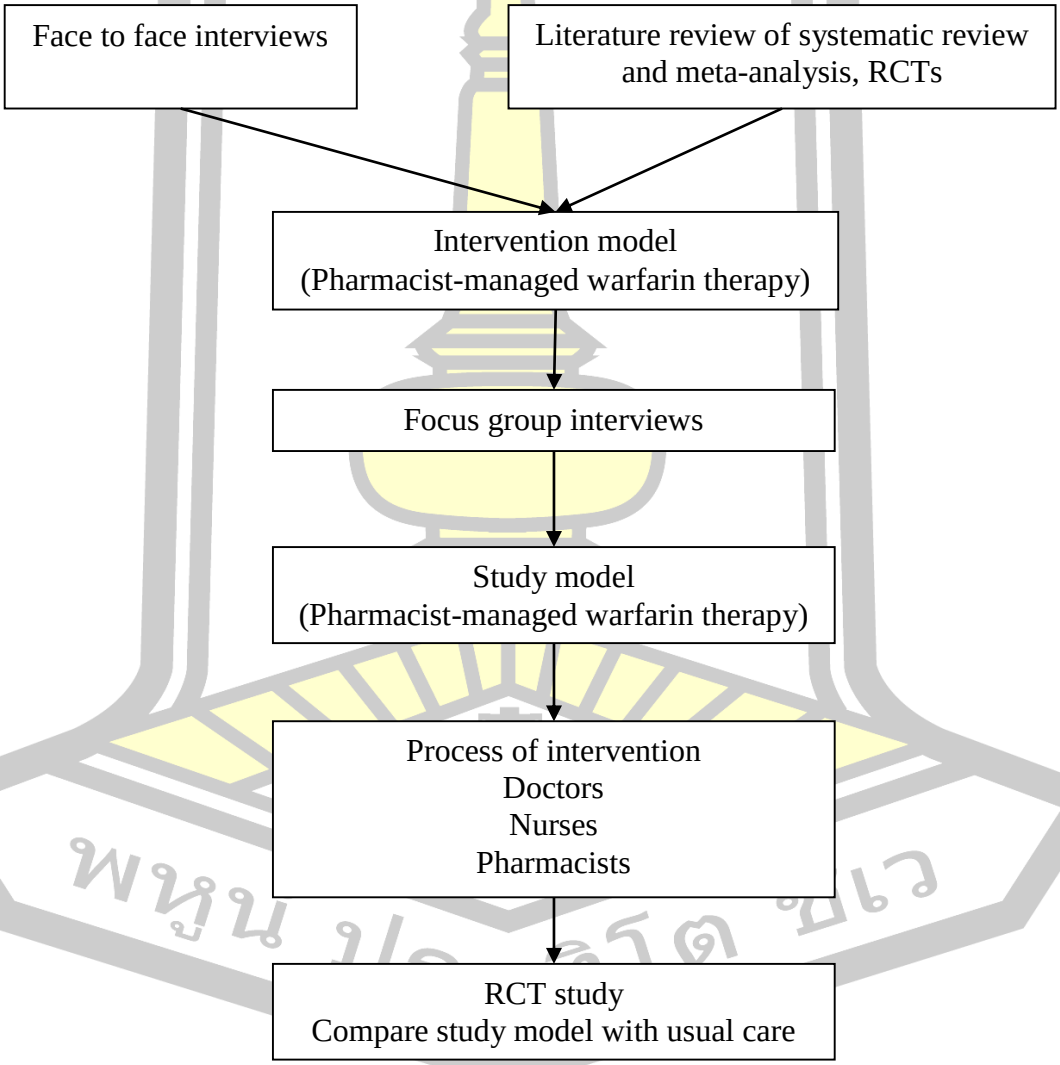
3.2.11.9 For categorical variables, a Cochran's test was used to compare within group, for each visit.

3.3 Protection of human participants

Ethical approval was received from National Ethics Committee for Health Research (NECHR) No 17/NECHR from Lao PDR, and Mahasarakham University Ethics Committee for Research Involving Human Subjects No 026/2019 and No 079/2019 (see appendix R). All voice recording and transcriptions were kept in secured place by the researcher, and were deleted after the study is done. All patient's data were in security and only researcher can access via password.

3.4 Planning process

Figure 3 Flowchart for planning process



CHAPTER IV

RESULTS

The objectives of this study were to develop pharmacist-managed warfarin therapy at Mahosot Hospital, and to assess its outcomes on patients using warfarin. There are two phases of this study:

Phase I: Qualitative interviews

In this phase, there were face to face and focus group interviews.

4.1 Face to face semi-structured interviews

The face to face interviews were conducted to investigate views of healthcare professionals including doctors, nurses and pharmacists on warfarin therapy. The details are as follows:

4.1.1 General information of healthcare professionals participating in the face to face interview

4.1.2 Healthcare professionals' experiences of current practice problems with warfarin therapy

4.1.2.1 Views of service and warfarin problems

4.1.2.2 Roles of healthcare professionals in current practice

4.1.2.3 Views of organizational barriers

4.1.3 Healthcare professionals' perspectives on ways to improve services and healthcare professionals' educations and training

4.1.3.1 Ways to improve services

4.1.3.2 Views of pharmacists' roles in warfarin clinic

4.1.3.3 Views of education or training and research

4.2 Focus group interviews

Focus group interview was undertaken to gain views of healthcare professionals involving in the provision of health care services for patients using warfarin in order to develop the practical intervention called pharmacist-managed warfarin therapy at Mahosot Hospital integrated with evidence-based intervention model.

4.2.1 General information of healthcare professionals participating in the focus group interview

4.2.2 Collaborations among healthcare professionals

4.2.3 Expectations of pharmacists' roles by healthcare professionals

4.2.3.1 How to take warfarin properly

4.2.3.2 Normal INR range

4.2.3.3 Drug-, Food-, Herb-, Alcohol-warfarin interactions

4.2.3.4 Adverse drug reaction and management

4.2.3.5 How to manage when receiving operations

4.2.3.6 Importance of following up doctors' appointment

4.2.3.7 Booklet information

4..2.4 Development of training program for healthcare professionals

Phase II: A Randomized Controlled Trial Study

This phase was conducted to evaluate the effects of pharmacist-managed warfarin therapy on patient clinical outcomes at Mahosot Hospital.

4.3 Patient characteristics

4.4 Efficacy outcomes

4.4.1 TTR (time in therapeutic range)

4.4.2 INR value

4.4.3 Patients' knowledge

4.4.4 Drugs related problems with warfarin therapy (DRPs)

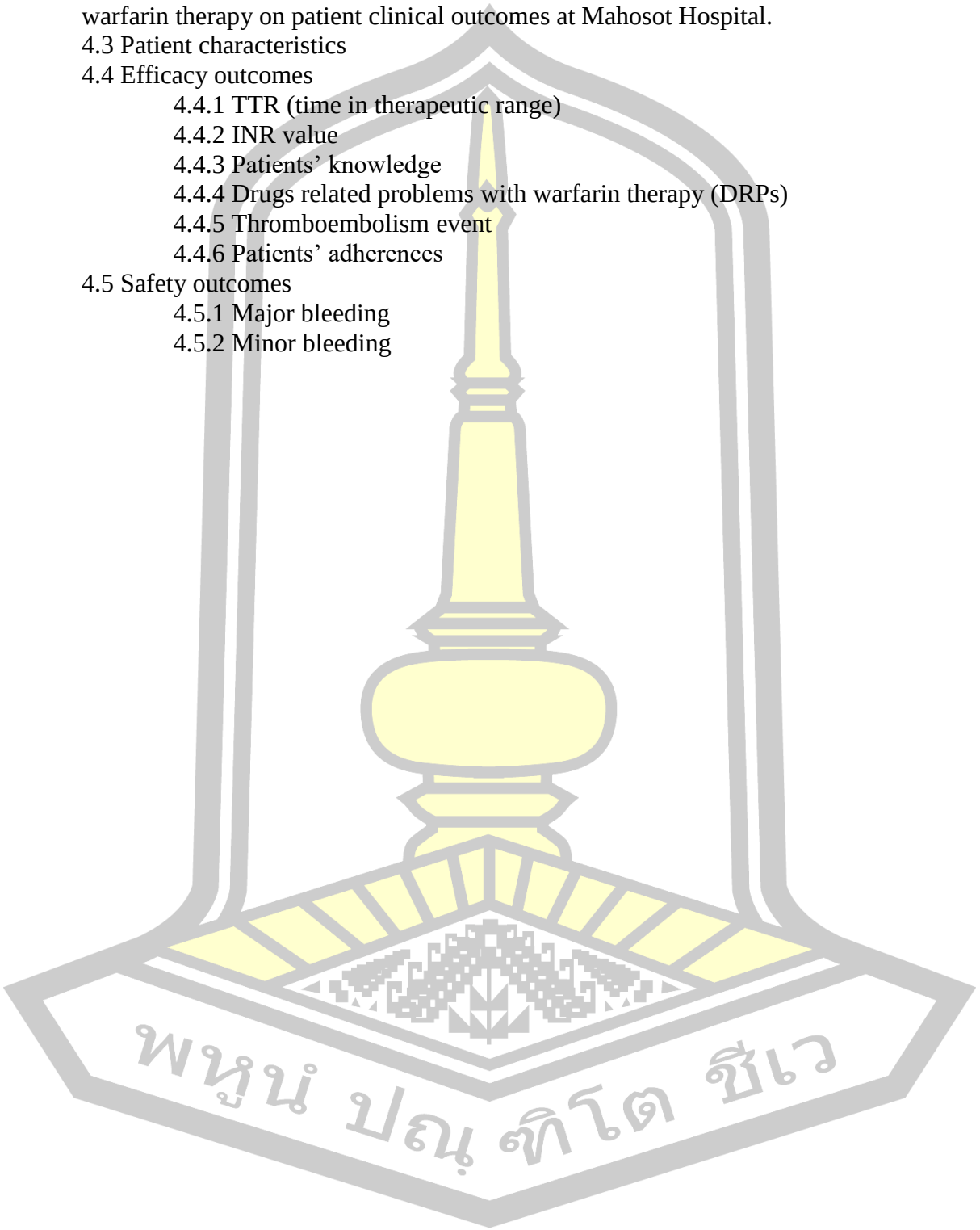
4.4.5 Thromboembolism event

4.4.6 Patients' adherences

4.5 Safety outcomes

4.5.1 Major bleeding

4.5.2 Minor bleeding



Phase I: Qualitative interviews

4.1. Face to face semi-structured interviews

The face to face interviews were conducted to investigate views of healthcare professionals including doctors, nurses and pharmacists. This face to face interview presented on 2 main themes: healthcare professionals' experiences of current practice problems with warfarin therapy; and healthcare professionals' perspectives on ways to improve services and healthcare professionals' educations and training. There were 3 sub-themes for each main themes. First main theme contains with views of service and warfarin problems, roles of healthcare professionals in current practice and views of organizational barriers. Second main theme was contained ways to improve services, views of pharmacists' roles in warfarin clinic and views of educations or trainings and research.

4.1.1 General information of healthcare professional's participant in the face to face interview

The total of nine healthcare professionals working at out-patient department (3 of doctors, 3 of nurses, and 3 of pharmacists), representing each of the main healthcare professionals taking care of patients using warfarin participated in the study. The average ages of doctors, nurses and pharmacists were 39, 41 and 30 years respectively. (as shown in Table 7)

Table 7 Characteristics of participants in the face to face interviews

Characteristics	**Doctor (D)**	**Nurse (N)**	**Pharmacist (P)**
Number	3	3	3
Sex			
Male	3	1	1
Female	0	2	2
Age			
Mean	39	41	30
	(30, 44, 42)	(30, 42, 51)	(27, 30, 33)
Years of clinical experiences			
Mean	14	9	5
	(4, 18, 20)	(7, 20, 30)	(1, 3, 10)

4.1.2 Healthcare professionals' experiences of current practice problems with warfarin therapy

Three major themes emerged from the face to face interviews included views of service and warfarin problems, roles of healthcare professionals in current practice and views of organizational barriers.

4.1.2.1 Views of service and warfarin problems

Doctors, nurses and pharmacists had the same views of warfarin problems that were needed more attention from the healthcare team. In addition, the other important problems found were not following up with doctors' appointment and buying warfarin by themselves at the drug store. In fact, warfarin is not legally allowed to sell in drugstores. Purchasing warfarin from these stores was commonly found in practice because it was very convenient for patients. It could cause patients' problems not coming for a regular follow-up, resulting in lack of INR test and non-adherence.

Patients were also lack of knowledge about how to take warfarin properly, its common side effects and its interaction with food and the others drugs. These problems then led to major or minor bleeding complications as well as poor health outcomes. These included minor bleeding or too low dose/too high dose of warfarin leading to poor clinical outcomes of individual patients.

"It's impossible for the doctor to adjust warfarin dose and as patients don't know that it could lead to dead due the brain hemorrhage. Patients ask for large amount of warfarin that would last for several months because they live far away from the hospital." D1M

"Patients live far away from the hospital so they ask for large amount of warfarin that will last for several months. I saw patients with cardio surgery not coming every month for INR test. They sometime are admitted with warfarin over dose, bleeding, ischemic stroke, hemolytic stroke, lower warfarin dose. Patients sometime admitted with a complication." D2M

"Some patients admitted with bleeding, skin bruising, teeth bleeding, vomiting of blood and high INR." N1F

"Most of the patients come with skin bruising, teeth bleeding, discontinuous drug use, paralyze, fatigue and bleeding." N3F

"Patients buy warfarin from pharmacy outside the hospital. They can't remember that they can't buy this drug outside the hospital. Patients can't remember the counselling from the doctor and they don't read or understand the information that the doctor provided, the doctor has to retell the instruction again and again. Patients can't remember what the warfarin are used for." D1M

"Patients start taking warfarin by our prescription but not coming for follow up. Some pharmacy provides warfarin. Patients take 3 mg dose but they bought 5 mg dose from a pharmacy and consider them as the same." D1M

"Patients think that they have overcome the disease so they stop taking medicine. There are some patients had a skin bruising and think that it was done by a ghost. Patients can't follow what doctor told them to do. Patients don't understand the importance of taking medicine." N2M

"The reason for patients discontinuing drug is they can't come to the hospital. It's hard for the elderlies to remember and dividing tablets for single use." N3F

In addition, there were many cases having INR value higher and/or lower than normal range. Patients were not aware of the importance of INR value and keeping up regular monitoring.

"Patients admitted with complications of nosebleed, teeth bleeding, skin bruising, black stool, bloody stool, red urine, hematoma." D3M

"Some patients admitted with bleeding, skin bruising, teeth bleeding, vomiting of blood and high INR." N1F

"There are many patients that admitted with bleeding, teeth bleeding, coughing up blood, red urine, using incorrect dose, warfarin discontinuous use, paralyzed, brain hemorrhage." N2M

In fact, patients need to adjust the dose of medicine depending on their blood test result. One more important thing that could be seen is the lacking of warfarin clinic. This problem has made some difficulties to healthcare professional since warfarin therapy are depending on doctor's decision. Pharmacist is only responsible for distributing medicines to patients. Other than that, some nurses and pharmacists were pointed out that there were still a mistaken on dispensing warfarin which is a mistake from pharmacist.

"There is no warfarin clinic. Nurses follow the doctors' suggestion. There is no contribution from a pharmacist, doctor is a leader, pharmacists only dispensing drug as by doctors' prescription." D2M

"Sometime pharmacists dispensed wrong medicines to patients and nurse notices that." N2M

"It's rarely seen problems, errors dispensing in case of incorrect warfarin dose of 3 mg but dispensing 5 mg." P1F

4.1.2.2 Roles of healthcare professionals in current practice

At Mahosot Hospital, currently doctor and nurse worked together. Doctors gave general counselling of warfarin use and provided regular monitoring for individual patients. Nurses provided warfarin counselling on how to safely use drug as prescribed, drug-drug and food-drug interactions, being aware of major or minor bleeding, and complications of diseases. However, pharmacists said that they just only dispensed warfarin to patients. They did not give a proper counselling for individuals due to workloads and times constraints.

"Doctors counsel patients on what to do when patient takes warfarin, not taking IV, IM without any doctor's prescription, takes this drug for a lifetime, asking back patients to give a review what they should do, makes a follow up check. There is less communication between pharmacists and patients." D1M

"Nowadays, nurses do the counselling for warfarin patients, tell them to come for follow up, tell them how to use drug correctly, tell them to taking care of themselves. Green vegetable should be avoided, continuing practicing what the doctor have recommends in order to prevent the bleeding and if there are any complications, they should come to hospital directly." N1F

"The doctor order, nurse following, it up to INR test result. Nurses follow whatever the doctors tell them to do and depend on the result of INR test." N2M

"I tell patients to ask a doctor how to use warfarin. Nowadays when we dispense drugs and see the problem we will tell patients to see with doctor. Sometimes patients ask questions and we have to tell them to ask doctors." P2M

4.1.2.3 Views of organizational barriers

Even though all doctors, nurses, and pharmacists realized about the provision of proper counselling to patients in practice, such counselling was not undertaken due to many barriers. These barriers were; for example, lack of human resources, hospital policy, and financial support for good health services. Doctors said that if the hospital had adequate budgets, then warfarin clinic would have been established and all health care team could have worked more robustly and closely. Warfarin booklet and home care services could have also been done among the healthcare team.

"Nowadays there is lack of healthcare professional. A person has to do many things. The system creates a waste of human resources and in some cases it is inappropriate. The financial is not matter but the human resource is limited. Patients said, it's incontinence for travelling back to the hospital so it's hard to control INR." D1M

"There is lack of human resource. If we are going on warfarin clinic project, we have to find the financial support from somewhere to pay for patients book with all

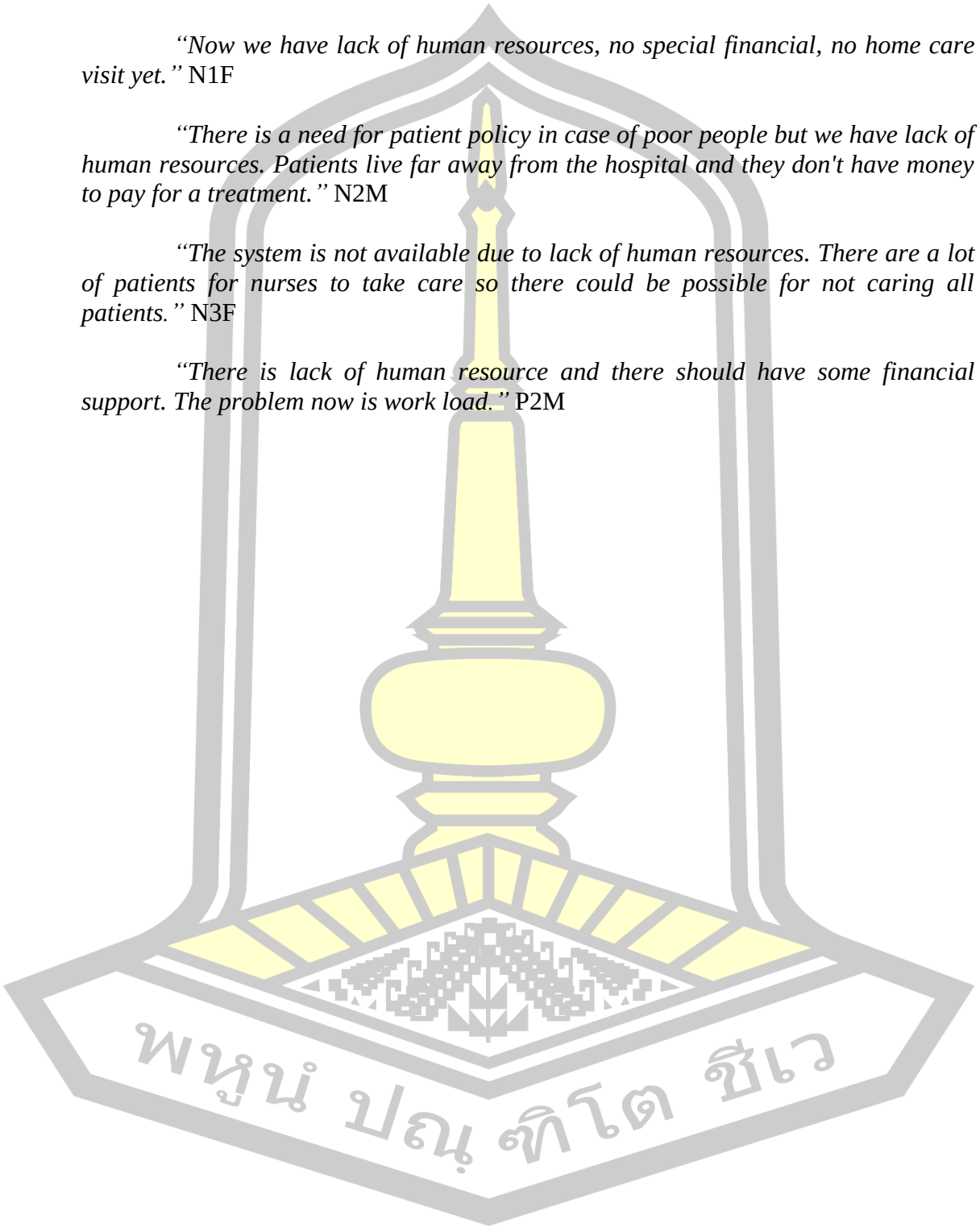
important information for patients taking warfarin therapy. The hospital does not have budget for this part." D3M

"Now we have lack of human resources, no special financial, no home care visit yet." N1F

"There is a need for patient policy in case of poor people but we have lack of human resources. Patients live far away from the hospital and they don't have money to pay for a treatment." N2M

"The system is not available due to lack of human resources. There are a lot of patients for nurses to take care so there could be possible for not caring all patients." N3F

"There is lack of human resource and there should have some financial support. The problem now is work load." P2M



4.1.3 Healthcare professionals' perspectives on ways to improve services and healthcare professionals' educations and training

Overall, healthcare professionals' perspectives on ways to improve services and healthcare professionals' educations and training included sub-theme of ways to improve services, views of pharmacists' roles and views of educations or trainings.

4.1.3.1 Ways to improve services

Healthcare professionals expressed the agreement on collaborations among the healthcare professional team including doctors, nurses, pharmacists, nutritionists, and psychologists for setting up a specific service for patients with warfarin use. Nurses clearly supported the contributions of nutritionists and psychologists. All healthcare professionals agreed on the benefits of establishing a warfarin clinic, it could help to improve overall patients' health outcomes as well as to reduce warfarin problems as mentioned before. This clinic would then be beneficial for elderly patients using warfarin. In addition, home care service could help patients living in remote areas, also be set up to having transportation problems and not having caregivers.

"From the beginning, the problems of warfarin must be prevented. Education of health or hygiene must be provided in order to prevent cardiovascular disease. It will better if there is nutritionist." D1M

"Special care from healthcare professionals need to be provided. Psychologists should be involved." N1F

"Pharmacists should be a part of warfarin treatment team, the important is nurse, a psychologist, and a nutritionist." N2M

"Special care should be provided. Everybody should be a part because patients are elderly." P1F

"It will be good if we can do a patient counselling, nowadays we just tell patients to ask a doctor." P3F

"Be able to set warfarin clinics to follow those patients and the patients' information is very important for the follow up. Establish warfarin clinic for patient using warfarin. The way of setting up a clinic warfarin in the future, can we set a day per week to examine the patients taking warfarin therapy. Patients counselling must be improved. If we have a good project we can suggest the director of the hospital to make the best decision, if we have a good condition and a human resource is sufficient, I think this is the new role to do like another country." D2M

Moreover, patient should have routine INR monitoring and the test must be valid, and fast.

