Effect of modified TaWai mobile system on adverse drug reaction reports in Lao PDR

Niphonh Mongkhonmath

A Thesis Submitted in Partial Fulfillment of Requirements for

degree of Doctor of Philosophy in Pharmacy

May 2023

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