"We must make it systematic by taking INR test monthly if possible, every 3 months if patient live far away, if patient get any complication they should come to hospital directly. INR test need to be done every time before adjusting warfarin dose. Doctors make a plan for next follow up." D2M

"INR test needs to be done in order to adjust warfarin dose and INR test must be done correctly. There should be contributions from every healthcare professional, patients will have received the right dose." D3M

"Patients should come for follow up by exact schedules. INR tests should be done faster. Using warfarin antidote in case of warfarin overdose. To recheck INR test result when seeing something abnormality." N1F

4.1.3.2 Views of pharmacists' roles in warfarin clinic

It is very interesting that all healthcare professionals agreed to have pharmacist counselling for patients using warfarin therapy. Doctors said that their roles are to prescribe drugs, give some important information to patients and keep up monitoring patients as necessary. Doctors and nurses had the same suggestions about pharmacists' roles; for instances, providing key information on how to take warfarin safety, its side effect, food-drug, drug-drug, herb-drug interactions, important things to be aware of, not buying warfarin at drug store. A private area for pharmacy counselling was also suggested. Doctors agreed that the importance and benefits of having pharmacist counselling were not just directly for the patients but also to help save time for doctors.

"It would be good to have pharmacist counselling, but the information provided need to be the same as doctor. After the doctors taking notes on patients' book, pharmacists have to explain to patients also. Pharmacists could schedule for patients counselling for 5 people or 10 people per time and doctors will choose the patients for pharmacists or pharmacists can be random selected for any patients." D1M

"This is a very good idea. Pharmacists will counsel the side effect of drugs, the effect of drug interaction for example which drug are increased or decreased dose of warfarin, pharmacists know best." D2M

"If pharmacist gives a contribution, doctors don't know the specific details of drugs. It's good because doctors don't have enough time to provide patients counselling. It would be good for example telling patients not buying warfarin from outside the hospital, what food they can eat and not to eat. Doctors will adjust warfarin dose. It would be good if pharmacists have a private place for patients counselling. Every patient who had cardio surgery or taking warfarin therapy have to visit these pharmacists for patient counselling. If we have time to do it would be good. If pharmacists do a patients counselling that would be good but for the hospital policy, we don't know yet if it's possible we will do as suggested." D3M

"We don't have the clinical pharmacists who do this. It would be good if pharmacists can do this. Pharmacists can provide patients counselling on what patients should do when taking warfarin. Now pharmacists only dispensing medicine and pharmacists don't have any contribution for this role. In the future there might be a new system but nowadays there is no pharmacists working on patients' counselling, just only nurses and doctors and if all healthcare professional work together it will be better." N1F

"I agreed to let pharmacists doing a patients counselling." N3F

4.1.3.3 Views of education or training and research

Pharmacists mentioned that they have no confidence to give proper suggestions or counselling about warfarin therapy to patients, but doctors and nurses have more knowledge and roles for patients' counselling. All pharmacists said that education and training were specifically needed for them. This was to help increase their knowledge and counselling skills and be able to confidently provide professional counselling for individual patient. Additionally, pharmacists thought that in order to set up a pharmacist-managed warfarin therapy, it was important to initially discuss with the other healthcare professionals.

"Pharmacists never provide counselling just tell patients to follow doctors' prescription. We can give advices if patients ask. I know about the drug interaction but I don't tell them because doctors already told them. If we have to do a patient counselling, first we should learn about this medication because we did not study this drug, I want to know more about every medicine in this cardio center using." P1F

"We don't have a knowledge on this medicine just heard from people that this drug can cause bleeding. We have to learn with the cardio specialists (doctors) because they know more than pharmacists about this drug, I want to learn and use for patient counselling." P2M

"We have to learn more about this medicine, how to use it. I know that this medicine can cause bleeding but I don't know deeply." P3F

"Normally pharmacists should work by teams but they don't have a chance if there is workshop or seminar, they should join. They should learn more about warfarin counselling." N2M

Furthermore, doctors also suggested that conducting research related to warfarin use was essential the first step of setting up a warfarin clinic and to continuously improve the service in the long run.

"Research data of warfarin need to be produced more in this hospital." D3M

4.2 Focus group interviews

Focus group interviews were undertaken to gain views of healthcare professionals involving in the provision of health care services for patients using warfarin. This was to develop the practical intervention model called pharmacist-managed warfarin therapy at Mahosot Hospital based on evidence-based intervention model. The key concepts of pharmacists' roles in providing pharmaceutical care services for patients using warfarin extracted from the meta-analysis and systematic reviews studies were integrated into the intervention model. Then the process of care delivering "pharmacist-managed warfarin therapy", was drafted and discussed in the focus group interviews.

Results from the literature review of systematic review and meta-analysis and RCT studies presented the pharmacist activities below:

1. Determine indication and duration of therapy
2. Establish a therapeutic range and/or warfarin dosing/adjustment
3. Educate of the patient and/or other healthcare provider
4. Assess compliance with regimen
5. Review medication, co-morbidities, food or drug interaction
6. Screen thromboembolism or bleeding events and recurrence
7. Schedule INR test interval or follow-up visit
8. Ordering/request INR test or point of care INR test
9. Prescribing warfarin

In addition, the summaries of a face-to-face interview of healthcare professionals at Mahosot Hospital presented 2 main themes: healthcare professionals' experiences of current practice problems with warfarin therapy; and healthcare professionals' perspectives on the ways to improve services and healthcare professionals' educations and training. There were 3 sub-themes for each main themes. First main theme contains with views of service and warfarin problems, roles of healthcare professionals in current practice and views of organizational barriers. Second main theme contains the ways for improving services, views of pharmacists' roles and views of educations or trainings.

Researcher created the practical intervention model to present at the focus group interview. The main topics discussed were as follows:

- The process of care for patients using warfarin (see Appendix K): it was established from the real practice at Mahosot Hospital and researcher had added one step of pharmacists' intervention on the end of the process.
- The pharmacists' roles for patients taking warfarin (see Appendix L): it was created by using the results of literature review of systematic review and meta-analysis and RCT studies by pharmacist activities for warfarin patients.
- The education tool for pharmacists (see Appendix M): it was recognized by using the results of face-to-face interview, especially from the sub-themes of views of pharmacists' roles that can be done at Mahosot Hospital.

During the interview, practical intervention model was proposed, discussed and summarized key points of the interviews based on the main topics guide. The pharmacist intervention model called "pharmacist-managed warfarin therapy" was finally developed after finishing focus group interviews.

Three major themes emerged during the focus group interviews included: collaborations among healthcare professionals; expectations of pharmacists' role by healthcare professionals; and development of training program for healthcare professionals.

4.2.1 General information of healthcare professional's participant in focus group interview

In total, 8 healthcare professionals working in the out-patient department (2 of doctors, 3 of nurses, and 3 of pharmacists) were interviewed. The average age was 43 years for doctors, 41 years for nurses, and 46 years for pharmacists. The average year of clinical experiences was 17 years for doctors, 19 years for nurses, and 22 years for pharmacists. (as shown in Table 8)

Table 8 Characteristics of participants in the focus group interviews

Characteristics	Doctor (D)	Nurse (N)	Pharmacist (P)
Number	2	3	3
Sex			
Male	2	0	1
Female	0	3	2
Age			
Mean	42.5	41	46
	(35, 50)	(30, 46, 47)	(41, 48, 49)
Year of clinical experiences			
Mean	17	19	22
	(8, 25)	(7, 24, 25)	(19, 23, 23)

4.2.2 Collaborations among healthcare professionals

The first theme described by doctors, nurses, and pharmacists was the collaboration among healthcare professionals including doctors, nurses, pharmacists, and nutritionists. All healthcare professionals had same the perspectives that it's necessary for having the collaborations among healthcare professionals in order to serve warfarin patients by setting up practical work plans and roles for individual healthcare professional. Each healthcare professionals should play their roles to help educate patients, create quality work and ultimately to improve patients' health outcome.

"I think in a near future we could work together whenever pharmacists and nurses are ready, doctors are willing to help on warfarin dose adjusting problem. In the past, we did not do as you (researcher) have suggested. I agree that it is a good thing in the future if we could work together corporately to establish warfarin clinic. Doctors have a responsibility of check patient, diagnose and prescribe medicine. Pharmacists and nurses have a responsibility of clearly advise patient on how to use medicine properly as the agreement with doctors. I think it would be good it could do this together, if we still continue doing what we are doing right now, we could not control the effectiveness of taking warfarin." D1M

"I have suggested the direction of taking different types of medicine to doctors, in the past pharmacists and nurses are helping each other. Moreover, nutritionist should concern the diet for patient. We will increase the quality of work. Pharmacist and nurse work together it will increase the quality of work since the diet affects the quality of medicine." N1F

"It would be great if there is an interaction and communication between pharmacist, doctor and nurse about taking this medicine." P2F

In the past, apart from dispensing medicines, pharmacists did not have a role on counselling patients. This is a good opportunity for the pharmacists to help patients' knowledge and understanding the proper and safe use of warfarin.

According to the statements above, all participants agreed that pharmacists should be responsible for providing advices to patients. In addition, pharmacists also would like to play a role on providing counselling services to patients for the maximum benefits of individual patient.

"Pharmacist did not have any interaction with patient. Pharmacist only has to ask patient again whether they know how to take medicine or not, is there any concern they want to ask? But in the future, pharmacist would help nurse in this role, for now, nurse do this role. I agree on this, it would be good if pharmacist could also participate. I don't think it would make any confusion. Patient will receive a better information so they could follow the instruction from prescription. The patient will get the most benefit." P1F

"It would be great if there is an interaction and communication between pharmacist, doctor and nurse about taking this medicine." P2F

Process of providing practical intervention model called "pharmacist-managed warfarin therapy" was proposed and discussed during the focus group interviews. How this service should be undertaken by individual healthcare professional (see Appendix B).

4.2.3 Expectations of pharmacists' roles by healthcare professionals

Regarding expectation of pharmacists' roles by doctors and nurses, our participants showed major concern about patients' safety. Therefore, roles of pharmacists should include: how to take warfarin properly, normal INR range, drug-, food-, herb-, alcohol-warfarin interactions, adverse drug reaction and management, how to manage when receiving operations, importance of following up doctors' appointment, and booklets information.

4.2.3.1 How to take warfarin properly

The important issue of giving counselling on "how to take warfarin properly" was discussed and summarized. In order to help patients using warfarin safety and properly.

"Nurses and pharmacists will often give information and advice patients on how to take medicine properly. Some patients may take warfarin incorrect way, nurses have written some instruction for taking warfarin but some patients were not followed those instructions, so we interview and ask them to show us the medicines or pills, sometimes they take overdose of warfarin." D1M

"For acknowledging information about warfarin to patient, cardiologist was specifying to patients that they should take this medicine after the operation." D2M

"For the understanding of patient, when we were distributing medicine to patients, they said they have understood. But once they went back home they take a wrong direction which make them come back to hospital with bleeding or thromboembolism." N1F

"Pharmacists should talk about the side effect and quality of medicines. So, it would be best if pharmacist could help us in the process of out-patient department. I want pharmacists to provide this information. Agree on advising and monitoring for the medicine's reaction." N2F

"Counted the numbers of warfarin (pill count) and asked patient to check whether they are taking in correctly or not." N3F

"If possible, pharmacist should provide advising or discussing. Roles of pharmacist are to check the prescription and give advice based on the doctor's suggestion." P3M

4.2.3.2 Normal INR range

In this study, evidences showed that patients should understand the normal INR range to better managed themselves. Therefore, pharmacists should emphasize the information of normal INR in range to patients and make them keep up doctors' appointment. This is all for the benefits of patients themselves.

"For both previous and current cases, we have always advised patients that if they take warfarin they will need to check INR level, if doctor has found that their INR level are within normal range (INR 2-3 or 2.5-3.5) that means they are taking warfarin correctly and should continue doing that. But if their INR level is too low or too high, doctor will also always give them some advices. I agree with doctor (D2) that we need to tell patient that we need to test INR because some patients could not remember and they just came with their previous bill, no INR testing result and tell doctor to do checkup." D1M

"We have asked patients and they said they took medicine but once they did blood test we have found INR rate for 1.3-1.4, they lied that they took medicines in fact they were not. For INR level of heart surgery patient, every time they come back to do checkup, doctors will give them some advices and tell them that their INR level should be between 2-3. If it is too low, doctor will increase medicine, if it is too high, doctor will decrease medicine. Doctor needs to explain to patients for their understanding." D2M

4.2.3.3 Drug-, Food-, Herb-, Alcohol-warfarin interactions

Doctors suggested that pharmacists should provide counselling to patients particularly significant drug interactions causing harmful side effect including major and minor bleedings. Doctors also mentioned that there were a few cases having harmful drug interactions causing hospital admissions.

"There was a case when doctor ordered warfarin and it came with other medicine that have drug interaction with warfarin such as omeprazole, antibiotics. In the future, I hope pharmacist will have more courage to report or give feedback to doctor. If pharmacist could help doctor with this problem, it would be great for patients. I wish pharmacist could help doctor on this. I said this from my heart because we could really help patients, if pharmacist checked and found there was something wrong in the prescriptions or medicine, just ask patients to go back to doctor and recheck the prescription. This will be the best thing for helping patients." D1M

"For the drug interaction with warfarin, pharmacist did not take any responsible for those, just distributes medicine." P1F

From the interview, participants mentioned symptom that's could possibly cause by drug-drug interaction but there is no any evidence to prove their words. To prevent this serious events, patients should be recommended to avoiding get or take medicines by themselves or visit doctors every time they had a side effect from taking medicines. Additionally, pharmacists should explain symptoms or dangers caused by drug-drug interaction.

"For cardiologist, when patients took warfarin and found the high INR level in the follow up, we will ask them whether they took any other medicines or not such as traditional medicine, painkiller pill or antibiotic medicine that could increase the effect of warfarin. Even, omeprazole also could increase the effect of warfarin. We need to ask patient clearly before adjusting a new warfarin dose. Ask for painkiller pill, most of the time patients take mefenamic acid. We have suggested some antibiotic, gastric medication or omeprazole, all drugs that could make interaction with warfarin. If they go to see doctor in a different hospital, they need to tell doctor that they took anticoagulant warfarin to avoid taking improper medicine." D1M

"In the real situation, we suggested patient that if there is any abnormal symptom, they should come to see doctor before taking any medicines because they should take the medicine given only by doctors." N3F

"I agree with doctor D1, because when we use warfarin, if the health check this time shows that INR level is high, doctor should reduce warfarin dosage and come to pharmacist for more information on how to take medicine to avoid taking painkiller, what medicine they could buy or use and patient needs to keep health check record book with them. For taking warfarin, pharmacist needs to suggest that we cannot do it now in our country. However, we might be able to do it in the future." P1F

"If possible, in the future if pharmacist could join us that would be great, secondly it would be nice if the knowledge about pharmacy should be informed to nurses regards to side effect and how to reduce those side effects of medicine by the involvement of pharmacist." N1F

There are few cases for drug-food interaction. Most cases were found to be patients taking herbs or food that contained components interacted with warfarin. Patients should be recommended to avoid those risk of herbs or foods. Doctors also accepted the role of pharmacist regarding the information on drug-, food-, herb-interactions by counselling doctors to help managing individual problem.

"Nurses have asked patients about what they ate, it could be painkiller or dietary supplement such as ginseng which will have effect on warfarin or there might be an affect after 2 days of having heavy alcohol drinking. We also need to ask about those questions to compare and report to doctor so doctors could have more information." N2F

"In fact, this medicine will decrease or increase the INR level depending on the diet of patient, especially garlic, ginger or fish oil because these could increase INR level, warfarin should not be taking with other medicine such as ASA, steroid that will decrease the level of INR. So there are many effects." P2F

4.2.3.4 Adverse drug reaction and management

All doctors and nurses agreed to the roles of pharmacists to inform patients about common ADRs and how to manage them. This is, for example, if patients had nose bleeding, pharmacist is expected to tell the patient how to manage it.

"But if we could have pharmacists to help it would be great, so pharmacist could give better information because our nurses only know from what they have learned in the past but for the deeper details only pharmacists know. The side effect of medicines would be clearer." N1F

"For advising about first aid such as what are side effects of warfarin." N2F

"If patient could not make it to hospital, patients should tell doctor that comes to their place that they are taking warfarin and are not allowed to do injection to, if there is gum bleed, bleeding in urine like a smoky urine, patient needs to meet doctor immediately." N3F

4.2.3.5 How to manage when receiving operations

There was such an important case for patients who just had an operation. Doctors and nurses would like pharmacists to emphasize patients to be aware of stopping the use of warfarin in case of any operations.

"We need to clearly suggest patients that if they have any surgery, they must tell doctor that they taking warfarin therapy." D2M

"To avoid the stop taking warfarin when patient take any operation or go to dental center." N1F

4.2.3.6 Importance of following up doctors' appointment

Most of the patients either living in the urban or rural areas did not realize the importance of following up doctors' appointment. This can cause poor health outcomes of individuals.

"Normally, doctor wants patient to do heath check with cardiologist before adjusting warfarin, after adjusted patient could come to see doctor once a month, but for patient who lives in another province or far away, they could come once every 3 months. Some people did not come until 6 months, this is a complicate problem. At central, patient needs to come once a month to do health check and adjust warfarin

depend on the health condition because before taking this warfarin we tell them that this disease needs to meet doctor." D1M

"If patients had heart surgery, patients should come back to do follow up checkup after 2 weeks of leaving hospital. They should come to do checkup at least once a month. If patients live in central or near hospital we expect them to come once every 3 months after the surgery, after that 6 months and one year but must be once every 3 months." D2M

4.2.3.7 Booklet information

At the time of this study, all participants mentioned about booklet information. It is very important and helpful for patients using warfarin. This content of booklet information recommended by doctors and nurses was as follows: how to take proper warfarin, food with negatively affect warfarin.

"In that book, we have provided a lot of information about how to take proper medicine and food that negatively affect warfarin. We asked the medicine company to produce this book, we will be asking for more books to distribute to patients." D1M

"Tools or equipment for advising patient, if possible, it would be good if our pharmacists could print this because it will benefit to patient and we could also advise them. The guiding book is very important, so is it possible for pharmacy department to propose to the company to print the book and design posters to attach in our ward or at pharmacy department. So our pharmacists could give an information about INR and other information so we could help each other." N2F

"For this, we would request for booklet and distribute to each nurse room and pharmacist room, and nurse and pharmacist could read it daily and if they could remember that information it would be great, make this happen." P1F

4.2.4 Development of training program for healthcare professionals

Pharmacists realized that they had inadequate knowledge and skills on warfarin counselling. Therefore, they suggest that it would be beneficial for both pharmacists and patients if specific training programs on pharmaceutical care service for patients using warfarin were established. Nurses also expressed their needs for this type of training programs.

"If there was training for pharmacists, I also think that doctors and nurses should participate in that training in order to gain more knowledge for all because this type of opportunity is hard to us to have. That's all I need. Thank you." N1F

"Nowadays, advising patient is very important because the more we know the better benefit patient will have. If we are all known, wherever the patient goes, we would be able to answer question to patient, this would reduce the tasks of doctors and nurses." P1F

"Now, pharmacist will have more knowledge because of the company who will import medicines. And since we never have any training before, we only read from this book or go to have training at school like today. Today we received some knowledge from teacher and D1 and from reading this book (guiding book). If professor could have more training, it would be good for gaining more knowledge." P2F

Doctors also supported this educational training programs. They agreed that this program can help produce pharmacy student having good knowledge and skills for practicing at warfarin clinic and assisting doctors and pharmacists to taking care of individual patient. this would then be taken further steps on establishing pharmacy students' rotation in the future.

"I want to suggest that from what I've learned from another country, pharmacy students will have opportunities to intern with doctors. at in-patient or out-patient department, when doctors have found any medicine that could not use together and is not dose, doctors will ask pharmacy students to go check and report the research to doctors, explain on which medicine could be or could not be used together. In the future, if we could send some pharmacist to work with doctor it would be great." D1M

Phase II: A Randomized Controlled Trial Study

This phase was conducted to evaluate the effects of pharmacist-managed warfarin therapy on patient's clinical outcomes at Mahosot Hospital. The intervention was conducted from phase I, qualitative interview study. Pharmacist-managed warfarin therapy included medication review, DRPs assessment and in case of any DRPs found, pharmacist was notified doctor and record the response of management in DRPs assessment form. Education about warfarin therapy (see Appendix N) was counseled to patient by pharmacist. (Figure 4)

All pharmacist interventions were from the result of interviews including collaborations among healthcare professionals that needed pharmacists to be a part of warfarin therapy at Mahosot Hospital. The second theme presented the expectations of pharmacists' roles by healthcare professionals including how to take warfarin properly, normal INR range, drug-, food-, herb- interactions, adverse drug reaction and management, how to manage when receiving operations, importance of following up doctors' appointment and booklet information. Which was used for the education tool by pharmacists for patients taking warfarin. Only booklet information that could not be provided for participants because of the limitation of budget.

The practical intervention model was discussed and accepted by all healthcare professionals from the focus group interviews, more information was as follow:

- The process of care for patients using warfarin was accepted to have pharmacist-managed warfarin therapy at the end of the service, after patient take a drug from pharmacist dispensing.

- The pharmacists' roles for patients taking warfarin was not accepted at all topics. Just some roles that was accepted from all healthcare professionals at Mahosot Hospital included: medication review, DRPs checking, patient adherence checking, screen for bleeding or thromboembolism events, and education of the patients.

- The education tool for pharmacists were discussed and accepted for all topics that researcher was presented in the focus group interview.

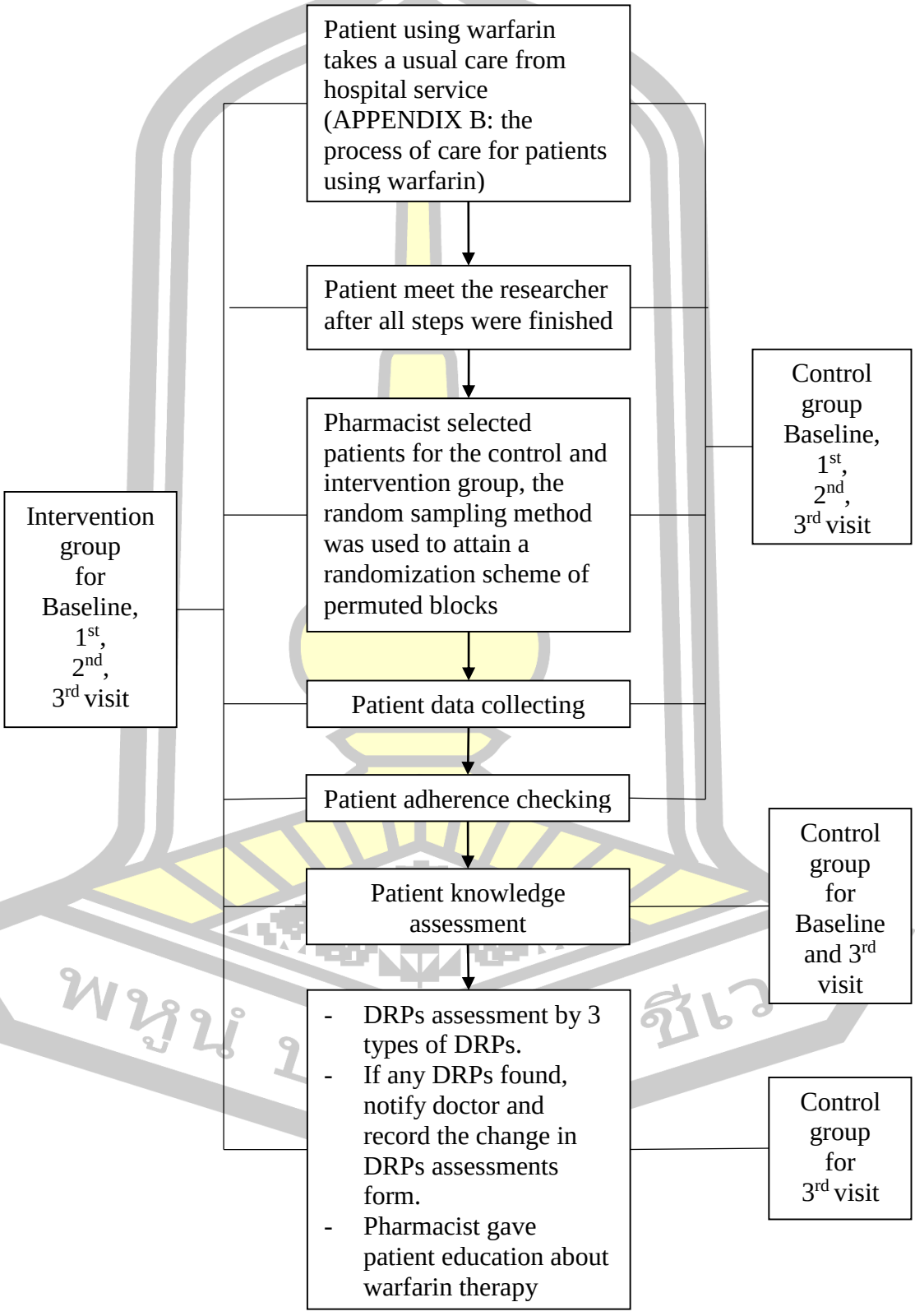
The data collecting tools were proofed by using validation and reliability test as follow:

- Two supervisors were requested to evaluate each item by giving the item a rating of +1 = agreement, -1 = no agreement, or 0 = not assurance for each objective. The final results of IOC score were 1 score for all questions, mean it was agreed from two supervisors.

- Cronbach's alpha was used for reliability. The experiment with 20 patients using warfarin therapy were used about a week for test reliability. The questionnaire for patients' knowledge assessment was 0.8444 for Cronbach's alpha calculate mean the internal consistency was good.

So, researcher was used this form to collect patients' data for RCT study. 72 patients were included by the inclusion criteria and no patient was excluded from our study.

Figure 4 The process of care for patient in pharmacist-managed warfarin therapy group and usual care group at out-patient department, Lao-Luxembourg Heart Centre, Mahosot Hospital.



4.3 Patient characteristics outcomes

From February to May 2019, seventy-two patients were eligible for inclusion. Table 9 summarizes the characteristics of all patients enrolled in the study. Thirty-six patients were pharmacist-managed warfarin therapy or intervention group that had the mean age of 53.1 ± 14.6 years old similar with usual care or control group, the mean age was 50.8 ± 14.0 years old. Most patients were female similar in both groups. For indication of warfarin therapy, the study found the numbers of patients with atrial fibrillation in the intervention group were higher than patients in the control group (50.0% vs. 38.9 %) but the patients with mitral valve replacement in the intervention group were lower than the control group (47.2 % vs. 58.3 %).

Therapeutic INR range of patients in the intervention group was 52.8 % for patients with INR of 2-3 higher than 41.7 % of patients in the control group. Furthermore, in the intervention group, 47.2 % of patients had therapeutic INR range of 2.5-3.5 lower than patients in control group who had therapeutic INR range 2.5-3.5 of 58.3 %. It was consistently with the indication of warfarin therapy. Most of comorbidity in the intervention group and control group were hypertension. (as shown in Table 9)

Table 9 Patients characteristic

Characteristic	**Intervention group n=36**	**Control group n=36**
	Number of patients (%)	
Age (mean ± SD)	53.1 ± 14.6	50.8 ± 14.0
Female sex	26 (72.2)	27 (75.0)
Indication of warfarin therapy		
Atrial fibrillation	18 (50.0)	14 (38.9)
Mitral valve replacement	17 (47.2)	21 (58.3)
Deep vein thrombosis	1 (2.8)	1 (2.8)
Therapeutic INR range		
2-3	19 (52.8)	15 (41.7)
2.5-3.5	17 (47.2)	21 (58.3)
Comorbidities		
Hypertension	8 (22.2)	5 (13.9)
Diabetes	2 (5.6)	3 (8.3)
Rheumatic heart disease	1 (2.8)	1 (2.8)
Heart failure	1 (2.8)	1 (2.8)
Gout	2 (5.6)	0
Embolic stroke	0	1 (2.8)

4.4 Efficacy outcomes

Patients' efficacy outcomes included patients' time in therapeutic range, international normalized ratio, warfarin knowledge score, thromboembolism events, patient adherence and drug related problems. The researcher met the sample patients 4 visits, each visit was 1 month of the doctor appointment.

4.4.1 Time in therapeutic range (TTR)

TTR was the time in therapeutic range of INR result calculated by using Rosendaal method (19). The percentage of TTR was calculated by the number of days with INR in therapeutic range divided by total number of days during first to third visit and multiplied with 100. TTR is a commonly used quality measure for warfarin. To calculate TTR in this study, three INR results after baseline visit were used. There were two types of TTR including INR in exact therapeutic range 2-3 for AF and DVT or 2.5-3.5 for MVR and INR in expanded therapeutic range that INR in exact therapeutic range ± 0.2.

The study presented the mean percentage of the time that patients' INR values within the exact therapeutic range. There was 63.3 ± 35.5 % of TTR in the intervention group which higher than 45.3 ± 39.9 % of TTR in the control group, with statistically significant difference between two groups (p-value = 0.046).

Otherwise, the mean percentage of the time that patients' INR values within the expanded therapeutic range in the intervention group was 77.3 ± 34.1 % that higher than 67.3 ± 36.5 % in the control group, with no statistically significant difference between two groups (p-value = 0.225).

Moreover, the number of patients with TTR within the exact therapeutic range of the intervention group which more than 60 % of 21 (58.3 %) patients was higher than 12 (33.3 %) patients in control group, with statistically significant difference between two groups (p-value = 0.033).

However, the number of patients with TTR within the expanded therapeutic range more than 60 % of 26 (72.2 %) patients in the intervention group was higher than 22 (62.1 %) patients in the control group, with no statistically significant difference between two groups (p-value = 0.317). (as shown in Table 10)

Table 10 TTR comparing intervention group with control group

Outcomes	Intervention group n=36	Control group n=36	p-value
Percentage of time that patients' INR values were within the exact therapeutic range	63.3 ± 35.5	45.3 ± 39.9	0.046[a]
Percentage of time that patients' INR values were within the expanded therapeutic range	77.3 ± 34.1	67.3 ± 36.5	0.225[b]
Number of patient had TTR within the exact therapeutic range > 60 %	21 (58.3)	12 (33.3)	0.033[c]
Number of patient had TTR within the expanded therapeutic range > 60 %	26 (72.2)	22 (62.1)	0.317[c]

[a] Student *t*-test, [b] Mann-Whitney *U* test, [c] Chi-squared test

4.4.2 INR value

The results of INR value were compared between groups and among each group. Comparison of INR value between intervention group and control group in each visit was presented in table below, including patients with INR range 2-3 and patients with INR range 2.5-3.5, the total number of patients with INR in goal for all visits.

Table 11 showed the comparison of INR value between intervention group and control group in each visit for patients with therapeutic INR range 2-3, 19 patients in the intervention group and 15 patients in the control group were included. The number of patients with INR in exact therapeutic range for the intervention group did not difference between baseline and first visit. But it increased to 78.9 % for second visit and to 89.5 % for third visit. The number of patients with INR in exact therapeutic range of the control group was 40.0 % at baseline then 66.7 % at first and second visit and 73.3 % of third visit.

The number of patients with INR in expanded therapeutic range of the intervention group increased to 78.9 % to 89.5 %, 94.7 % and 94.7 % for baseline to third visit respectively. The number of patients with INR in expanded therapeutic range of the control group also increased to 53.3 % to 80.0 % and 100 % for baseline to second visit respectively. The second to the third visit, the number of patients decreased from 15 (100 %) to 13 (86.7 %).

Mean INR result of all patients in the intervention group at baseline was 2.1 ± 0.5, as well as at first visit 2.1 ± 0.3. The result of mean INR was in the therapeutic range 2-3. However, the mean INR increased from first visit to second and third visit (2.1 ± 0.3, 2.2 ± 0.4 and 2.5 ± 0.3 respectively). All mean INR value were in the therapeutic range 2-3. In addition, the mean INR for patients in the control group was 1.8 ± 0.4 at baseline visit then increased to 2.4 ± 0.5 at first visit but it decreased to 2.2 ± 0.3 and 2.2 ± 0.4 at the second and third visit. Just for the baseline visit, patients with mean INR value of the control group was not in therapeutic range 2-3. In

conclusion, there was statistically significant difference between mean INR value in each visit for both groups by p-value was 0.001.

Total of patient with INR in goal for all visits in the intervention group was compared with the control group. Our study found that the percentage of patients' INR in therapeutic range in the intervention group was higher than the percentage of patient in the control group 73.7 % with 61.7 %. (as shown in Table 11)

Table 11 Comparison the number of patient with INR value between the intervention group and the control group in each visit for therapeutic INR range 2-3

Outcomes	Baseline	1st visit	2nd visit	3rd visit	Mean	p-value*
INR value in exact therapeutic range						
Intervention (n = 19)	12 (63.2)	12 (63.2)	15 (78.9)	17 (89.5)	56 (73.7)	0.161[a]
Control (n = 15)	6 (40.0)	10 (66.7)	10 (66.7)	11 (73.3)	37 (61.7)	0.208[a]
p-value**	0.300[b]	1.000[b]	0.462[b]	0.370[b]	-	-
INR value in expanded therapeutic range						
Intervention (n = 19)	15 (78.9)	17 (89.5)	18 (94.7)	18 (94.7)	68 (89.5)	0.308[a]
Control (n = 15)	8 (53.3)	12 (80.0)	15 (100)	13 (86.7)	48 (80.0)	0.011[a]
p-value**	0.151[b]	0.634[b]	1.000[b]	0.571[b]	-	-
Mean INR result						
Intervention (n = 19)	2.1 ± 0.5	2.1 ± 0.3	2.2 ± 0.4	2.5 ± 0.3	-	0.001[c]
Control (n = 15)	1.8 ± 0.4	2.4 ± 0.5	2.2 ± 0.3	2.2 ± 0.4	-	0.001[c]
p-value**	0.172[d]	0.035[d]	0.916[e]	0.016[d]	-	-

[a] Cochran's test, [b] Fisher's exact test, [c] Repeated-measure ANOVA test, [d] Student *t*-test, [e] Mann-Whitney *U* test, * p-value is to compare within group, ** p-value is to compare between intervention and control group in each visit.

Table 12 showed the comparison of INR value between the intervention group and control group in each visit for patients with therapeutic INR range 2.5-3.5. Seventeen patients for the intervention group and 21 patients of the control group were reported. Interestingly, the number of patients with INR value in exact therapeutic range of the intervention group increased from 5.8 % to 52.9 % for baseline to first visit then the outcome was stable from first visit to third visit.

Also, the number of patients with INR value in the exact therapeutic range of the control group increased from 14.3 % to 38.1 %, 57.1 % and 61.9 % for baseline to first, second, and third visit, respectively. In addition, there was no statistically significant difference between INR value in exact therapeutic range between the intervention group and the control group. Moreover, the number of patients with INR value in expanded therapeutic range for the intervention group increased from 17.6 % to 64.7 % for the baseline to first visit. The following visit, the number of patients was decrease to 58.8 % in the second visit. Then, the third visit increased to 64.7 % again.

Furthermore, the number of patients with INR value in expanded therapeutic range of the control group was the same from baseline to first visit, but it was increased from 52.4 % to 57.1 % and 80.9 % for first visit to second and third visit. The results showed statistically significant difference between the INR value in expanded therapeutic range for the intervention group and the control group (p-value = 0.043) at the baseline visit. So, for the first, second and third visit were not significant difference between both groups.

Additionally, the mean INR value of patients in the intervention group was 2.2 ± 0.7 at baseline visit. It was lower than therapeutic range 2.5-3.5 for patients with MVR. Similar with the first, second and third visit had the mean INR value of 2.4 ± 0.4 lower than therapeutic range 2.5-3.5. So, the mean INR value for patients in the control group was 2.2 ± 0.5 at baseline visit, lower than therapeutic range 2.5-3.5. But, mean INR value of the first visit had increased to 2.8 ± 0.9 stay in the therapeutic range 2.5-3.5. For the second and third visit was the same results with first visit. Patients in the control group had mean INR value in therapeutic range 2.5-3.5 by the mean outcomes of 2.5 ± 0.6 and 2.6 ± 0.4. In summary, there was no statistically significant difference between the mean INR in each visit for patients in the intervention group by p-value 0.344. But, there was statistically significant difference between the mean INR in each visit for patient in the control group (p-value = 0.011). (as shown in Table 12)

Table 12 Comparison of the patient with INR value between the intervention group and the control group in each visit for therapeutic INR range 2.5-3.5

Outcomes	Baseline	1st visit	2nd visit	3rd visit	Mean	p-value*
INR in exact therapeutic range						
Intervention (n = 17)	1 (5.8)	9 (52.9)	9 (52.9)	9 (52.9)	28 (41.2)	0.011[a]
Control (n = 21)	3 (14.3)	8 (38.1)	12 (57.1)	13 (61.9)	32 (38.1)	0.003[a]
p-value**	0.613[b]	0.513[b]	1.000[b]	0.743[b]	-	-
INR in expanded therapeutic range						
Intervention (n = 17)	3 (17.6)	11 (64.7)	10 (58.8)	11 (64.7)	35 (51.5)	0.014[a]
Control (n = 21)	11 (52.4)	11 (52.4)	12 (57.1)	17 (80.9)	45 (53.6)	0.120[a]
p-value**	0.043[b]	0.521[b]	1.000[b]	0.293[b]	-	-
Mean INR result						
Intervention (n = 17)	2.2 ± 0.7	2.4 ± 0.4	2.4 ± 0.4	2.4 ± 0.4	-	0.344[c]
Control (n = 21)	2.2 ± 0.5	2.8 ± 0.9	2.5 ± 0.6	2.6 ± 0.4	-	0.011[c]
p-value**	0.360[e]	0.307[e]	0.560[d]	0.234[d]	-	-

[a] Cochran's test, [b] Fisher's exact test, [c] Repeated-measure ANOVA test, [d] Student *t*-test, [e] Mann-Whitney *U* test, * p-value is to compare within group, ** p-value is to compare between intervention and control group for each visit.

4.4.3 Patients' knowledge

Patient's knowledge was assessed by the mean score of 15 questions in the questionnaire. There were 8 items of warfarin's knowledge and 7 items of patient's behavior about warfarin therapy. The study assessed 3 types of mean score. First, patients' knowledge was assessed for all 15 questions, the mean baseline score of the patients in the intervention group was found 5.2 ± 2.6. One-month post counselling, the patients' knowledge of the intervention groups was reassessed and found the mean score increased to 9.4 ± 2.5. Also, one-month later the knowledge of the patients in the intervention group increased again to 13.4 ± 2.1. However, the third visit of our study found the mean score of 13.2 ±1.4 similar with second visit. By 4 visits from baseline to third visit, the outcome showed statistically significant difference between each visit (p-value = 0.001).

For the control group, our study assessed only the baseline and third visit. The results showed that patient's knowledge was 7.1 ± 3.7 at baseline visit similar with 7.1 ± 3.6 at the third visit, with no statistically significant difference between 2 visits (p-value = 0.628).

There was statistically significant difference of patients' knowledge between the intervention and control group at baseline and third visit (p-value = 0.013). So, from the baseline visit, patients in the intervention group has the mean knowledge scores lower than patients in the control group. However, the third visit, after 3 times of being counselled by pharmacist, patients' knowledge of the intervention group was higher than patients in the control group with a statistically significant difference between two groups (p-value = 0.001).

The warfarin's knowledge was divided to assessment of 8 out of 15 items in the questionnaires. The mean score for patient in the intervention group was 2.8 ± 1.6 at baseline visit. It was increased to 5.1 ± 1.7, 7.2 ± 1.1 and 6.6 ± 0.8 for the first, second and third visit, respectively. The score showed statistically significant difference between each visit (p-value = 0.001).

The mean score of warfarin's knowledge for patient in the control group was not statistically significant difference between baseline 3.3 ± 2.1 and third visit 3.5 ± 2.2.

At baseline visit, the mean score of warfarin's knowledge of patients in the intervention group was lower than the patients in the control group (2.8 ± 1.6 vs. 3.9 ± 2.0, p-value = 0.015). In the third visit, there was statistically significant difference between two groups. But, the mean score of warfarin's knowledge of patients in the intervention group was higher than the control group (6.6 ± 0.8 vs. 3.6 ± 1.9 p-value = 0.001).

Patient's behavior about warfarin therapy was divided to assessment by 7 out of 15 items in the questionnaires. The mean score for patients in the intervention group was 2.4 ± 1.5 at the baseline visit. It increased to 4.3 ± 1.9, 6.3 ± 1.3 and 6.6 ± 0.9 for the first, second and third visit, respectively. There was statistically significant difference between each visit (p-value = 0.001).

For the control group, these was the same from 3.3 ± 2.1 for the baseline visit with 3.5 ± 2.2 for the third visit.

In addition, at the baseline visit, patient's behavior was statistically no significant difference between in the intervention and control group (2.4 ± 1.5 vs. 3.3

± 2.1, p-value = 0.052). But, the mean score at the third visit showed significant difference of the intervention group 6.6 ± 0.9 and 3.5 ± 2.2 of the control group with a p-value = 0.001. (as shown in Table 13)

Table 13 Comparing patients' knowledge between intervention group and control group in each visit

Outcomes	Baseline	1st visit	2nd visit	3rd visit	p-value*	Mean dif
All questionnaires (Total score = 15)						
Intervention	5.2 ± 2.6	9.4 ± 2.5	13.4 ± 2.1	13.2 ± 1.4	0.001[a]	8.1 ± 2.0
Control	7.1 ± 3.7	-	-	7.0 ± 3.6	0.628[b]	0
p-value**	0.013[c]	-	-	0.001[d]	-	0.001[c]
Warfarin's knowledge (Total score = 8)						
Intervention	2.8 ± 1.6	5.1 ± 1.7	7.2 ± 1.1	6.6 ± 0.8	0.001[a]	3.8 ± 2.0
Control	3.9 ± 2.0	-	-	3.6 ± 1.9	0.019[b]	0
p-value**	0.015[c]	-	-	0.001[c]	-	0.001[d]
Patient's behavior (Total score = 7)						
Intervention	2.4 ± 1.5	4.3 ± 1.9	6.3 ± 1.3	6.6 ± 0.9	0.001[a]	4.2 ± 1.0
Control	3.3 ± 2.1	-	-	3.5 ± 2.2	0.073[b]	0
p-value**	0.052[c]	-	-	0.001[c]	-	0.001[c]

[a] Repeated-measure ANOVA test, [b] Paired *t*-test, [c] Student *t*-test, [d] Mann-Whitney *U* test, * p-value is to compare within group, ** p-value is to compare between intervention and control group for each visit, Mean dif is mean difference.

4.4.4 Drug-related problems (DRPs) with warfarin therapy

The DRPs assessment was modified from Hepler and Strand's criteria (21). The focus categories of DRPs were to identify actual or potential DRPs as following 3 items:

1. Sub-therapeutic dosage is an assessment of doctor's prescription (looking for patient's INR below therapeutic range for each visit).

2. Over dosage is an assessment of doctor's prescription (looking for patient's INR over therapeutic range for each visit).

3. Drug interactions are drug-drug, drug-food, drug-herb and drug-alcohol (22) interaction which can increase or decrease warfarin effect. For drug-drug interactions were investigated in only significant level 1 and 2 that cited by Drug Interaction Facts 2012 (56). For drug-food and drug-herb were used for reference from the study of warfarin and its interactions with foods, herbs and other dietary supplements (24).

The study assessed DRPs on each of 4 visits for patients in the intervention group. But, only the third visit was assessed DRPs for patients in the control group. Twenty DRPs found in 16 patients in the intervention group at baseline visits. Also, the result shown DRPs decreased from baseline to first visit in the intervention group (20 DRPs to 6 DRPs). There were similarly found 6 DRPs from the first visit same as the third visit. But, at the second visit, 8 DRPs were found in patients in the intervention group.

The most type of DRPs from 4 visits were sub-therapeutic dosage which consist of 30 cases for patients in the intervention group (12, 6, 6 and 6 cases at the baseline, first, second and third visit, respectively). Following by drug interactions, 9 cases and drug over dosage 1 case. For patients in the control group, the most DRPs found were from third visit assessment, consist of 10 cases of drug interaction, 5 cases of sub-therapeutic dosage, and there was no case found for over dosage from patients in the control group. For sub-therapeutic dosage found, a researcher consulted with doctors to adjust warfarin dose by increasing the dose using international guideline. however, some cases were not accepted by doctors and patients had to keep taking same dose and then monitoring their symptom of thromboembolism or bleeding.

There were 10 patients who had DRP more than one time. Seven patients had DRP 2 consecutive visits and 3 patients had DRP 3 consecutive visits. However, none of patients had any thromboembolism symptom or diagnosis. DRPs were accepted by doctors and patients which pharmacists suggested the solution of DRPs at baseline to third visits 60.0 %, 33.3 %, 25.0 % and 16.7 % of DRPs in the intervention group, respectively. More information on DRPs assessment was shown in appendix P and Q.

For drug interaction with warfarin, 8 cases were found in the intervention group at the baseline visit and 1 case at the second visit. A drug-drug interaction found at the baseline visit was the interaction of warfarin and acetaminophen as same as the second visit but it was from different patients. When a drug interaction was found, a researcher was counselling patients on taking acetaminophen not over 4 grams per day to avoids the interaction from warfarin. For food-drug interaction, 5 cases at baseline visit were found. Three cases were warfarin interacting green leafy vegetables and 2 cases were warfarin interacting green tea. The researcher was counselling patients focusing on food which could lead to high or low INR value

included vegetable with high vitamin K. Two cases of alcohol-drug interaction found at baseline visit. Then, patient got counselled about alcohol interaction with warfarin which can increasing risk of bleeding. At the next follow up, the study did not find any cases of food-drug interaction which after patients got the counselling from pharmacists. No case of herb-drug (ginkgo, fish oil, garlic, ginger, onion, vitamin E) interaction found in this study.

Only one case of drug-drug interaction found at the third visit of the control group which was simvastatin with warfarin. A researcher consulted with doctors and changed other statins which not interact warfarin. However, doctors continued prescribing simvastatin and monitoring drug interaction's sign and symptoms such as bleeding or thromboembolism events. Six cases of drug-food interactions and 3 cases alcohol-drug interaction were found. After that, these patients were doing the same as patients in the intervention group. (as shown in Table 14)

Table 14 DRPs for patient in the intervention and control group

Outcomes	Baseline	1st visit	2nd visit	3rd visit
Total DRPs (cases)				
Intervention group	20	6	8	6
Control group	-	-	-	15
Sub-therapeutic dosage				
Intervention group	12 (60.0)	6 (100.0)	6 (75.0)	6 (100.0)
Control group	-	-	-	5 (33.3)
Over dosage				
Intervention group	0	0	1 (12.5)	0
Control group	-	-	-	0
Drug interaction				
Intervention group	8 (40.0)	0	1 (12.5)	0
Control group	-	-	-	10 (66.7)
Drug-drug				
Intervention group	1 (12.5)	0	1 (100.0)	0
Control group	-	-	-	1 (10.0)
Drug-food				
Intervention group	5 (62.5)	0	0	0
Control group	-	-	-	6 (60.0)
Drug-alcohol				
Intervention group	2 (25.0)	0	0	0
Control group	-	-	-	3 (30.0)
Number of patients				
Intervention group	16 (44.4)	6 (16.7)	8 (22.2)	6 (16.7)
Control group	-	-	-	14 (38.9)
Number of patients had >1 DRP				
Intervention group	5 (13.9)	0	0	0
Control group	-	-	-	1 (2.8)
Doctors/patients accept DRPs				
Intervention group	12 (60.0)	2 (33.3)	2 (25.0)	1 (16.7)
Control group	-	-	-	10 (66.7)

4.4.5 Thromboembolism event

Thromboembolism event was defined as patients who was diagnosed to thromboembolism events and were investigated by a doctor at out-patient department. Patient who had sub-therapeutic dosage of INR value might have a risk to be thromboembolism event more than who have INR in therapeutic range. Main cause of thromboembolism event for patients with warfarin therapy was patients' adherences and drug-interaction with warfarin which could decrease effect of warfarin. Our study, patients were assessed for the thromboembolism events in each visit for both groups. Some patients were presented INR result is out of therapeutic range for each visit. However, our study did not find any thromboembolism event at any visit.

4.4.6 Patients' adherences

Patients' adherences were assessed by the Morisky, Green, and Levine (MGL) 4 items scale. Scoring the MGL questionnaire was defined as Yes and No (Yes = 1 and No = 0). Patients who had good adherence were those who got zero score from MGL questionnaire. The highest number of patients' good adherence was 36 patients (100.0 %) and the lowest was 25 patients (69.4 %). However, patients in both groups showed good adherences as at the first, second and third visit. For the baseline visit, patients' adherence in the intervention group was 69.4 % lower than other visits, following by 97.2 % at the first, 100.0 % second and third visit. Nonetheless, patients in the control group were 88.9 % who got the good adherence at baseline visit. The following visit was 100.0 % for first and second visit, 97.2 % for third visit. (as shown in Table 15)

Table 15 Patients' adherences assessed by MGL questionnaire of both groups

Number of patients' adherences	Baseline	1st visit	2nd visit	3rd visit
Intervention group (n = 36)	25 (69.4)	35 (97.2)	36 (100.0)	36 (100.0)
Control group (n = 36)	32 (88.9)	36 (100.0)	36 (100.0)	35 (97.2)
p-value [a]	0.079	1.000	1.000	1.000

[a] Fisher's exact test

Moreover, pill count was the other method that used to assessment the patient adherence. The mean percentage of pill count in the intervention group was 87.3 ± 16.9 higher than 81.8 ± 15.7 of patient in the control group, with no significant difference between two groups p-value = 0.207. (as shown in Table 16)

Table 16 Outcome of patients' adherences assess by pill count of both groups

Percentage of pill count	1st visit	2nd visit	3rd visit	Mean
Intervention group n=36	86.4 ± 25.1	97.8 ± 24.9	77.7 ± 16.1	87.3 ± 16.9
Control group n=36	77.3 ± 23.9	88.5 ± 32.7	79.6 ± 25.3	81.8 ± 15.7
p-value [a]	0.249	0.076	0.945	0.207

[a] Mann-Whitney *U* test

4.5 Safety outcomes

Major and minor bleeding event was assessed for all patients.

4.5.1 Major bleeding

Major bleeding was assessed by the doctors' diagnosis such as severe bleed that requiring blood transfusion, intracranial bleed, intraspinal bleed, intraocular bleed or retroperitoneal bleed. This study was not found any major bleeding event for patients in both intervention and control group.

4.5.2 Minor bleeding

Minor bleeding was assessed by the pharmacist assessment such as bruising, nose bleeding, gum bleeding, bleeding in urine or stool. By asking the patient to a clinical and symptom of bleeding in any part of their bodies during one month prior to follow up. Also, some case of bruising, nose bleeding, gum bleeding and bleeding in stool still found in some visit. After we found that event, patients in the intervention group was counselled more about how to do in case of bleeding, exactly first aid. In case of bruising, patients must follow their symptom and the area of bruising. In case of nose bleeding patient have to sit down and firmly pinch the soft part of their nose, just above the nostrils, for at least 10-15 minutes and could place an ice pack or bag of frozen vegetables covered by a towel on the bridge of patient's nose. Moreover, patient must stay upright, rather than lying down, as this reduces the blood pressure in the blood vessels of their nose and will discourage further bleeding. In case of gum bleed, patient have to apply a piece of gauze to the area for about 10 minutes or until the bleeding stops. In case of bleeding in stool that our study had found, patients must follow their symptom and come to the hospital immediacy when it happens. In case of bruising, nose bleeding or gum bleeding was continued more than 15 minutes, patients were told to come to the hospital or the healthcare center which near their house.

A minor bleeding decreased from 11.11 % in baseline visit to 0 % in fourth visit. Almost 6 cases in 6 patients presented a minor bleeding in the intervention group and 9 cases in 9 patients in the control group.

Of 6 cases found of bruising in the intervention group, there were 4 cases at baseline visit and 2 cases at first visit.

Of 9 cases found of bruising in the control group, there were 3 cases at baseline visit and 1 case at first visit. One case of nose bleeding found at first visit. A case of gum bleeding found at second visit and another one case found at first visit. A

case of bleeding in stool found at second visit and a case at third visit. Two case of bleeding in stool were from the same patient. (as shown in Table 17)

Table 17 Minor bleeding for patient in the intervention compared with the control group

Outcomes	Baseline	1st visit	2nd visit	3rd visit
Minor bleeding (case)				
Intervention group	4	2	0	0
Control group	4	3	1	1
Bruising				
Intervention group	4 (100.0)	2 (100.0)	0	0
Control group	3 (75.0)	1 (33.3)	0	0
Nose bleeding				
Intervention group	0	0	0	0
Control group	0	1 (33.3)	0	0
Gum bleeding				
Intervention group	0	0	0	0
Control group	1 (25.0)	1 (33.3)	0	0
Bleeding in stool				
Intervention group	0	0	0	0
Control group	0	0	1 (100.0)	1 (100.0)
Number of patients				
Intervention group	4 (11.1)	2 (5.6)	0	0
Control group	4 (11.1)	3 (8.3)	1 (2.8)*	1 (2.8)*

* Same patient

CHAPTER V

CONCLUSION, DISCUSSION and LIMITATION

5.1 Conclusion

A semi-structured, face-to-face interviews were conducted to find out the views of healthcare professionals toward pharmacists' roles and process of care for patients with warfarin use. The present study was based on interviewing 9 healthcare professionals: 3 doctors, 3 nurses and 3 pharmacists. The clinical experiences were varied from one to thirty years. This could help for having different views and broadly ideas.

Two major themes emerged from the face-to-face interviews, consisted of (1) healthcare professionals' experiences of current practice problems with warfarin therapy; and (2) healthcare professionals' perspectives on ways to improve services and healthcare professionals' educations and training. There were 3 sub-themes emerged from the first main theme including: (1) views of service and warfarin problems, (2) roles of healthcare professionals in current practice and (3) views of organizational barriers. Three sub-themes of the second main theme consisted of (1) ways to improve services, (2) views of pharmacists' roles in warfarin clinic, and (3) views of educations or trainings and research.

The results from the face-to-face interviews were used to develop the intervention of this study, called "pharmacist-managed warfarin therapy". The key concepts of pharmacists' roles in providing pharmaceutical care services for patients using warfarin were extracted from the meta-analyses and systematic reviews. Then, the process of care delivering "pharmacist-managed warfarin therapy" was drafted and discussed in the focus group interviews.

The focus group interviews were conducted among healthcare professionals. There were 2 doctors, 3 nurses and 3 pharmacists who were different person from the face-to-face interviews but they were within the same healthcare team, working at Lao Luxembourg heart center, Mahosot Hospital, Lao PDR. The clinical experiences were varied from 7 years to 25 years.

The major themes emerged during the focus group interviews included (1) collaborations among healthcare professionals (2) expectations of pharmacists' roles by healthcare professionals and (3) development of training program for healthcare professionals. In addition, the second major theme included 7 sub-themes: how to take warfarin properly; normal INR range; drug-, food-, herb-, alcohol-warfarin interactions; adverse drug reaction and management; how to manage when receiving operations; importance of following up doctors' appointment; and booklets information.

The results of the focus group interviews were used to conduct a randomized controlled trial study (RCT) and evaluated the effect of pharmacist-managed warfarin therapy on patients' clinical outcomes. The key concept of RCT study were to assess the efficacy and safety outcomes. The efficacy outcomes were the percent of time in therapeutic range (TTR), INR value, patients' knowledge score, drug-related

problems with warfarin therapy (DRPs), thromboembolism events, and patients' adherences. Safety outcomes were the major and minor events.

All subjects were followed up for 3 months including the baseline (month 0), first (month 1), second (month 2) and third (month 3) visit. Most patients in both groups aged 30-50 years old. The indications of warfarin therapy were atrial fibrillation (AF), mitral valve replacement (MVR), and deep vein thrombosis (DVT). The majority of patients in both groups were female. Therapeutic INR ranges in both groups were 2-3 and 2.5-3.5. The most comorbidity in both groups was hypertension.

By analyzing the TTR of 72 patients enrolled in our study, the results of TTR was 63.3 ± 35.5 % for patients in the intervention group and 45.3 ± 39.9 % for patients in the control group, with statistically significant difference between two groups (p-value = 0.046). Also, the number of patients with INR in therapeutic range 2-3 was not statistically significant difference between two groups in 4 visits. This study found that the percentage of patients with INR in therapeutic range in the intervention group was higher than the percentage of patients in the control group (73.7 % and 61.7 %, respectively). Moreover, the number of patients with INR in therapeutic range 2.5-3.5 was not statistically significant difference between two groups. For patients' knowledge score, there were statistically significant increasing from baseline to first, second and third visit (5.2 ± 2.6, 9.4 ± 2.5, 13.4 ± 2.1 and 13.2 ± 1.4, p-value = 0.001) in the intervention group. Also, comparing of knowledge score between the intervention and control group at third visit showed statistically significant difference (13.2 ± 1.4 vs. 7.0 ± 3.6, p-value = 0.001). The most type of DRPs from 4 visits were sub-therapeutic dosage which consist of 30 cases in the intervention group (12, 6, 6 and 6 cases at the baseline, first, second and third visit, respectively). Patients' adherences were assessed by Morisky, Green, and Levine (MGL) 4 items scale, the results showed patients in both groups had good adherences at the first, second and third visit. For the baseline visit, patients' adherence in the intervention group was 69.4 % lower than other visits, following by 97.2 % at the first, 100.0 % at second and third visit. Nonetheless, patients in the control group were 88.9 % who got the good adherence at baseline visit. The following visit was 100.0 % for first and second visit, and 97.2 % for third visit. The mean percentage of pill count in the intervention group was 87.3 ± 16.9 % that higher than 81.8 ± 15.7 % in the control group, with no significant difference. Similar with thromboembolism events. This study did not find any major bleeding events for all visits but minor bleeding events presented 4 cases for both groups at the baseline visit. During the study, minor bleeding events still found at the first visit for 2 cases in the intervention group.

5.2 Discussion

5.2.1 Qualitative study

The results of the face-to-face interviews were consistent with previous study conducting a qualitative meta-synthesis study (57). with regards to the acceptance of doctors and nurses in pharmacist's roles of providing pharmaceutical care services for patients using warfarin. This was due to their time constraints on providing services

for individual patients. Other health care professionals also had the same views on the impacts of such services on patients' health outcomes.

The important problem found in the face-to-face interview was patients were not following up with doctors' appointment. This could be caused by inconvenient transportations, inadequate knowledge and understanding of diseases and how to take warfarin properly and safely. These reasons cause patients' problems resulting in loss of taking INR test and non-adherence. This finding was consistent with the study by Decker and colleagues (58), the physicians identified many factors associated with loss of follow-up; for example, dislike of taking lab test and traveling time.

In this study, pharmacist mentioned that they had lack of confidence in giving proper suggestions or consultation of warfarin therapy for patients. In this case, pharmacist mentioned that the education and training were specifically needed. This could help increasing their knowledge and counselling skills and be able to confidently provide professional counselling for individual patients. Decker and colleagues (58). reported that the key to ensuring successful anticoagulation for AF was getting the patient to understand the importance of the medication at the very beginning". Improving service and healthcare professionals' education are very important and made the need of participants since the result was asset.

Once of the result from the focus group interviews was the experiences of collaborations among healthcare professionals, there was consistent with those of Decker and colleagues (58), who noted that "ineffective communication between medical specialties and care settings was consistent at barriers to effective management of patient using warfarin therapy". The study supported that it is essential for all healthcare professionals to play their roles, express empathy, deliver services with caring mind for benefits of individual patients.

To contribute pharmacist-managed warfarin therapy, all the requirements need to be made and all roles need to be satisfied. Regarding expectation of pharmacists' role by doctors and nurses, our participants showed major concerns about patients' safety. Our study mentioned many points of counselling from all healthcare professionals. Therefore, roles of pharmacist should include how to take warfarin properly, normal INR range, drug-, food-, herb-, alcohol-interactions with warfarin, its ADR and management, how to manage when receiving operations, importance of following up doctors' appointment, and booklet information for patients. That was consistency with the study of Stafford (18), "patient felt that they were not fully aware of the required frequency of INR testing and had little understanding of why they were taking warfarin". If patients don't understand, it means that there is lack of people to give suggestions. The contents of counselling need to be clear and specify.

The needs from the interviews of healthcare professionals both face-to-face interviews and focus group interviews which needing pharmacists to educate patients on warfarin uses. It is relevant to a systematic review of Saokaew and colleagues and Manzoor and colleagues (12, 45) included RCT studies for comparing the pharmacist's intervention group with the control group. The result presented pharmacist activities such as dosage adjustment, bridging assessment and next INR appointment or follow-up, education role to patients. Everything that pharmacists can do, they could improve clinical outcomes which better than the ones that do not have pharmacists included. These activities made patients more thoughtful on warfarin

therapy. When pharmacist intervention was involved, it leads to accurate and safe use of warfarin.

Overall, the results from qualitative interviews were consistent with previous studies regarding the impacts of pharmacist roles on health outcomes of patients using warfarin. The pharmacist interventions were then developed based on the focus group interviews and collaborations among healthcare professionals that needed pharmacists to be a part of warfarin therapy at Mahosot Hospital. The expectations of pharmacists' roles by healthcare professionals was used for the education tool by pharmacists for patients taking warfarin. This practical intervention model developed was discussed and accepted by all healthcare professionals from the focus group interviews, more information was as follow: the process of care for patients using warfarin was accepted to have pharmacist-managed warfarin therapy at the end of the service, after patient took a drug from pharmacist dispensing. The pharmacists' roles were accepted from all healthcare professionals at Mahosot Hospital including medication review, DRPs checking, patient adherence checking, screen for bleeding or thromboembolism events, and patient education.

In summary, it is essential for researchers to conduct pharmacist-managed warfarin therapy developed to evaluate the outcomes by using the design of RCT. This would then be taken forward for health policy maker and administration team to consider the implementations of the developed intervention in clinical practice.

5.2.2 RCT study

All the processes of care for patients in the pharmacist-managed warfarin therapy in this study were conducted at out-patient department. Patients met pharmacists after doctors' follow up. Pharmacists collected patients' data then assessed patients' knowledge by questionnaires. DRPs were assessed and notified with doctors if DRPs were found. Patient adherences were assessed by Morisky, Green, and Levine (MGL) 4 items scale and together with pill counted. At the end, pharmacists provided education on warfarin therapy to patients. Educating patients was the face-to-face counselling with individual patient. The contents of the counselling were various including warfarin use, how to behave and any side effects.

There were several pharmacists activities that differ from each previous study such as Wilson and colleagues (51) compared pharmacists with physicians. The details of pharmacists' activities were all patients receiving a standardized educational package including the indication for therapy, the importance of complying with the regimen, the need for the close monitoring, the potential risk of taking other medications, dietary considerations and the importance of self-monitoring for evidence of bleeding or thromboembolic complications. Once patients had a stable warfarin dose in an anticoagulant clinic, they were randomly allocated to either continuing to be managed at the anticoagulation clinic or having their family physician responsible for anticoagulant monitoring over the next 3 months. The similar things of this study were the way of educating patients which was individual face-to-face counselling. The previous study did not explain clearly on materials used in educating patients which was opposite from this study.

Processing pharmacist-managed in each setting was different, depending on possibility of health care professionals of each hospital or country. Our intervention

was from the literature reviews and the ideas by the interview from healthcare professionals working at Mahosot Hospital who worked with warfarin patients at out-patient department. This intervention cannot apply for all practical pharmacists in warfarin clinic because of the difference of status, but expecting for development and possibility in applying in mentioned hospital. The main factors that not able to apply for all process of patient service, could be difficulties in healthcare team about pharmacist should meet patients before or after physician. Others factor could be warfarin dosage adjustment by pharmacist, which could be able to do in the future study depending on readiness of target hospital and acceptance of healthcare professionals.

The length of follow up in each study was also different. Our study had a total 4 follow up. Each follow up was a month long and depended on patients also. There were 3 months in total for a patient. Wilson et al, Jackson et al, and Chan and colleagues (51, 59, 60) had the same length of follow up of 3 month as our study. But Lalonde and colleagues (49) had 6 months length of follow up and Katemateegaroon (61) 10 months. Previous studies showed the length of follow up was different that not effect the efficacy and safety outcomes of the study. In order to follow up warfarin patients, there should be 3 or more INR test for TTR value and compare efficacy outcomes clearly, so the recommended length for future studies would be 3 or more than 3 months.

Characteristic of our study found that the mean age was 53.1 ± 14.6 years old for patients in the intervention group and 50.8 ± 14.0 years old in the control group. Recent data from Verret el al. (47) showed nearly same of the mean age was 58.4 ± 10.1 years old for patients in the intervention group and 57.0 ± 10.9 years old for patients in the control group. All previous studies had higher mean age of patients included (46, 51, 60). One of the risk factors of causing AF and MVR is the age of patients that most of the patients were elderly (62).

Indication in warfarin use was also different. Chan and colleagues (60) presented the most common indications for warfarin therapy were AF (53.0 %), mechanical valve replacement (MVR) (1.8 %), DVT (12 %) and pulmonary embolism (7.0 %). Despite the indications of warfarin therapy were MVR was 47.2 % of patient in the intervention group and 58.3 % of patient in the control group followed by AF 50.0 % with 38.9 % and DVT 2.8 % for both groups. Due Mahosot Hospital is the only hospital serve the mechanical heart valve operation, patients need warfarin lifelong after operation. The number of DVT patients was less because the length of taking medicines was just 6 months which caused ineligible patients for this study. For AF patient who have a high or moderate risk of having a stroke are usually prescribed warfarin for lifelong. Incidence and prevalence of AF have increased in recent years, although great variability still exists in Asian countries (63).

Patients' comorbidity was found the most in hypertension 22 % of patient in the intervention group and 13.9 % of patients in the control group. Drug use with comorbidity might be interact with warfarin. Pharmacist need to be carefully about drug interactions. Bungard and colleagues (46) showed most comorbidity of diseases that related to non-communicable disease (hypertension, heart failure and diabetes mellitus). Medication use to treat that comorbidity such as aspirin, simvastatin and etc., can be increase or decrease effect of warfarin therapy which make INR value not stable.

Therefore, the present finding of our study show a significant data. The results presented that if patients had the managed warfarin therapy by all healthcare professionals including pharmacists, it would produce the excellent level of warfarin monitoring. This study TTR was 63.3 ± 35.5 % of TTR in the intervention group which higher than 45.3 ± 39.9 % of TTR in the control group, with statistically significant difference between two groups (p-value = 0.046). Similar with a systematic review and meta-analysis study by Hou et al, which including 8 RCTs and 9 observational cohort studies with 9,919 patients included. The previous results found that TTR control pharmacist-led management group was significant higher than the control groups from overall results (weight mean difference: 8.03, 95 % CI: 2.19-13.88, p-value = 0.007) (11). TTR value is useful for seeing the quality of treatment by warfarin therapy. When patients had high TTR results, it means that patients have low risk of thromboembolism or stroke events.

In Thailand, Saokaew and colleagues (12) studied of 433 patients comparing pharmacist intervention with usual care group. The study found that at the end of follow-up period, patients in the pharmacist intervention group had significantly higher actual TTR (48.3 % vs. 40.1 %, p-value < 0.001) and expanded TTR (62.7 % vs. 53.9 %; p-value < 0.001) compared to those in the usual care group. The result shown that TTR was lower than our study. A reasonable reason could be the difference of the intervention which was the clinical pharmacists optimized the warfarin therapy and suggested recommendations (e.g., dose adjustment, safer alternative drugs, and follow-up time) to physicians. For TTR is INR ± 0.2 units for both studies. However, the presented TTR in European ancestries that the therapeutic and the expanded therapeutic INR ranges were achieved 40-64 % (64). That range can use to prevent thromboembolism event.

The analysis of the outcome of patients who were randomized to warfarin therapy in the SPORTIF III and V study indicated that the risk of death and stroke or embolic events was lower in patient with TTR ≥ 60 % than in those with TTR < 60 % (65). The mean patients with high TTR had low risk of death or stroke. Our TTR outcomes showed the percentage of patients who had TTR > 60 % was 58.3 % in the intervention group better than 33.3 % in the control group. A previous report showed that TTR > 60 % in pharmacist managed warfarin therapy was higher than usual care group which the low risk of death and stroke were found.

The definition of INR value in expanded therapeutic range in each study was different. Our study had the INR ± 0.2 which same as Chan and colleagues (60). There were studies that had INR in expended range ± 0.3 by Verret and colleagues (47) and Bungard and colleagues (46) INR in the actual range ± 0.5 and an expanded range was INR ± 0.7. Aiming at ± 0.2 could better prevent the thromboembolism events or stroke and bleeding. The expansion is very useful for real practice of adjusting warfarin dosage.

Furthermore, the percentage of time that patients' INR values were within the expanded therapeutic range were 77.3 % versus 67.3 %. Difference from the result of Wilson and colleagues (51) shown the percentage of time that INR values of patients managed by anticoagulation clinics was within the expanded therapeutic range 82.0 % versus 76.0 % for patients in the family physician group (p-value = 0.034). The expanded therapeutic range in both studies means INR ± 0.2 units. From what we observed, the pharmacist group had higher value which mean that the good

quality. By comparing both studies, we found that the previous study had higher value than this study. As the characteristic of population that were new users defined as those who had been prescribed warfarin for less than 1 month. INR for new warfarin patient must be in therapeutic range before discharge with warfarin therapy. Moreover, the sample size was difference between the previous study 221 patients and this study 72 patients.

There was also a strong focus on patient's education as part of this intervention as studies have generally shown a relationship between intervention and control groups of patients' knowledge of warfarin therapy. Patient's knowledge score showed significantly increases, from 5.2 ± 2.6 to 13.2 ± 1.4 after pharmacist-managed warfarin therapy. Due to the pharmacists educating in each visit and assessing the knowledge from the questionnaire, the result of the last assessment of both groups showed that there was significant difference between patient's knowledge scores (intervention group 13.2 ±1.4 vs. control group 7.0 ± 3.6, p-value = 0.001). The obvious reason of what make the different result is that the patients in the intervention group were educated by pharmacist in every visit. When pharmacists participated the routine care on warfarin's knowledge and patients' behavior, the patients would have better quality use of warfarin, proving by the TTR which higher in the intervention group. Several studies reported that patients' knowledge outcomes improved after patients' education becomes a part of pharmacist intervention (20, 44, 66). However, the present patients' knowledge outcome was inconsistent with the finding by Hasan and colleagues (67) which the outcome was no significant differences between pharmacist and non-pharmacist that run anticoagulant clinic. Although, the method of knowledge assessment in these 2 studies were difference. Hasan and colleagues focused on the patients' knowledge score of the mechanism of action of warfarin, the interaction between warfarin and alcohol and knowledge on the side effects of warfarin. But our study focused on warfarin's knowledge and patients' behavior of warfarin therapy.

The most type of DRPs from 4 visits were sub-therapeutic dosage which consist of 30 cases in the intervention group (12, 6, 6 and 6 cases at the baseline, first, second and third visit, respectively). Following by drug interactions, 9 cases and over dosage 1 case. Comparing with the study of Apichat el al. (68), a descriptive cross-sectional study at out-patient department of Vachiraphuket Hospital found that 131 events from 60 patients and 2 months follow up, 33.6 % was drug interaction with warfarin, 28.2 % of adverse drug reaction and 16.0 % of sub-therapeutic dosage. Since Mahosot Hospital did not have the protocol for warfarin dosage adjustment, doctors have to adjust the dosage by their routine experience and based on INR value. Also, due the awareness of bleeding events, the doctors adjust the dosage lower than normal. However, there were no reported of thromboembolism event in this study.

Doctors and patients accepted DRPs and solved the problem by 60.0 %, 33.3 %, 25.0 % and 16.7 % for the intervention group in the first, second, third and fourth visit, respectively. The percentage was lower than 92.0 % and 93.5 % which physicians and patients/caregiver accepted DRPs and solved the problem at the recent study (68). The results showed that the accepted DRPs which pharmacists assessed was still too low. It could be that most of DRPs were sub-therapeutic dosage and doctors accepted the INR value, so warfarin dosage was not adjusted. One of the possible reasons could be being not acceptable from the perspective of doctors by the

challenging and new for pharmacists. For Mahosot Hospital, the establishing the clinical pharmacist that we just did, was the first time in the heart center. In the future, there would be high potential in continuing the DRPs assessment incorporate with doctors to produce the best care quality for patients (68).

The effect of pharmacist-managed warfarin therapy on thromboembolism event was not found in this study. It could mean that the length of the follow up was too shot and also the number of patients included were too small. Support by the study "the effectiveness of pharmacist-participated warfarin therapy management: a systematic review and meta-analysis" showed the results of 661 articles identified, 24 studies with 728,377 patients were included with the thromboembolic events (RR, 0.79; 95% CI, 0.33–1.93) (12). Even the number of participants was high but the number of thromboembolism events found was low and considered as the positive side for warfarin patients. The cause of thromboembolism events was from the patients who has INR lower than therapeutic dose. When we look at the details of the thromboembolism events clearly, we can see the length and number of patients of the study was different which increase the chance that the events found or the genetics population and characteristic itself which cause thromboembolism events. The cultural of eating behavior could also be different that lead to low INR value and caused the thromboembolism events. Due to some foods contain high vitamin K will make ineffective of warfarin. Difference with the study of Wilson et al., they found 1 case of thromboembolism event during 3 months. It is maybe because patients included were new case of warfarin therapy. There is high chance of having INR not in therapeutic range in patients who take warfarin for some distance.

The evaluation of patients' adherence had different method but there is not any specific method for warfarin. This study used the questionnaires and pill counting. The questionnaire is MGL 4 item-scale (25) and pill counting which is the way to find out the percentage of patients' adherence and counting pills that patients had in every visit to find the percentage of pills taken. From the result of the study, we could see the adherence assessment method for were better effective should be the pill count method because we could see clearly if the patients forgot and how many time to take warfarin. If the patients not recognize or remember how many time they missed taking warfarin, it could lead to wrong warfarin dosage adjustment. Moreover, previous study reported that adherence as measured by medication event monitoring systems caps identified more non-adherence than either clinician assessment or patient self-reports and was associated with anticoagulation control (69).

Also, for patients' adherences assessed by MGL 4 items scale, the results shown patients in both groups had good adherences as at the first, second and third visit. A cross-sectional survey of 52 patients (70) was assessed patient adherence by used MGL 4 items scale survey. Adequate adherence was patients self-reported by 50 % of patients and was significantly associated with good anticoagulation control (p-value = 0.01). Previous study used the same questionnaires to assess patient adherence, showing very low value and had the great different when comparing to this study. Despite, in Singapore a cross-sectional survey aimed to validate a patient reported medication adherence measure, the Morisky Medication Adherence Scale (MMAS) 8 items, within a convenience sample of 151 patients taking warfarin. It was found that respondents with higher MMAS 8 items scores are more likely to have a higher percentage of INRs within the therapeutic range (p-value = 0.01). This study

showed that the 8-item MMAS has good validity and moderate reliability in patients taking warfarin (71). Since the similarity of the questionnaire 4 items and 8 items, the result showed good patients' adherence, opposite with pill count assessment method. So, to use the questionnaire in assessing might not be the best choice for warfarin patients.

Pill count in the intervention group was 87.3 %. Similar with Parker and colleagues (69) evaluated 145 patients of warfarin therapy. The method used was electronic pill caps which was not available in Lao PDR yet. The percent of days that the incorrect warfarin dose was taken by medication event monitoring systems cap when they were supposed to take a pill or opened it more than once divided by the number of days in the monitored period. The result showed participants had a correct medication event monitoring systems cap opening on 79.2 % of days and the percentage found was not difference to this study. Counting medicines by pharmacist pill count and electronic pill count had similar outcome.

Kimmel and colleagues (72) studied on a prospective cohort study at 3 anticoagulation clinics to determine the effect of adherence on anticoagulation control. There were 136 patients included in total. All participants were observed for a mean of 32 weeks which 92 % had at least 1 missed or extra bottle opening, 36 % missed, more than 20 % of their bottle openings, and 4 % had more than 10 % extra bottle openings similar with our study that not all patients had adherence. In order to solve the patients' adherence, we need to better understand and gain more knowledge of warfarin therapy. Tang and colleagues reported that patients with better understanding and knowledge of warfarin therapy had better therapeutic control (73).

For major bleeding events, there was no case found in our study. However, minor bleeding event still presented in our outcomes. All patients who faced such events had already counselled by pharmacists, including how to behavior after those events and how to handle the bleeding caused by warfarin with similar with Wilson and colleagues (51) which also giving more suggestions to patients who served bleeding. Not just educating patients, controlling INR value is very important too. Some previous studies, pharmacists could adjust warfarin dosage with doctor or physician. Bungard and colleagues and Chan and colleagues (46, 60) found that events if pharmacists involving in dosage adjustment, there was still reports of bleeding in pharmacist group (2 patients and 1 patient, respectively). For minor bleeding, there is a chance of improvement event the patients' INR in therapeutic range. From previous studies, there were reports of minor bleeding in warfarin patients. A systematic review study of Saokaew and colleagues (12) included 4 RCT studies. The result found total bleeding of 14 of 367 patients in the pharmacist group compare with 29 of 368 patients in the usual care group. Most of the minor bleeding events reported were similar causes from our study. In each study, RCTs had difference definitions of major and minor bleeding which is one point that could not be all compared.

5.3 Limitation of study

First limitation of this interviews study was that we only interviewed healthcare professionals of about 20 % of the doctors, nurses and pharmacists at the out-patient department, Lao Luxembourg heart center, Mahosot Hospital. It means we

could possible missed other majors' opinion or ideas from the remaining healthcare professionals.

There was no electronic medical record in Mahosot Hospital which was our second limitation. The only way to check or know the patients' record was the patients' book which they bring back home every time and they may forget it at home sometime when they come for follow up. Moreover, there was not any record of the ADR or DRPs of warfarin which we recommended future study continuing collecting these data for baseline and reducing missing number of patients admitted. Due to lacking of patients' record, researcher could not be sure about number of all warfarin patients, numbers of follow up patients in each visit.

Third limitation was found from RCT study. The number of patients included in the study was too small, so it was difficult for comparing the results of both groups. For example, the result of INR value which was not found the difference. There were just 36 people in each group which was very hard to find thromboembolism event and major bleeding. If we could have more patients, we could increase the chance of finding thromboembolism event and major bleeding.

Fourth limitation is that the follow up period was relatively short. It could be possible due the time consuming and the difference in compliance or follow up which could affect the efficacy and safety of pharmacist-managed warfarin therapy. The longer follow up was recommended to better understand the understanding of patients, patients' adherence, efficacy and safety outcomes, and any issue caused by warfarin toward the information provided.

5.4 Future research

For future researches, there should increase the number of healthcare professional for the interviews study in order to gain ideas which could be different from this study. This could better develop pharmacists' intervention model for patient using warfarin in this setting.

It could be interesting if the future study assessing the satisfaction of healthcare professional on pharmacist-managed warfarin therapy because the interviews study found that they need and suggest this role to pharmacists. From RCT study result, there should be a reassessment to identify and solve the drug-related problems found.

For interviews and RCT study, there was a problem of warfarin dosage adjustment guideline which need to be agreed by all health care professionals. More studies are still required and/or creating the guidelines to better understanding on warfarin dosage adjustment among doctors. It would better be understanding between doctors and pharmacists if there's warfarin clinic in the future and the pharmacists' role would be accepted.

The same with interviews study, the next RCT study should be increased for number of patients in order to increase the chance of recovering the thromboembolism and major bleeding events which not discovered in this study. Also, the time of follow up is recommended to be extended.

5.5 Application in clinical practice

In phase I, it was problems identification and developing to generating the intervention which used in phase II. It was not covered all problems in phase I due the budget limitation but the quality of patients' life could be better. From the warfarin patient interviews, there should be more policies to support their needs and to solve the problems of organization barrier and strengthen pharmacists' role in hospital.

In summary, the result of warfarin therapy by pharmacist-managed warfarin therapy was better than usual care with no pharmacists involved. This result could be a decision making of making clinic warfarin which would be beneficial for healthcare professionals and patients themselves. The pharmacists' role was the main point of this study which needed to be enhanced in order to meet the expectation of all parties in the hospital. Pharmaceutical care at this study could help to assess DRP, to educate patient, to be a benefit for patient, and to develop a pharmacist role in this hospital.

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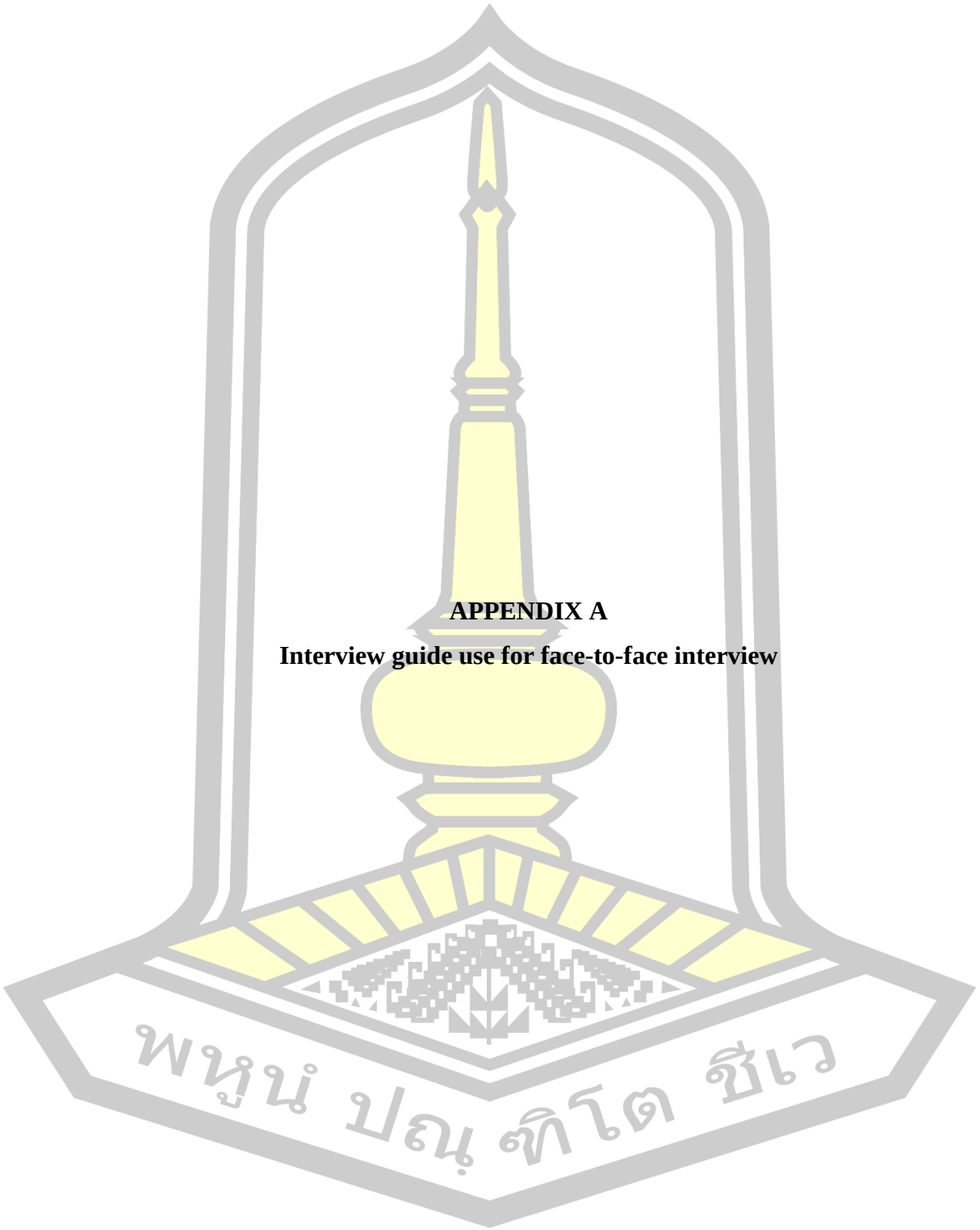
APPENDIX



APPENDIX A

Interview guide use for face-to-face interview

Interview guide use for face-to-face interview

Age……
Year of work experience on patients using warfarin…….

Q1. Have you ever experienced the problems of patients taking warfarin? If yes. What is the problems?

Q2. Currently, how do patients with warfarin receive the usual care?

Q3. Apart from question, do you think patients taking warfarin should receive special care from other healthcare professional? And what or how should they receive?

Q4. From question 1. What would you like to improve? Who do you think that they would be able to contribute improvement?

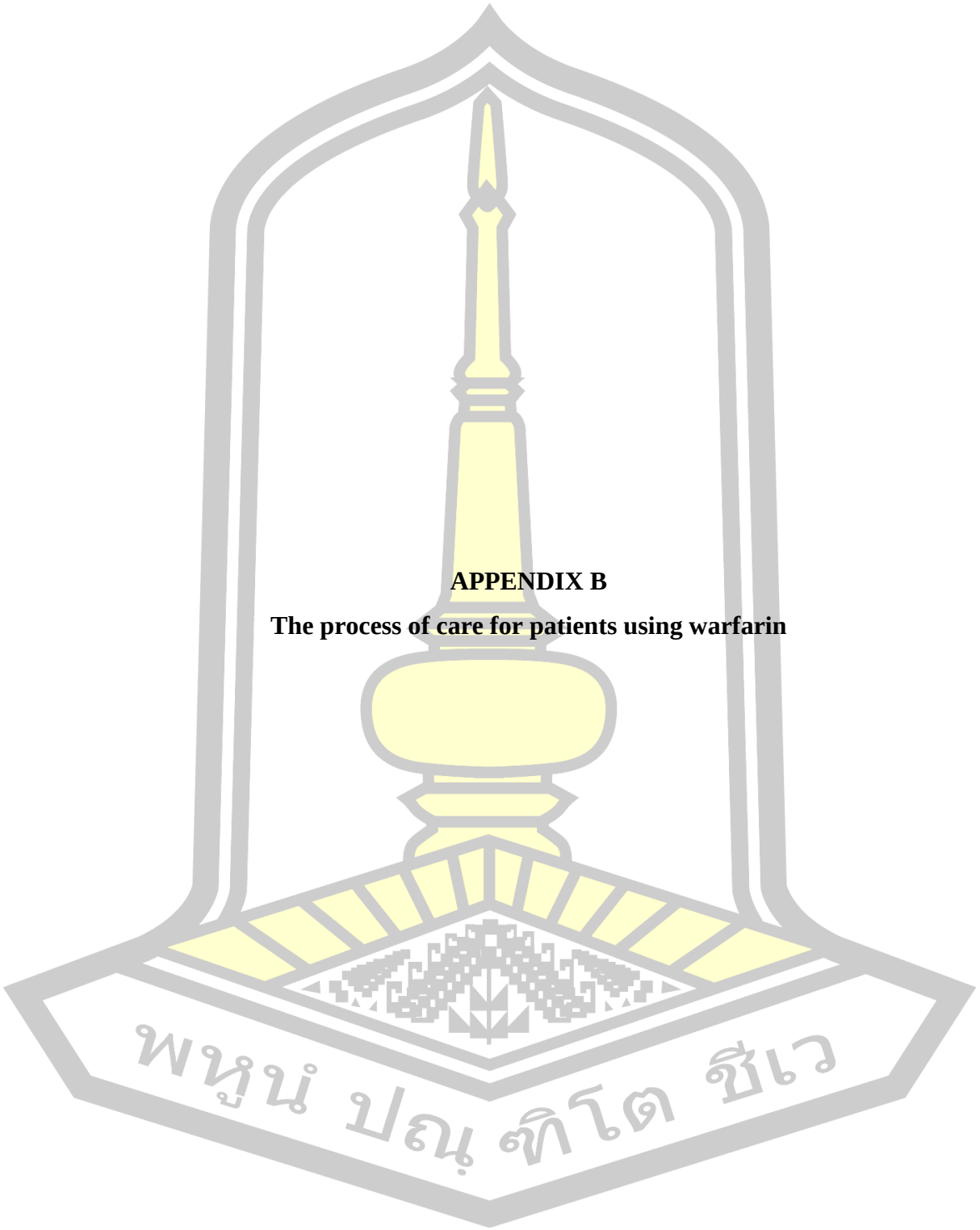
Q5. What do you think if pharmacists-managed warfarin therapy is provided?

Q6. If all healthcare professional is involved in the care of patients taking warfarin, do you think the policy, the system, the manpower and the budget are sufficient or not?

Additional interview guide for pharmacists is:

Q1. Have you ever advised warfarin patients? What advices do you give?

Q2. Do you think the advices you give are sufficient or not? If no, what could be the best for you giving sufficient advises to patients?

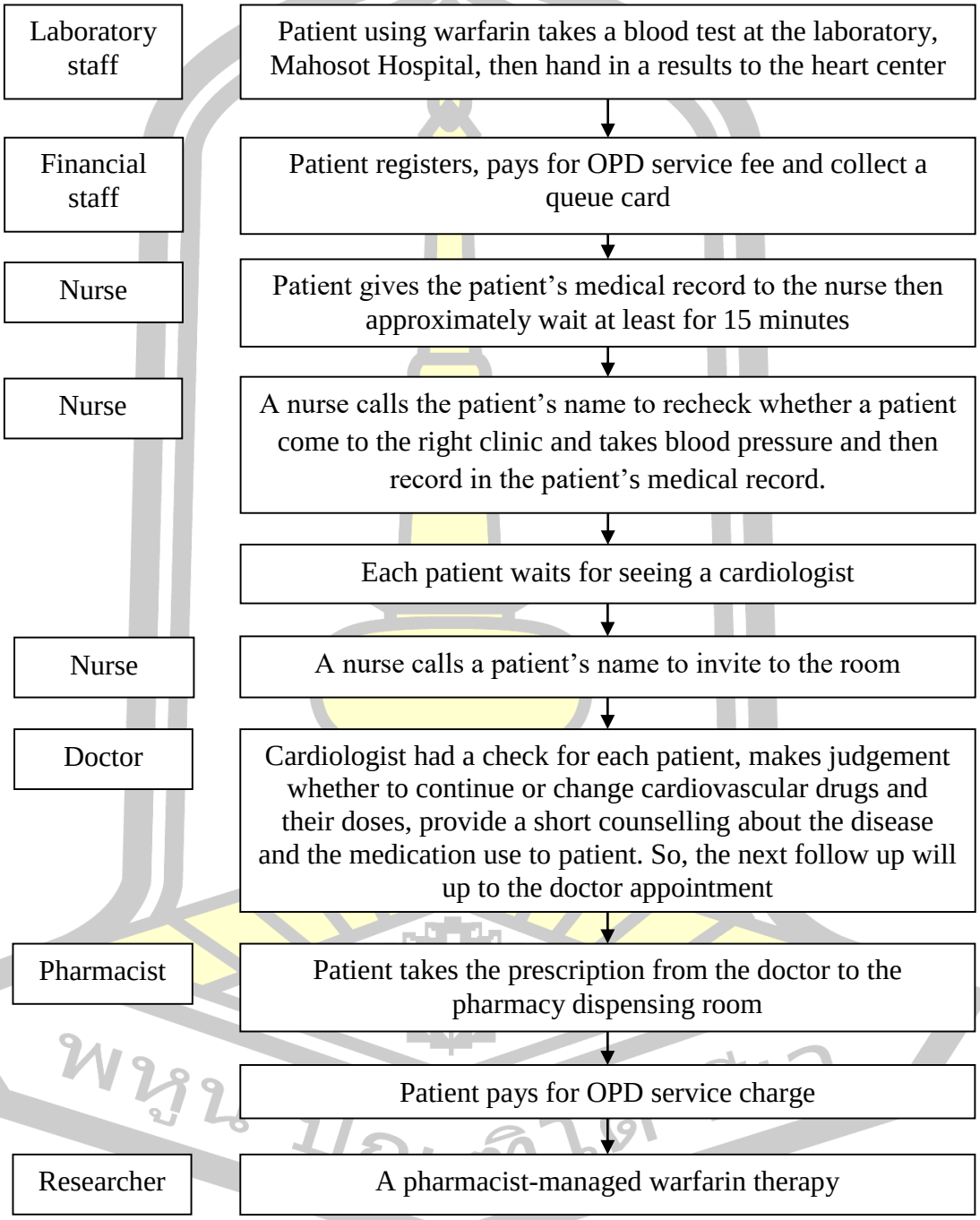


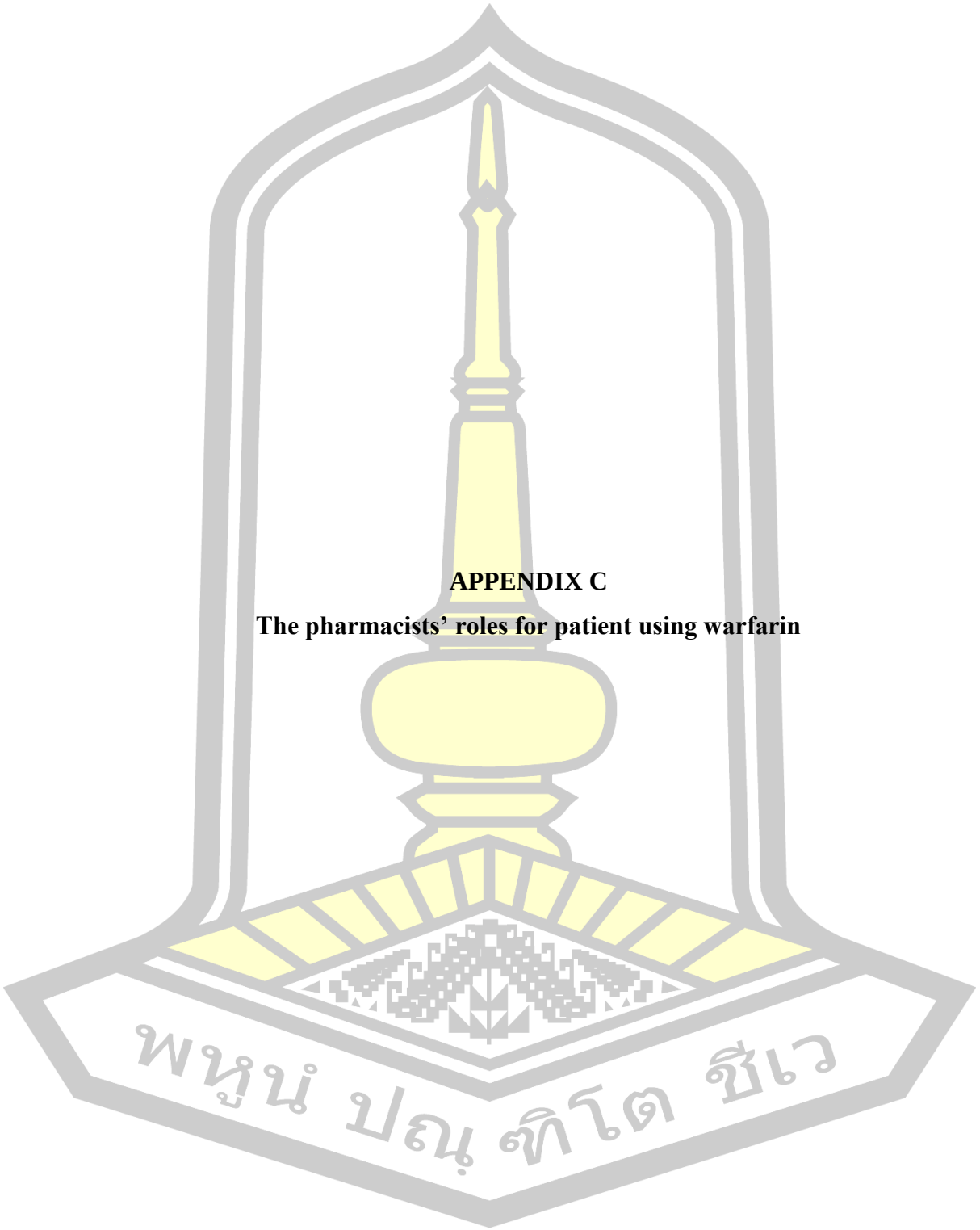
APPENDIX B

The process of care for patients using warfarin

The process of care for patients using warfarin

A flowchart of the process of care for patient using warfarin at out-patient department, Lao-Luxembourg Heart Centre, Mahosot Hospital.





APPENDIX C

The pharmacists' roles for patient using warfarin

The pharmacists' roles for patient using warfarin

The literature review of pharmacist-managed warfarin therapy showed the pharmacist's role for patient using warfarin as follows:

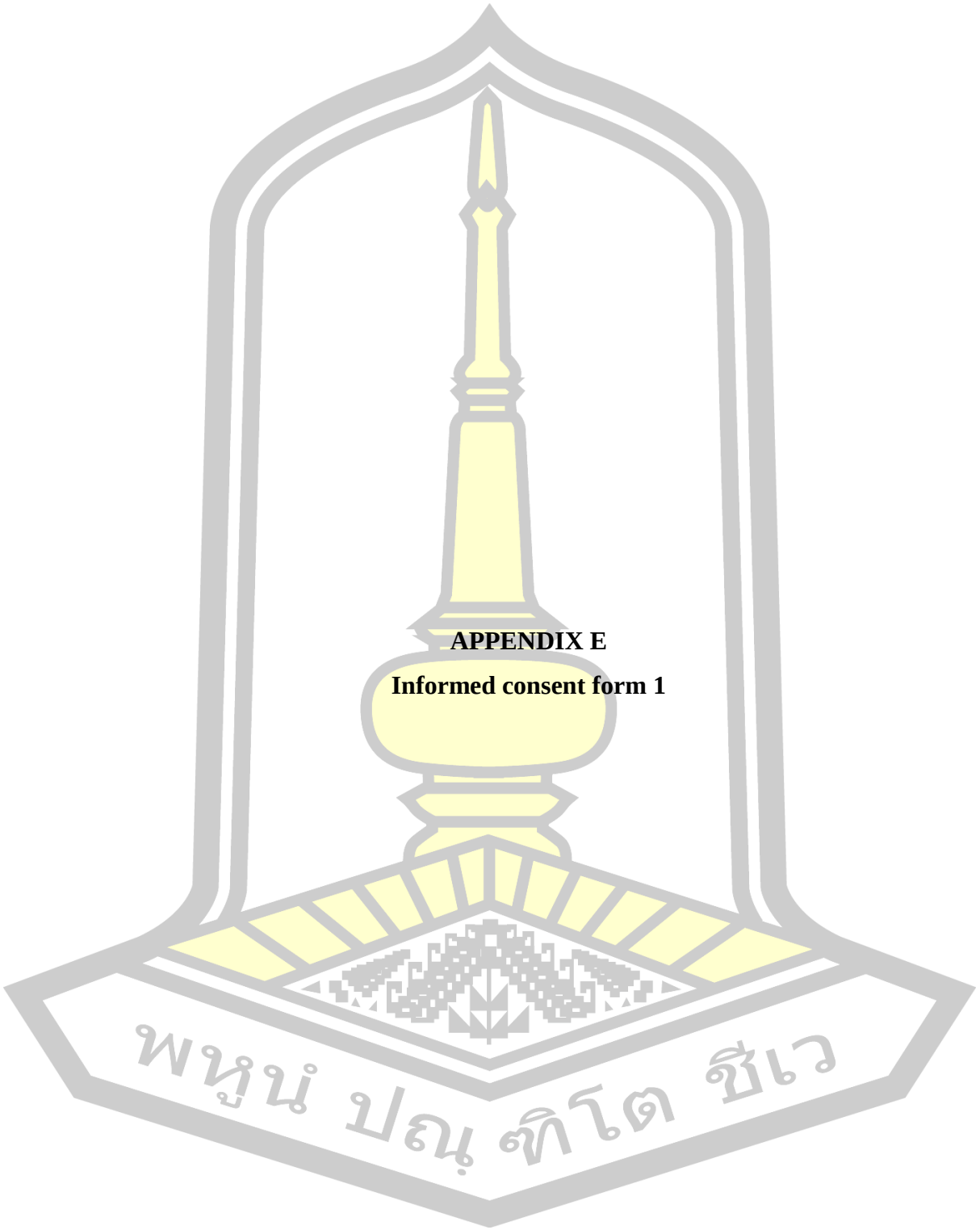
Pharmacists' roles	Participants	Tools
Dosage adjustment	Doctor Pharmacist	Schedule for dosage adjustment
Scheduled INR test appointment and follow-up visit	Doctor Pharmacist	Schedule for dosage adjustment
Education provision to patients	Pharmacist Nurse	Education tool
Assess compliance with regimen	Pharmacist	Pill count Morisky, Green and Levine (MGL) 4 item scale
Review medications, comorbidities, diet, and drug interactions	Pharmacist	Data collection form
Screen for side effects, thromboembolism or bleeding events and recurrence	Doctor Pharmacist	Data collection form

APPENDIX D
The education tool by pharmacists for patient using warfarin

The education tool by pharmacists for patient using warfarin

The following detail is an education provided by pharmacist:

1. Warfarin was used to preventing or treating blood clot in patients with AF or VTE or MVR. To educate this information is depending on doctor's diagnosis note in patient's book.
2. Patient must know their current dose of warfarin. To educate this information is depending on doctor's note. Patient must take warfarin exactly as prescribed, never increase or decrease the dose unless instructed to do so by the healthcare provider.
3. Patient must be knowing the INR test is important for adjust warfarin dose. Patient must be knowing the target INR is 2-3 or 2.5-3.5 depended on diseases or doctor prescribe. For example, INR 2-3 for patient with AF, VTE and INR 2.5-3.5 for patient with MVR. A frequently to check INR is 1week for patient who have INR without therapeutic range or at least 1 month for patient who have INR within therapeutic range, it depends on doctor order.
4. Warfarin should be taken at the same time every day because to protect the forgetfulness.
5. In case of missing or forgetting the dose over 12 hours, patient have to skip, and take the same dose at the same time in the next day.
6. If patient take double dose, INR maybe increased and patient will have a risk of bleeding. In this case, patient must tell the health care professional when they come to follow up.
7. In case of seeing other doctor, dentist, or having some type of surgery while on warfarin, patient must tell doctor that he/she taking warfarin.
8. Food with high of vitamin K intake (papaya, grapefruit, mango ripe, soy milk, avocado, green tea)-green leafy vegetables (collard greens, coriander, kale, spinach, watercress) can affect warfarin therapy by decreasing INR level. So, patient must take the same amount of food every day.
9. Drug interaction and herb interaction with warfarin therapy is: NSAIDs (aspirin, ibuprofen, diclofenac, naproxen, meloxicam, celecoxib) which can increase risk of bleeding. In addition, drugs that can decrease warfarin effect include vitamin K, phenytoin, carbamazepine, and etc. Herb that can increase risk of bleeding include ginger, gingko, fish oil, garlic.
10. In case of nose/gum bleeding, the first Aid is to sit upright and lean forward until the blood not bleed. In case of any cut or wound of patient body, the first Aid is to apply direct pressure on the cut or wound with a clean cloth, tissue, or piece of gauze until bleeding stops. Patient must go to hospital if bleeding lasts for more than 30 minutes.
11. While traveling or working abroad, carry your medications with you at all times. Let your doctor know and they will prescribe enough dose of warfarin for you.
12. The possible side effects of warfarin are bruise, blood in urine or stool, nose/gum bleed, bleeding in any part of your body.



APPENDIX E

Informed consent form 1

Informed consent form 1

AF 05-10/3.0

Mahasarakham University Institutional Review	Informed Consent Form

Research title: Development of Pharmacist-managed Warfarin Therapy at Mahosot Hospital, Lao PDR.

Date: _____ Healthcare professional's ID: _____

Willingness to participate in the research of Development of Pharmacist-managed Warfarin Therapy at Mahosot Hospital, Lao PDR. I have been informed about the source and purpose of the research, detailed steps, to be interviewed, expected benefits of research and the risk that may arise from participating in this research. Including the prevention and corrective measures if any. Also, I had received the explanation about the question from the researcher of the research project.

I volunteered to participate in this project:

If I have been interviews incorrectly, as stated in the participant's explanation. I will be able to contact the human research ethics board at the Lao PDR National Ethic Committee for Health Research, call +856-21-250670-207 or 208. If I have question about the research process during the project, I will be able to contact the researcher Miss Vanlounni Sibounheuang throughout 24 hours on call: +856-20-77714406.

The foregoing information has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I consent voluntarily to participate as a participant in this research.

Sign.....Contributor and consent message

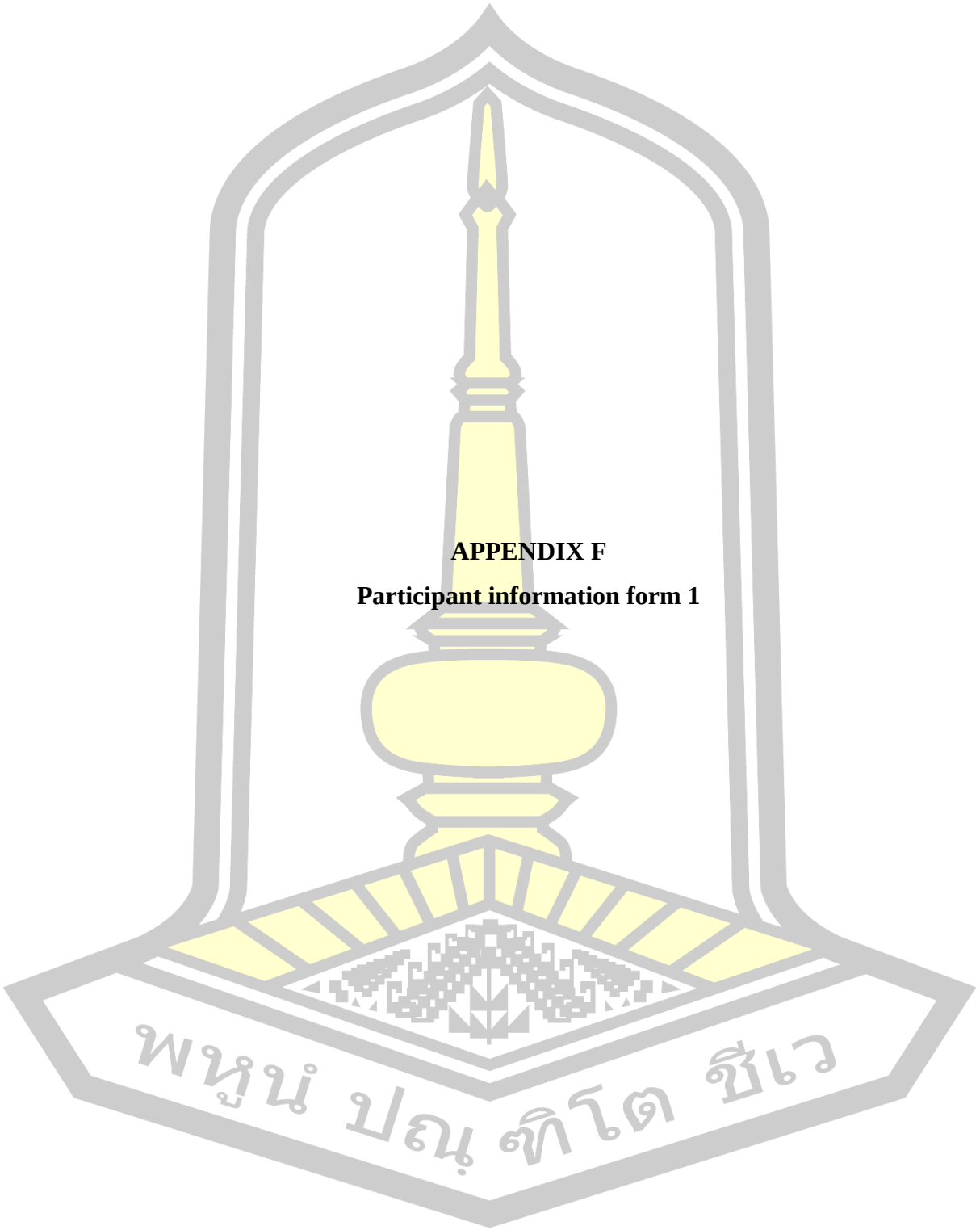
(.....) Date.....

Sign.....Researcher

(Vanlounni Sibounheuang) Date.....

Sign..... Witness

(.....) Date.....



APPENDIX F

Participant information form 1

Participant information form 1

AF 04-10/3.0

	Mahasarakham University Institutional Review Board	Information Sheet for Research Participant

Research projects: Development of Pharmacist-managed Warfarin Therapy at Mahosot Hospital, Lao PDR.

Sponsor Research: Faculty of Pharmacy, Mahasarakham University
Researcher: Miss. Vanlounni Sibounheuang
Address: Master student, Faculty of Pharmacy, Mahasarakham University
Telephone: 0969893085, E-mail Vanlounny@gmail.com
Co-Researcher 1: Dr. Wanarat Anusornsangiam
Address: Faculty of Pharmacy, Mahasarakham University
Telephone: 043754360, E-mail: Wanarat.a@msu.ac.th
Co-Researcher 2: Asst. Prof. Dr. Pattarin Kittiboonyakun
Address: Faculty of Pharmacy, Mahasarakham University
Telephone: 043754360, E-mail: pattarin.k@msu.ac.th

Dear all participation,

You are invited to participate in this research project, before you decide to join or not. Please, carefully read all the text in this document or listen from the researcher to know why were you invited to participate in this project. This document may contain some unclear words, please ask the researcher to explain until you understand. To participation in this research project must be voluntary. No compulsion on who do not participating or withdrawing from this research project, it will not affect you anyhow. Please, do not sign document until you are sure that you wish to participate in this research project.

Background and important of the research

Warfarin remains the most widely available anticoagulant in supply chain and is the only oral anticoagulants (OACs) in the world health organization's (WHO) model list of essential medicines. To help patients recognize the signs and symptoms of bleeding or clotting from warfarin use, well knowledge on warfarin must be provided. There were evidences proved that when warfarin was managed by pharmacists, patients produced better clinical outcome.

Research objective

Aim of the study is to develop pharmacist-managed warfarin therapy at Mahosot Hospital. The specific purposes are to investigate views of healthcare professionals including doctors, nurses and pharmacists on pharmacists' roles, and process of care for patients with warfarin use. To explore views of healthcare professionals including doctors, nurses and pharmacists on pharmacist-managed warfarin therapy developed by researches.

Method related to research

After you consent to participate in this research project, a researcher will request to interview you follow to the interview guides.

- For the face-to-face interviews, it will be used about 20 minutes.
- If you are in case of focus group interview, it will be used 4 hours in the meeting.

Responsibilities of the volunteers participating in the research project

To make this research successful. The researcher would like to cooperate with you to answer the questions. In case of any unusual questions that occur to you during the interview, please report to the researcher.

Risks that may be received

You might be get minimal risk such as wasting time and inconvenience. Please inform the researcher in case of your inconvenience.

The benefit from this study

You will not get any benefit from participating in this research. But the study results will be implement the pharmaceutical care model for patients using warfarin at out-patient department. It does not guarantee that the study will improve the pharmacist-managed warfarin therapy.

The practice while participating in the research project

Please do the following:

- Please provide your information to do with the truth.
- Please inform the researcher immediately if you don't want to continues the interview.

Possible risks of participating in the research project and the responsibilities of the researcher

This study is an interview by face-to-face. However, if any problems arise during the study, the participant can stop the interview immediately.

Protecting confidential information of participants.

Information that may lead to your disclosure will be covered and will not be disclosed to the public. The researcher will be stressed that all information would be kept anonymous and that the audiotaped, videotaped interviews will be stored in a locked cupboard that only the research team can access by using password.

If you are not protected as shown in the data explanations for participant's information sheet in the research. You can complain at the Lao PDR National Ethic Committee for Health Research, call +856-21-250670-207 or 208.

Thank you for your cooperation.

APPENDIX G

Patients' data collecting form

Patients' data collecting form

Patient's ID code: …… Address: ……

Part 1: General information

Gender: □ Male □ Female Age: ……years

Part 2: Efficacy outcomes

Indication: □ AF □ VTE □ MVR □ others …….

Therapeutic INR: □ 2 - 3 □ 2.5 - 3.5 □ others …….

Duration with warfarin therapy: (past) ……. months (future) ……. Months

INR results and Warfarin order:

Visit	Date	INR result	Warfarin dosage regimen	Total warfarin dispensing	Warfarin remaining (mg)	Warfarin should remaining (mg)
Baseline						
1st						
2nd						
3rd						

Comorbidities (can be more than one):

Comorbidities	Baseline	1st visit	2nd visit	3rd visit
None				
Hypertension				
Diabetes mellitus				
Renal disease				
Asthma				
Coronary heart disease				
Dyslipidemia				
Rheumatic heart disease				
Hypothyroidism				
COPD				
Other ……				

Medication used (can be more than one):

Medication used	Baseline	1st visit	2nd visit	3rd visit
None				
Aspirin				
Simvastatin				
Fenofibrate				
Clarithromycin				
Levothyroxine				
Propylthiouracil				
Acetaminophen				
Other ……				
Other ……				

Food interaction with warfarin (can be more than one):

Food	Baseline	1st visit	2nd visit	3rd visit
None				
Papaya				
Grapefruit				
Mango (ripe)				
Green leafy vegetables				
Soy milk				
Avocado				
Green tea				
Other ……				
Other ……				

Herb interaction with warfarin (can be more than one):

Herb	Baseline	1st visit	2nd visit	3rd visit
None				
Ginkgo[a]				
Fish oil[a]				
Garlic[a]				
Ginger[a]				
Onion[a]				
Vitamin E[a]				
Alcohol[a]				
Other ……				
Other ……				

Thromboembolism event:

Date	Yes	No	Doctor's diagnosis
Baseline			
1st visit			
2nd visit			
3rd visit			

Part 3: Patient adherences

Questions	Base line	1st visit	2nd visit	3rd visit
Do you ever forget to take your warfarin?				
Do you ever have problems remembering to take your warfarin?				
When you feel better, do you sometimes stop taking your warfarin?				
Sometimes if you feel worse when you take warfarin, do you stop taking it?				

Part 4: ADRs

Major bleeding	Baseline	1st visit	2nd visit	3rd visit
None				
Bleed requiring blood				
Intracranial bleed				
Intraspinal bleed				
Intraocular bleed				
Retroperitoneal bleed				
Other ……				
Other ……				

Minor bleeding	Baseline	1st visit	2nd visit	3rd visit
None				
Bruising				
Hematoma				
Nosebleeds				
Gum bleeding				
Blood in urine				
Blood in stool				
Other ……				

APPENDIX H

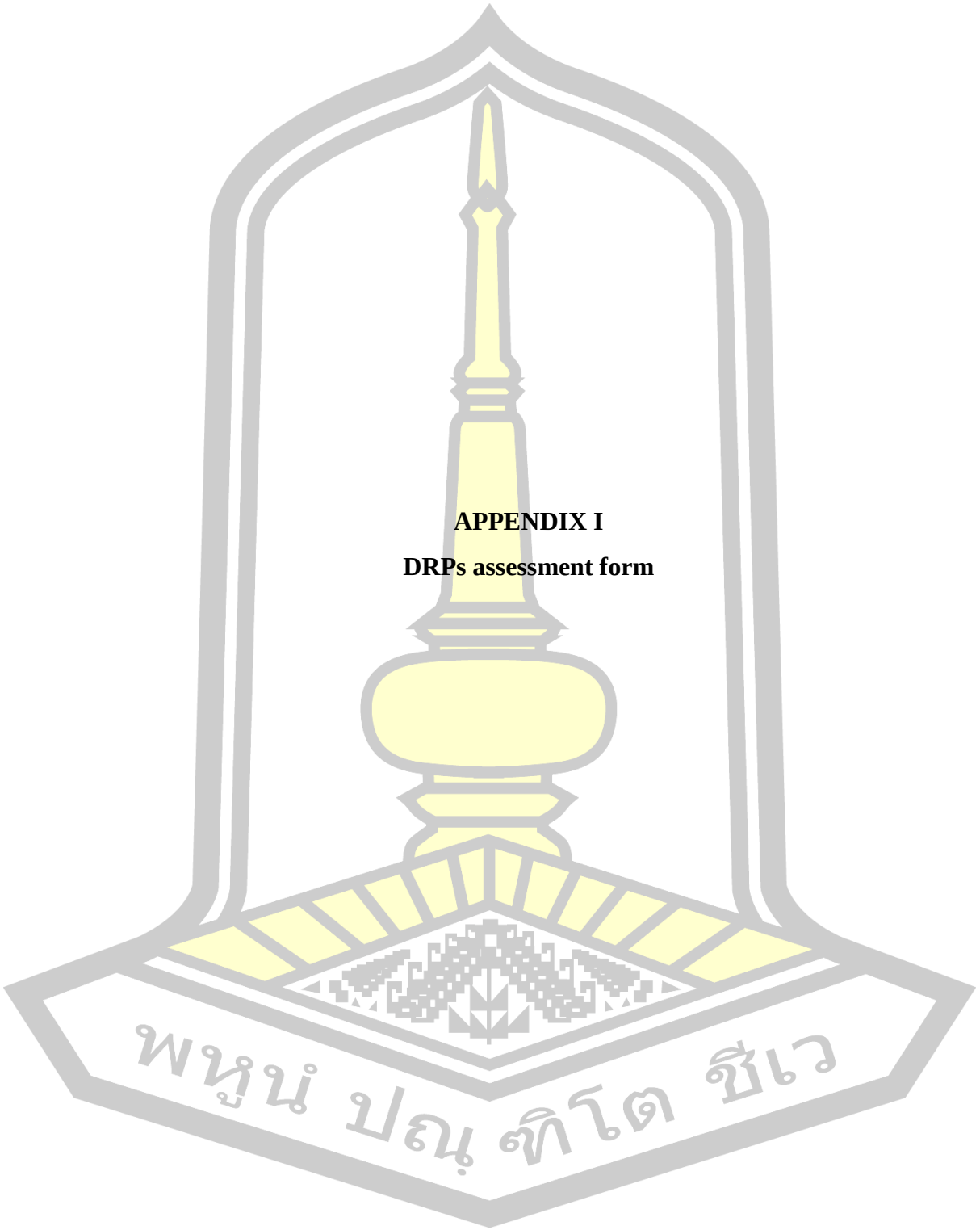
Question for patients' knowledge assessment

Question for patients' knowledge assessment

Patient's ID code: ……

No.	Questions	baseline	1st visit	2nd visit	3rd visit
1	What is warfarin? Why you have been prescribed warfarin?				
2	What is your current dose of warfarin?				
3	Who is responsible for adjusting your warfarin dose?				
4	What is the important of INR testing?				
5	What is your target INR?				
6	How frequently should you check INR?				
7	When should warfarin be taken and why?				
8	What will you do in case of a missed dose?				
9	What will happen when you take double dose of warfarin?				
10	What will you do in case of surgery, dental work, or some type of invasive procedures while on warfarin?				
11	Which types of foods affect warfarin therapy?				
12	Do you know that some of the drugs, alcohol, herbal medications can affect warfarin's action?				
13	What will you do in case of bleeds from nose/gum?				
14	What should you do if you plan to go on holidays?				
15	What are the possible side effects of warfarin?				

Note: For patient in usual care group will used for baseline and 3rd visit.



APPENDIX I

DRPs assessment form

DRPs assessment form

ID	DRPs	Yes or No	Management	Result of management
Baseline				
1	Sub-therapeutic dosage			
2	Over dosage			
3	Drug interactions			
1st visit				
1	Sub-therapeutic dosage			
2	Over dosage			
3	Drug interactions			
2nd visit				
1	Sub-therapeutic dosage			
2	Over dosage			
3	Drug interactions			
3rd visit				
1	Sub-therapeutic dosage			
2	Over dosage			
3	Drug interactions			

APPENDIX J

Informed consent form 2

Informed consent form 2

AF 05-10/3.0

Mahasarakham University Institutional Review Board	Informed Consent Form

Research title: Development of Pharmacist-managed Warfarin Therapy at Mahosot Hospital, Lao PDR.

Date: _____ Patient's ID: _____

Willingness to participate in the research of Development of Pharmacist-managed Warfarin Therapy at Mahosot Hospital, Lao PDR.

I have been informed about the source and purpose of the research, detailed steps, to be treated or treated, expected benefits of research and the risk that may arise from participating in this research. I understand all full text in the participant handout. Also, I had received the explanation and all answered about the question from the researcher of the research project. I volunteered to participate in this project:

If I have been treated incorrectly, as stated in the participant's written explanation. I will be able to contact the human research ethics board at the Lao PDR National Ethic Committee for Health Research, call +856-21-250670-207 or 208.

I know the right to get more information in both benefits and penalties from participating in the research. I do not have to take part in this research if I do not wish to do so and refusing to participate will not affect my treatment at this hospital in any way. I will still have all the benefits that I would otherwise have at this hospital. I may stop participating in the research at any time that I wish without losing any of my rights as a patient here. My treatment at this hospital will not be affected in any way.

The researcher confirms that all information that I give to them, they will be kept confidential. Information about me that will be collected during the research will be put away and no-one but the researchers will be able to see it. Any information about me will have a number on it instead of my name. only the researchers will know what my number is. It will not be shared with or given to anyone except the researcher only.

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

Sign.....Contributor and consent message

(.....) Date.....

Sign.....Researcher

(Vanlounni Sibounheuang) Date.....

Sign..... Witness

(.....) Date.....

APPENDIX K

Participant information form 2

Participant information form 2

AF 04-10/3.0

	Mahasarakham University Institutional Review Board	Information Sheet for Research Participant

Research projects: Development of Pharmacist-managed Warfarin Therapy at Mahosot Hospital, Lao PDR.
Sponsor Research: Faculty of Pharmacy, Mahasarakham University
Researcher: Miss. Vanlounni Sibounheuang
Address: Master student, Faculty of Pharmacy, Mahasarakham University
Telephone: 0969893085, E-mail Vanlounny@gmail.com
Co-Researcher 1: Dr. Wanarat Anusornsangiam
Address: Faculty of Pharmacy, Mahasarakham University
Telephone: 043754360, E-mail: Wanarat.a@msu.ac.th
Co-Researcher 2: Asst. Prof. Dr. Pattarin Kittiboonyakun
Address: Faculty of Pharmacy, Mahasarakham University
Telephone: 043754360, E-mail: pattarin.k@msu.ac.th

Dear all participation,

You are invited to participate in this research project, before you decide to join or not. Please, carefully read all the text in this document or listen from the researcher to know why were you invited to participate in this project. This document may contain some unclear words, please ask the researcher to explain until you understand. To participation in this research project must be voluntary. No compulsion on who do not participating or withdrawing from this research project, it will not affect you anyhow. Please, do not sign document until you are sure that you wish to participate in this research project.

Background and important of the research

Warfarin remains the most widely available anticoagulant in supply chain and is the only oral anticoagulants (OACs) in the world health organization's (WHO) model list of essential medicines. Warfarin therapy could possibly lead to bleeding. To help patients recognize the signs and symptoms of bleeding or clotting from warfarin use, well knowledge on warfarin must be provided.

Research objective

Purpose of the study is to evaluate the effect of pharmacist-managed warfarin therapy on patients' clinical outcome. 60 patients will be included to the study.

Method related to research

After you consent to participate in this research project, the researcher will request to ask you following to a question form. You will be asked for a general information, your behavior of taking food and herb, your adherence for warfarin use, any adverse drug reactions events that you might meet, and your knowledge about warfarin therapy.

If you meet the criteria for inclusion, you will be invited to see a pharmacist (researcher) according to the date your doctor made an appointment. During the research project between February to June 2018 you have to meet the researcher 4 times.

Responsibilities of the volunteers participating in the research project

To make this research successful. The researcher would like to cooperate with you for 4 times. You will be asked to follow the instructions of the researcher strictly. Please, inform the abnormal symptoms that occurred to you during your participation in the research project.

For safety, to avoid drug-drug interactions, you should consult your doctor before take prescription drug and over the counter drugs. This is because the drug may affect with warfarin therapy. Therefore, please inform the researcher about the drugs you received while you were in the research project.

Risks that may be received

You might be get minimal risk such as wasting time and inconvenience. Please inform the researcher in case of your inconvenience. Side effect from warfarin usual use can be severe or normal but it is not from the study. However, you should inform the researcher immediately that you meet the event.

Risk from blood collection

The blood collection for INR test is a usual care of the hospital. The researcher will be only collected the results of INR test from patient' book. You might have the opportunity to cause pain, bleeding, bruising from blood collection. Swelling in the area of blood or blackouts and the likelihood of infection, the area where blood collection is very rare.

The benefit from this study

You will not get any benefit from participating in this research. But the study results will be implement the pharmaceutical care model for patients using warfarin at out-patient department. Participation in this research project may get benefit of better health outcomes. Or may reduce the rate of hospital admission and save money. It does not guarantee that your health will improve or the severity of the disease will decrease.

Other treatment methods available for volunteers

You do not need to join this research project for the benefit of treating by warfarin therapy. Because usual care is available for your treatment. Therefore, should read the information before deciding to participate in the research.

The practice while participant in the research

You will be interview for at 4 times during the project. Please do the following:

- Please provide your medical information in the past and present to the researcher with truth.
- Please inform the researcher of the irregularities that occurred while you participated in the research project.

- Please inform the researcher immediately. If you have received medications other than the doctor prescription for the duration of the research project.
- Please bring all of your warfarin that are left from eating to the researcher every time you make an appointment.

Possible risks of participating in the research project and the responsibilities of the researcher

If found the danger event of research, you will receive appropriate treatment immediately. A signing the consent document does not mean that you have waived the legal rights you normally have. This study is an interview by face-to-face by the questionnaire. However, if any problems arise during the study, or you need to additional information to the research, you can contact the researcher immediately at call +856-20-77714406, faculty of pharmacy, university of health sciences, Lao PDR.

Your expenses for participating in research

You will receive the intervention form a researcher in the researcher project without charge. Other expenses from usual care that are not related to research project such as medical fees and laboratory analysis fees; researcher will not be responsible for all including travel expenses.

Participation and termination of participation in the research project

Participation in this research project is voluntary. If you do not voluntarily participate in the study you can withdraw at any time. Requests for withdrawal from the research project will not affect the treatment of your disease in any way.

Protecting confidential information of volunteers

Information that may lead to your disclosure will be covered and will not be disclosed to the public. In case the research results are published. Your name and address must always be kept secret. This will only be used for your research project ID. Your data will destroy after the study was finished in the end of year 2019.

By signing the consent of the researcher. Researchers can access your medical records even after the research is completed. If you want to cancel the authorization you can notify Miss Vanlounni Sibounheuang, call +856-20-77714406.

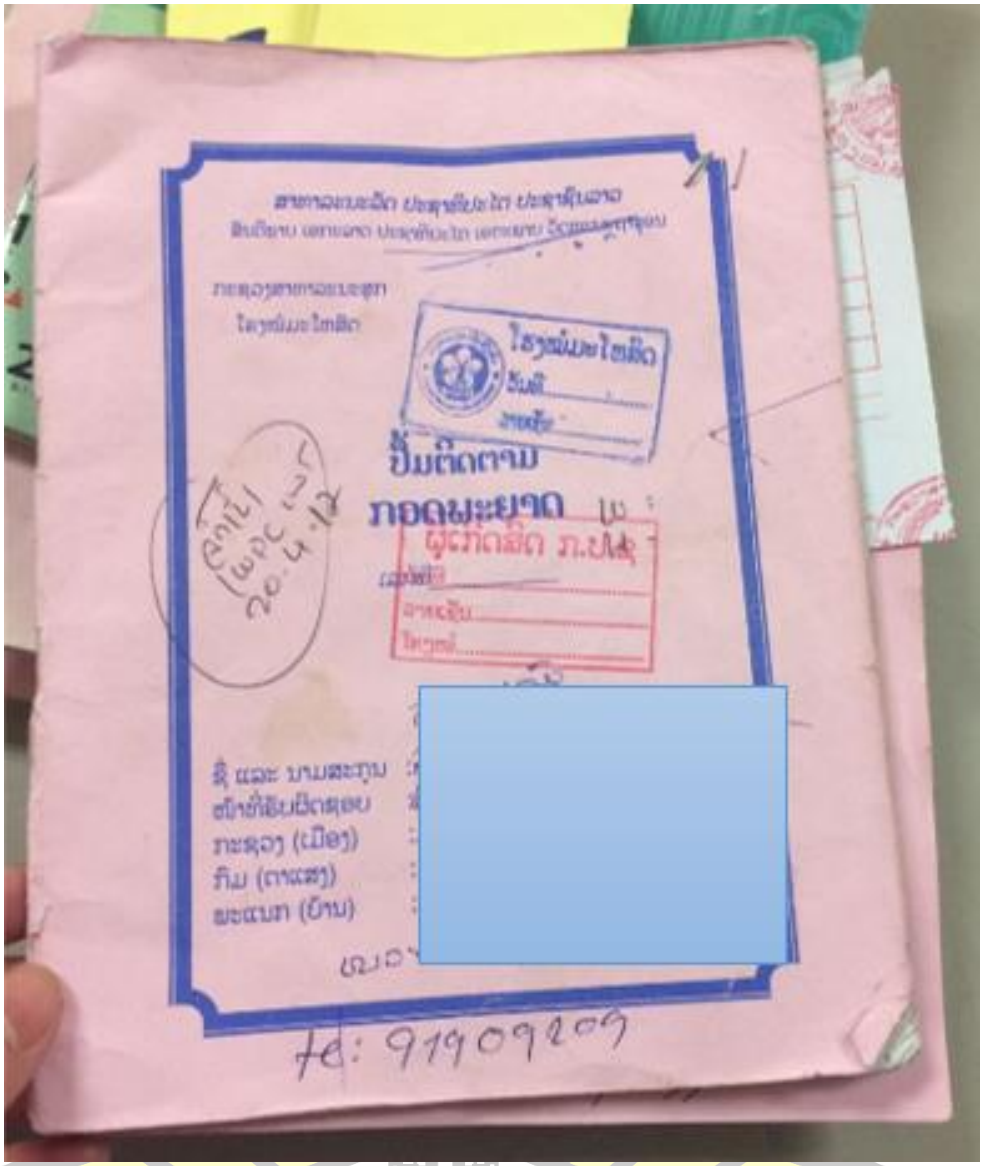
If you are not compensated for any illness that occurs directly from the research or you are not treated as shown in the information leaflet for participants in the research. You can complain the Lao PDR National Ethic Committee for Health Research, call +856-21-250670-207 or 208.

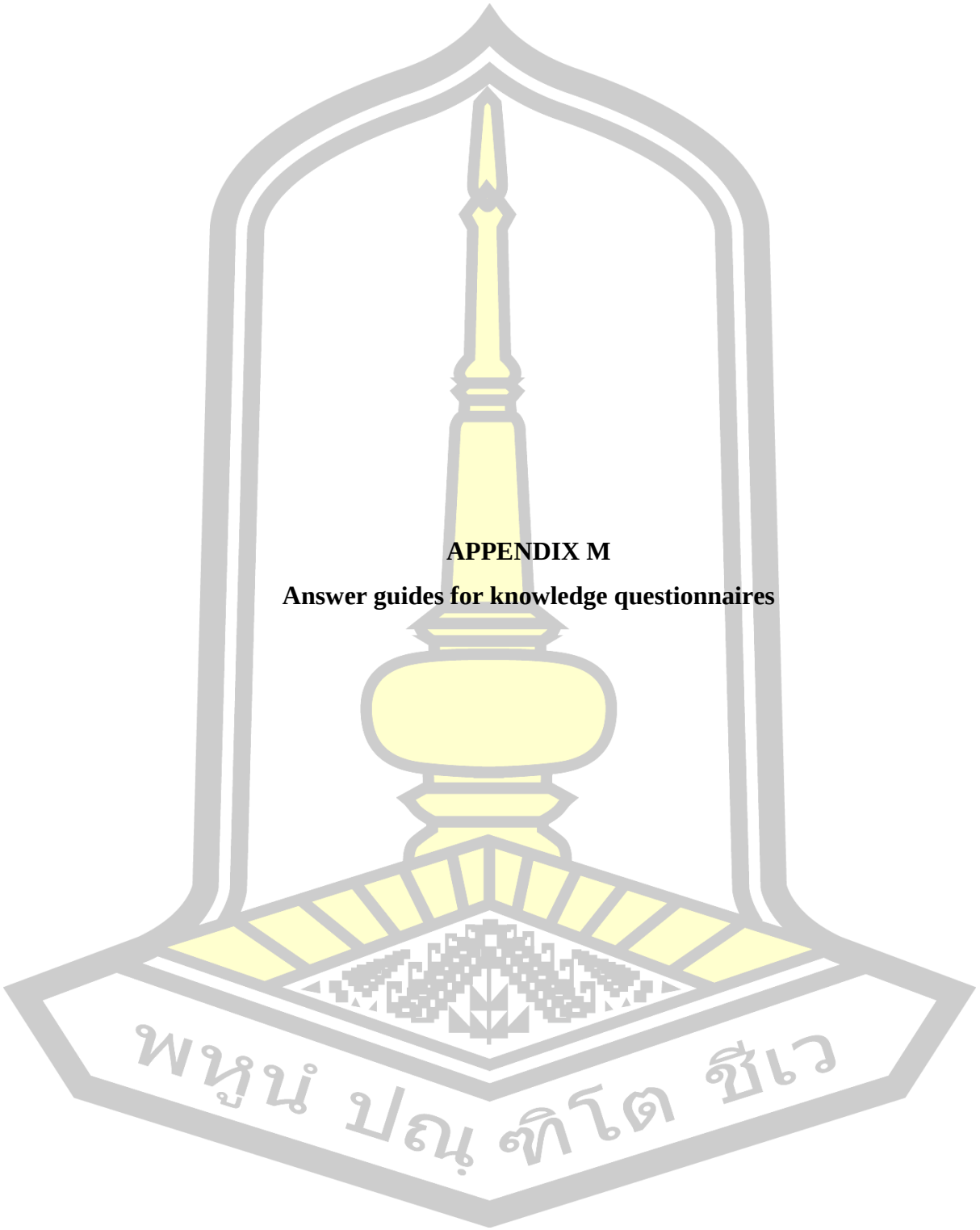
Thank you for your cooperation.

APPENDIX L

Patient books

Patient books





APPENDIX M

Answer guides for knowledge questionnaires

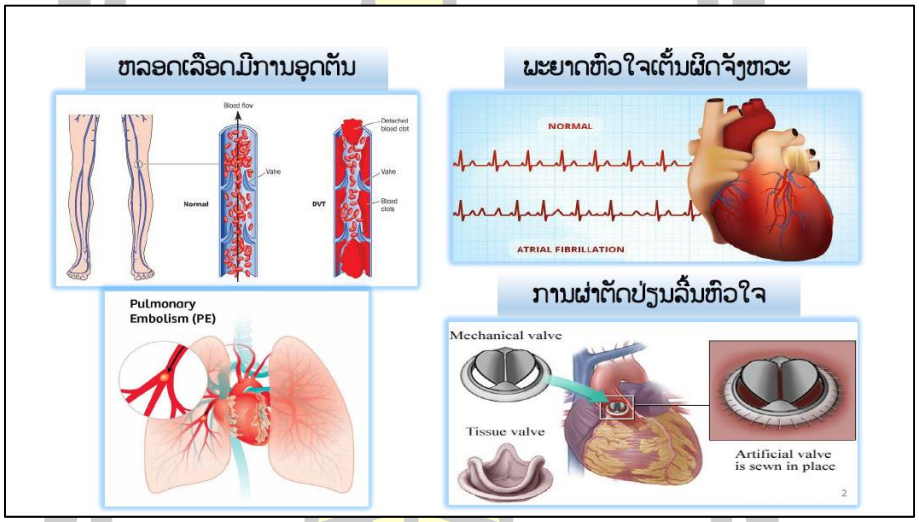
Answer guide for knowledge questionnaires

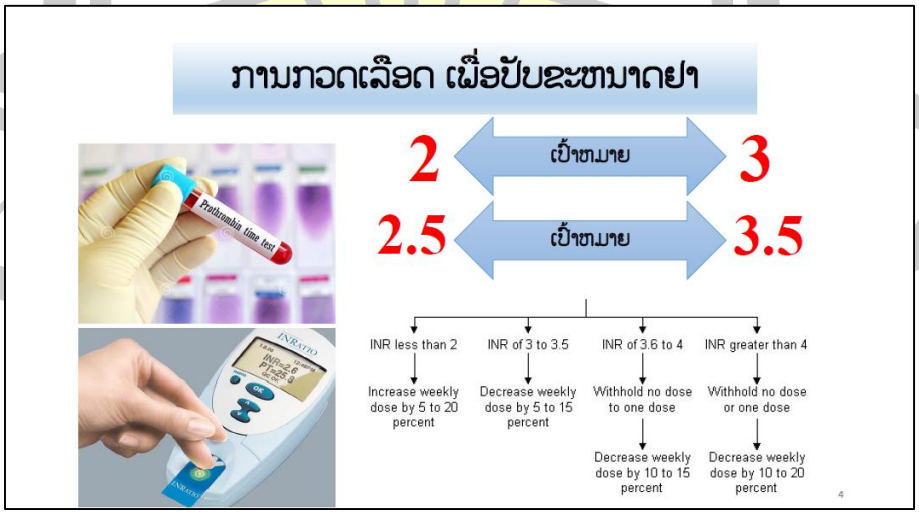
No.	Questions	Answers
1.	What is warfarin? Why you have been prescribed warfarin?	- Warfarin was used to preventing or treating blood clot - In patients with AF or VTE or MVR
2.	What is your current dose of warfarin?	Look at the patient book to see the current dose
3.	Who is responsible for adjusting your warfarin dose?	Doctor
4.	What is the important of INR testing?	To adjust warfarin dose
5.	What is your target INR?	2-3 or 2.5-3.5
6.	How frequently should you check INR?	2 weeks or 4 weeks
7.	When should warfarin be taken and why?	The same time every days
8.	What will you do in case of a missed dose?	Skip the dose if you missed it over 12 hours, then take the next dose at the normal time
9.	What will happen when you take double dose of warfarin?	INR maybe increase and patient will get a risk of bleeding
10.	What will you do in case of surgery, dental work, or some type of invasive procedures while on warfarin?	Tell your doctor that you are taking warfarin therapy
11.	Which types of foods affect warfarin therapy?	Food with high of vitamin K intake-green leafy vegetables
12.	Do you know that some of the drugs, alcohol, herbal medications can affect warfarin's action?	Drug: NSAIDs (aspirin, ibuprofen, diclofenac, naproxen, meloxicam, celecoxib), and etc. Herb (Ginger, Gingko, garlic, and etc.)
13.	What will you do in case of bleeds from nose/gum?	Do first Aid, then go to hospital if bleeding not stop
14.	What should you do if you plan to go on holidays?	While traveling, carry your medications with you at all times
15.	What are the possible side effects of warfarin?	Hematoma, blood in urine or stool, gum bleed, bleeding in any part of your body

APPENDIX N

The education tool by pharmacists for patient using warfarin

The education tool by pharmacists for patient using warfarin





ຕ້ອງໄດ້ກວດເລືອດເລື້ອຍປານໃດ?

ຮູບພາບຕົວຢ່າງປະຕິທິນການກວດເລືອດ

SUN	MON	TUE	WED	THU	FRI	SAT
		1	2	3	4	5
6	7	8	9	10	11	12
13	14	15	16	17	18	19
20	21	22	23	24	25	26
27	28	29	30	31		

ກວດທຸກໆ 1 ອາທິດ
ສຳລັບຄົນທີ່ມີຄ່າເລືອດ INR
ບໍ່ຢູ່ໃນຊ່ວງເປົ້າຫມາຍ

ກວດທຸກໆ 1 ເດືອນ
ສຳລັບຄົນທີ່ມີຄ່າເລືອດ INR
ຢູ່ໃນຊ່ວງເປົ້າຫມາຍ

5

ກໍລະນີລືມກິນຢາຕ້ອງເຮັດແນວໃດ?

ຖ້າລືມກິນຢາ
ເກີນ 12 ຊົ່ວໂມງ
ໃຫ້ຂ້າມຢາມື້ນັ້ນໄປເລີຍ

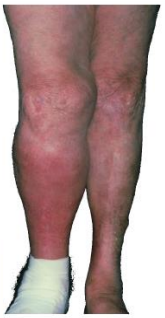
6

ຄວາມສ່ຽງທີ່ຈະເກີດເມື່ອລືມກິນຢາ

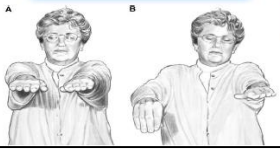
ເຈັບຫົວຫລາຍກວ່າປົກກະຕິ

ປາກບ້ຽວ / ເວົ້າອອກສຽງລຳບາກ

ຂາບວມ ແດງ ອອກຮ້ອນ



ແຂນ ຂາ ອ່ອນແຮງ

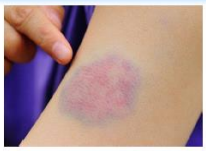


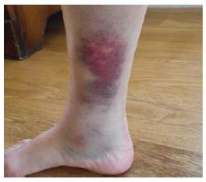
ຖ້າມີອາການດັ່ງກ່າວນີ້
ໃຫ້ມາຫາແພດທັນທີ

7

ຄວາມສ່ຽງເມື່ອກິນຢາເກີນຂະໜາດ

ມີຮອຍຊ້ຳຕາມຕົນໂຕເປັນຈ້ຳໆ





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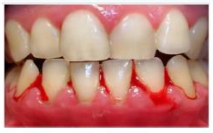


ເລືອດດັ່ງອອກ/ຮາກອອກເລືອດ

ຢ່ຽວ ຫລື ອາຈົມ ເປັນເລືອດ/ເປັນສີດຳ

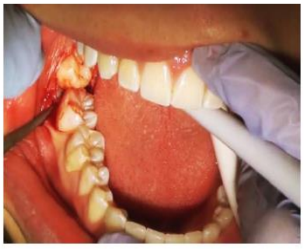
ຖ້າມີອາການດັ່ງກ່າວນີ້ ໃຫ້ຢຸດກິນຢາ ແລະ ມາຫາແພດທັນທີ

8

ຕ້ອງບອກໃຫ້ທຸກຄົນຮູ້ວ່າກຳລັງກິນຢາວາຟາຣິນຢູ່

ກ່ອນໄປຊື້ຢາ ຢູ່ຮ້ານຂາຍຢາ

ກ່ອນໄປພົບ ທ່ານໝໍ / ທ່ານໝໍແຂ້ວ



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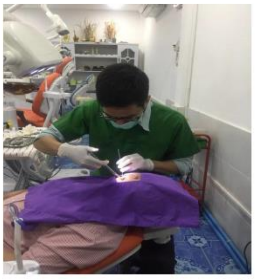


9

ອາຫານທີ່ມີວິຕາມິນເຄສູງ / ຢາບາງຊະນິດ ຈະຫລຸດການອອກລິດຂອງຢາວາຟາຣິນ

10

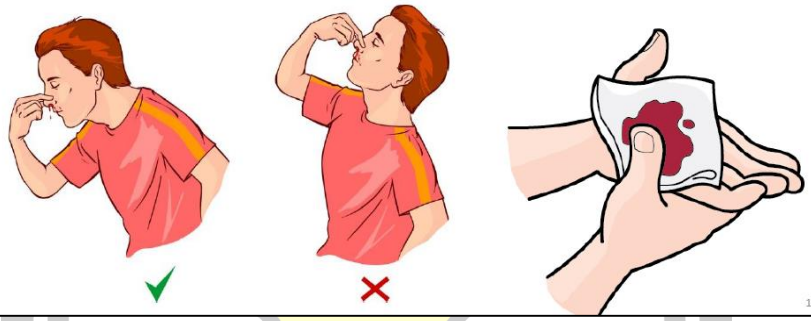
ຢາ/ ສະຫມຸນໄພ / ອາຫານເສີມ ບາງຊະນິດ ເພີ່ມຄວາມສ່ຽງຂອງການເກີດເລືອດໄຫລ

ຢາກຸ່ມ NSAIDs

- Aspirin
- Ibuprofen
- Diclofenac
- Naproxen
- Meloxicam
- Celecoxib

11

ກໍລະນີມີເລືອດໄຫລຜິດປົກກະຕິ ໃຫ້ເຮັດການປະຖົມພະຍາບານຂັ້ນຕົ້ນ ກ່ອນໄປພົບທ່ານຫມໍ



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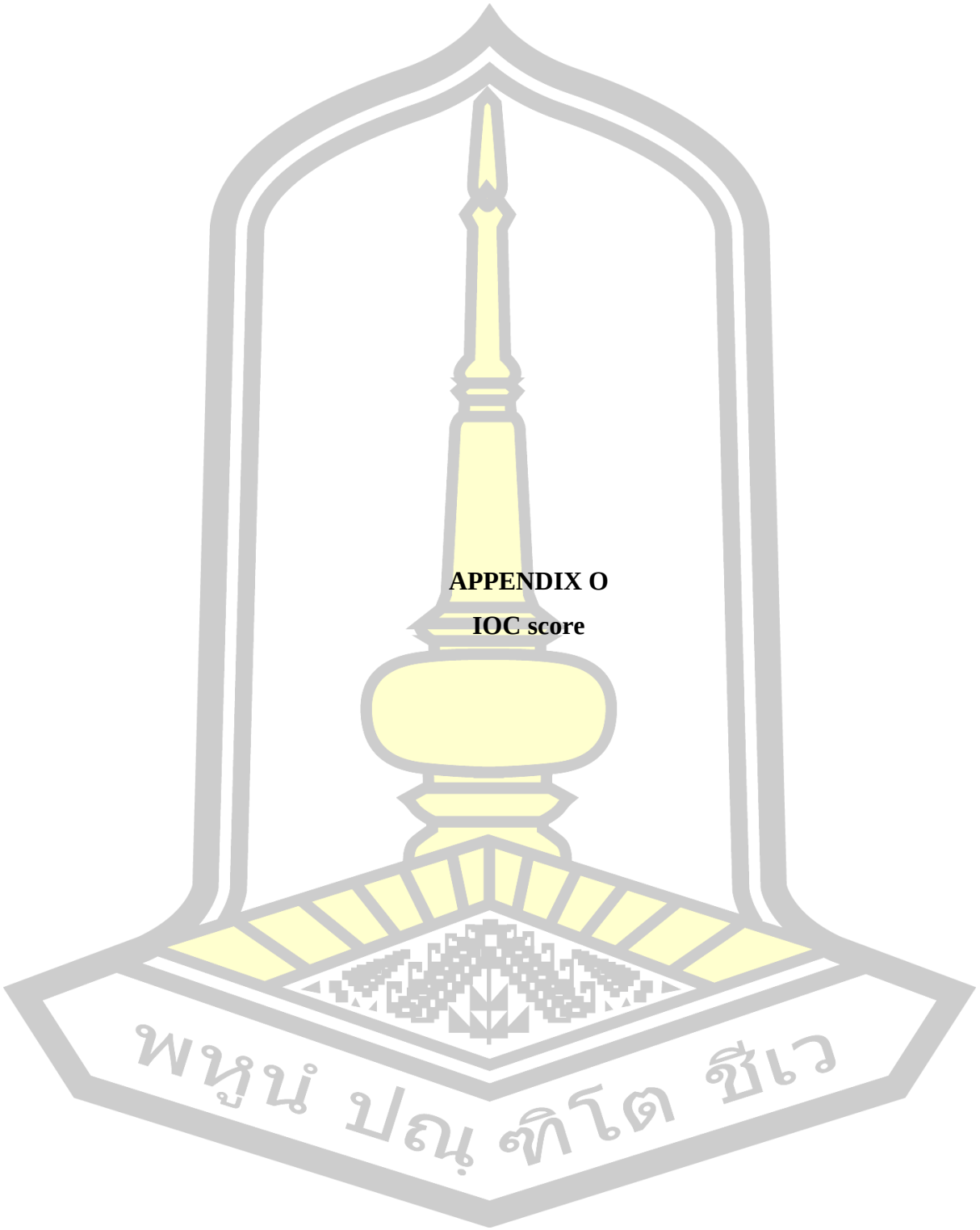

APPENDIX O

IOC score

IOC score

+1 = Agreement, 0 = Not assurance, and -1 = No agreement

Patients' data collecting form

	Content/Rating	+1	0	-1	Comment
Part 1: General information					
1	Gender: Male, Female				
2	Age				
Part 2: Efficacy outcomes					
3	Indication:				
	AF				
	VTE				
	MVR				
	Others				
4	Target INR range				
	2-3				
	2.5-3.5				
	Others (>3.5)				
5	Duration with warfarin therapy				
6	Result for INR test				
7	Comorbidities				
8	Medication use				
9	Food interaction with warfarin				
10	Herb interaction with warfarin				
Part 3: Patient adherences					
11	Do you ever forget to take your warfarin?				
12	Do you ever have problems remembering to take your warfarin?				
13	When you feel better, do you sometimes stop taking your warfarin?				
14	Sometimes if you feel worse when you take warfarin, do you stop taking it?				
Part 4: ADRs					
15	Major bleeding				
16	Minor bleeding				

Patients' knowledge

Q	Content/Rating	+1	0	-1	Comment
1	What is warfarin? Why you have been prescribed warfarin?				
2	What is your current dose of warfarin?				
3	Who is responsible for adjusting your warfarin dose?				
4	What is the importance of INR testing?				
5	What is your target INR?				
6	How frequently should you check INR?				
7	When should warfarin be taken and why?				
8	What will you do in case of a missed dose?				
9	What will happen when you take double dose of warfarin?				
10	What will you do in case of surgery, dental work, or some type of invasive procedures while on warfarin?				
11	Which types of foods affecting warfarin therapy?				
12	Do you know that some of the drugs, alcohol, herbal medications can affect warfarin's action?				
13	What will you do in case of nose/gum bleeding?				
14	What should you do if you plan to go on holidays?				
15	What are the possible side effects of warfarin?				

Score

1. Patients' data collecting form (15 items)					
Q	Expert rater no. 1	Expert rater no. 2	R	N	IOC
1.	1	1	2	2/2	1
2.	1	1	2	2/2	1
3.	1	1	2	2/2	1
4.	1	1	2	2/2	1
5.	1	1	2	2/2	1
6.	1	1	2	2/2	1
7.	1	1	2	2/2	1
8.	1	1	2	2/2	1
9.	1	1	2	2/2	1
10.	1	1	2	2/2	1
11.	1	1	2	2/2	1
12.	1	1	2	2/2	1
13.	1	1	2	2/2	1
14.	1	1	2	2/2	1
15.	1	1	2	2/2	1
16.	1	1	2	2/2	1
Patients' knowledge (15 items)					
Q	Expert rater no. 1	Expert rater no. 2	R	N	IOC
1.	1	1	2	2/2	1
2.	1	1	2	2/2	1
3.	1	1	2	2/2	1
4.	1	1	2	2/2	1
5.	1	1	2	2/2	1
6.	1	1	2	2/2	1
7.	1	1	2	2/2	1
8.	1	1	2	2/2	1
9.	1	1	2	2/2	1
10.	1	1	2	2/2	1
11.	1	1	2	2/2	1
12.	1	1	2	2/2	1
13.	1	1	2	2/2	1
14.	1	1	2	2/2	1
15.	1	1	2	2/2	1

APPENDIX P

DRPs assessment in the intervention group

DRPs assessment in the intervention group

Visit	No.	DRP type	Age	Gen-der	Indication	INR	Management with doctors or patients	Accept
Base-line visit	1	(1)	78	M	AF	1.3	(a)	Yes
	2	(1)	44	F	MVR	2.2	(a)	No
	3	(1)	38	M	MVR	1.2	(a)	No
	4	(1)	40	F	AF	1.7	(a)	No
	5	(1)	57	F	MVR	2.2	(a)	No
	6	(1)	55	M	AF	1	(a)	Yes
	7	(1)	60	M	AF	1.2	(a)	Yes
	8	(1)	59	F	MVR	1.9	(a)	No
	9	(1)	36	F	MVR	2.2	(a)	No
	10	(1)	36	M	MVR	2.1	(a)	No
	11	(1)	46	F	MVR	1.7	(a)	No
	12	(1)	53	M	MVR	1.1	(a)	Yes
	13	(3)*	30	M	MVR	1.8	(a) (b) (c)	Yes
	14	(4)	40	F	AF	1.7	(a) (d)	Yes
	15	(4)	60	M	AF	1.2	(a) (d)	Yes
	16	(4)	46	F	AF	2.0	(a) (d)	Yes
	17	(4)	25	F	MVR	2.2	(a) (d)	Yes
	18	(4)	46	F	MVR	1.7	(a) (d)	Yes
	19	(5)	55	F	MVR	2.2	(a) (e)	Yes
	20	(5)	25	F	MVR	2.2	(a) (e)	Yes
	21	(5)	36	M	MVR	2.1	(a) (e)	Yes
1st visit	1	(1)	38	F	MVR	2.0	(a)	Yes
	2	(1)	55	M	AF	1.5	(a)	No
	3	(1)	47	F	MVR	2.1	(a)	No
	4	(1)	67	F	AF	1.7	(a)	Yes
	5	(1)	39	M	MVR	1.9	(a)	No
	6	(1)	51	F	MVR	1.9	(a)	No
2nd visit	1	(1)	38	F	MVR	2.2	(a)	No
	2	(1)	57	F	MVR	2.1	(a)	No
	3	(1)	47	F	MVR	1.9	(a)	No
	4	(1)	36	M	MVR	2.1	(a)	Yes

	5	(1)	39	M	MVR	1.7	(a)	Yes
	6	(1)	39	F	MVR	2.1	(a)	No
	7	(2)	63	M	AF	3.5	Decrease dosage regimen per week for 5-10 %	Yes
	8	(3)*	40	F	MVR	2.6	(a) (b) (c)	No
3rd visit	1	(1)	40	F	AF	1.7	(a)	No
	2	(1)	59	F	MVR	2.1	(a)	Yes
	3	(1)	36	F	MVR	2.1	(a)	No
	4	(1)	36	M	MVR	2.2	(a)	No
	5	(1)	39	M	MVR	2.1	(a)	No
	6	(1)	46	F	MVR	1.7	(a)	No

(1) Sub-therapeutic dosage, (2) Over dosage, (3) Drug-drug interaction, *warfarin with acetaminophen, (4) Food-drug interaction, (5) Alcohol-drug interaction, (a) Continues warfarin same dose and monitor, (b) Patient counselling especially focuses on drug-drug interaction with warfarin, (c) Tell patient to use acetaminophen not exceed 4g per day, (d) Patient counselling especially focus on food-drug interaction, (e) Patient counselling especially focus on alcohol-drug interaction, M is male and F is female, Accept was mean doctor or patient accepted DRPs and solve the problems.

APPENDIX Q

DRPs assessment in the control group

DRPs assessment in the control group

No.	DRP type	Age	Gender	Indication	INR	Management with doctors or patients	Accept
1	(1)	46	F	MVR	2.1	(a)	No
2	(1)	48	F	MVR	2.1	(a)	No
3	(1)	50	F	MVR	1.9	(a)	No
4	(1)	73	F	AF	1.4	(a)	No
5	(1)	47	M	MVR	1.4	Increase dosage regimen per week for 10 to 20 %	No
6	(3)*	86	M	AF	1.9	(a) (b)	No
7	(4)	45	F	MVR	2.1	(a) (d)	Yes
8	(4)	48	F	MVR	2.1	(a) (d)	Yes
9	(4)	40	F	DVT	2.5	(a) (d)	Yes
10	(4)	75	M	AF	2.2	(a) (d)	Yes
11	(4)	41	F	MVR	3.4	(a) (d)	Yes
12	(4)	24	F	MVR	2.4	(a) (d)	Yes
13	(5)	64	F	MVR	2.7	(a) (e)	Yes
14	(5)	60	M	MVR	2.7	(a) (e)	Yes
15	(5)	30	M	MVR	2.9	(a) (e)	Yes

(1) Sub-therapeutic dosage, (2) Over dosage, (3) Drug-drug interaction, * warfarin with simvastatin, (4) Food-drug interaction, (5) Alcohol-drug interaction, (a) Continues warfarin same dose and monitor, (b) Patient counselling especially focuses on drug-drug interaction with warfarin, (c) Tell patient to use acetaminophen not exceed 4g per day, (d) Patient counselling especially focus on food-drug interaction, (e) Patient counselling especially focus on alcohol-drug interaction, M is male and F is female, Accept was mean doctor or patient accepted DRPs and solve the problems.

APPENDIX R

Ethical approval

Lao People's Democratic Republic
Peace Independence Democracy Unity Prosperity
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Ministry of Health
National Ethics Committee
for Health Research (NECHR)

No 17 /NECHR
Vientiane Capital 31/01/2019

Approval Notice

Ms Vanlounni Sibounheuang
Email: vanlounnysbh@gmail.com
Tel: 020 77714406

RE: Ethical Approval for Health Research

Title: "Development of Pharmacist-managed Warfarin Therapy at Mahosot Hospital, Lao PDR" (Submission ID: 2019.3.Vie)

Dear Ms Vanlounni Sibounheuang

The National Ethics Committee for Health Research of the Lao People's Democratic Republic have reviewed and approved your research.

Please note the following information about your approved research protocol:

Approval period: February 2019 – February 2020
Approved Subject Enrollment: 77
Study Site: Vientiane Capital
Sponsor: by self. **Budget**: 5 000 000 Kip (LAK)
Implementing Panel/Project Investigator: Ms Vanlounni Sibounheuang

Please note that the Ethics Committee reserves the right to ask for further questions, seek additionnal or monitor the conduct of your research and consent process.

Principle Investigator is required to notify the Secretary of the National Ethic Committee for Health Research:

- **Any significant change to the project and the reason for that change, including an indication of ethical implications (if any);**
- **Serious adverse effects on participants and the action taken to address those effects;**
- **Any other unforeseen events or unexpected developments that merit notification;**
- **The inability of the Principal Investigator to continue in that role, or any other change in research personnel involved in the project;**
- **Any expiry of the insurance coverage provided with respect to sponsored clinical trials and proof of re-insurance;**
- **A delay of more than 12 months in the commencement of the project; and,**
- **Termination or closure of the project.**

Additionally, the Principal Investigator is required to submit a progress report on the anniversary of approval and on completion of the project.

President of National Ethics Committee for Health Research

Prof.Dr. Douangdao SOUKALOU

MAHASARAKHAM UNIVERSITY ETHICS COMMITTEE FOR RESEARCH INVOLVING HUMAN SUBJECTS

Certificate of Approval

Approval number: 026 / 2019

Title : Development of Pharmacist-managed Warfarin Therapy at Mahosot Hospital, Lao PDR. (Phase I)

Principal Investigator : Miss Vanlounni Sibounheuang

Responsible Department : Faculty of Pharmacy

Research site : Mahosot Hospital, Lao PDR

Review Method : Expedited review

Date of Manufacture : 20 February 2019 **expire :** 19 February 2020

This research application has been reviewed and approved by the Ethics Committee for Research Involving Human Subjects, Mahasarakham University, Thailand. Approval is dependent on local ethical approval having been received. Any subsequent changes to the consent form must be re-submitted to the Committee.

.....

(Assoc.Prof. Thiensak Meldkapanopas)

Chairman

Approval is granted subject to the following conditions: (see back of this Certificate)

MAHASARAKHAM UNIVERSITY ETHICS COMMITTEE FOR RESEARCH INVOLVING HUMAN SUBJECTS

Certificate of Approval

Approval number: 079 / 2019

Title : Development of Pharmacist-managed Warfarin Therapy at Mahosot Hospital, Lao PDR. (Phase II)

Principal Investigator : Miss Vanlounni Sibounheuang

Responsible Department : Faculty of Pharmacy

Research site : Lao

Review Method : Expedited review

Date of Manufacture : 26 March 2019 **expire :** 25 March 2020

This research application has been reviewed and approved by the Ethics Committee for Research Involving Human Subjects, Mahasarakham University, Thailand. Approval is dependent on local ethical approval having been received. Any subsequent changes to the consent form must be re-submitted to the Committee.

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(Assoc.Prof. Thiensak Mekkaparopas)

Chairman

Approval is granted subject to the following conditions: (see back of this Certificate)

BIOGRAPHY

NAME	Vanlounni Sibounheuang
DATE OF BIRTH	10/11/1993
PLACE OF BIRTH	Vientiane capital city, Lao PDR
ADDRESS	House number 102, Unit 10, Kang Village, Hardxaifong District, Vientiane, Lao PDR
POSITION	Assistant Lecturer at Faculty of Pharmacy, University of Health Sciences, Vientiane, Lao PDR
PLACE OF WORK	Department of Pharmaceutical Care, Faculty of Pharmacy, University of Health Sciences, Samsenthai Rd, Kaoyord Village, Sisattanak District, Vientiane, Lao PDR, Zip code 7444
EDUCATION	2016 Bachelor's degree of Pharmacy, Faculty of Pharmacy, University of Health Science, Lao PDR 2019 Master degree in Clinical Pharmacy, Faculty of pharmacy, Mahasarakham University, Thailand
Research grants & awards	Thesis support fund for graduate students, Faculty of Pharmacy, year 2018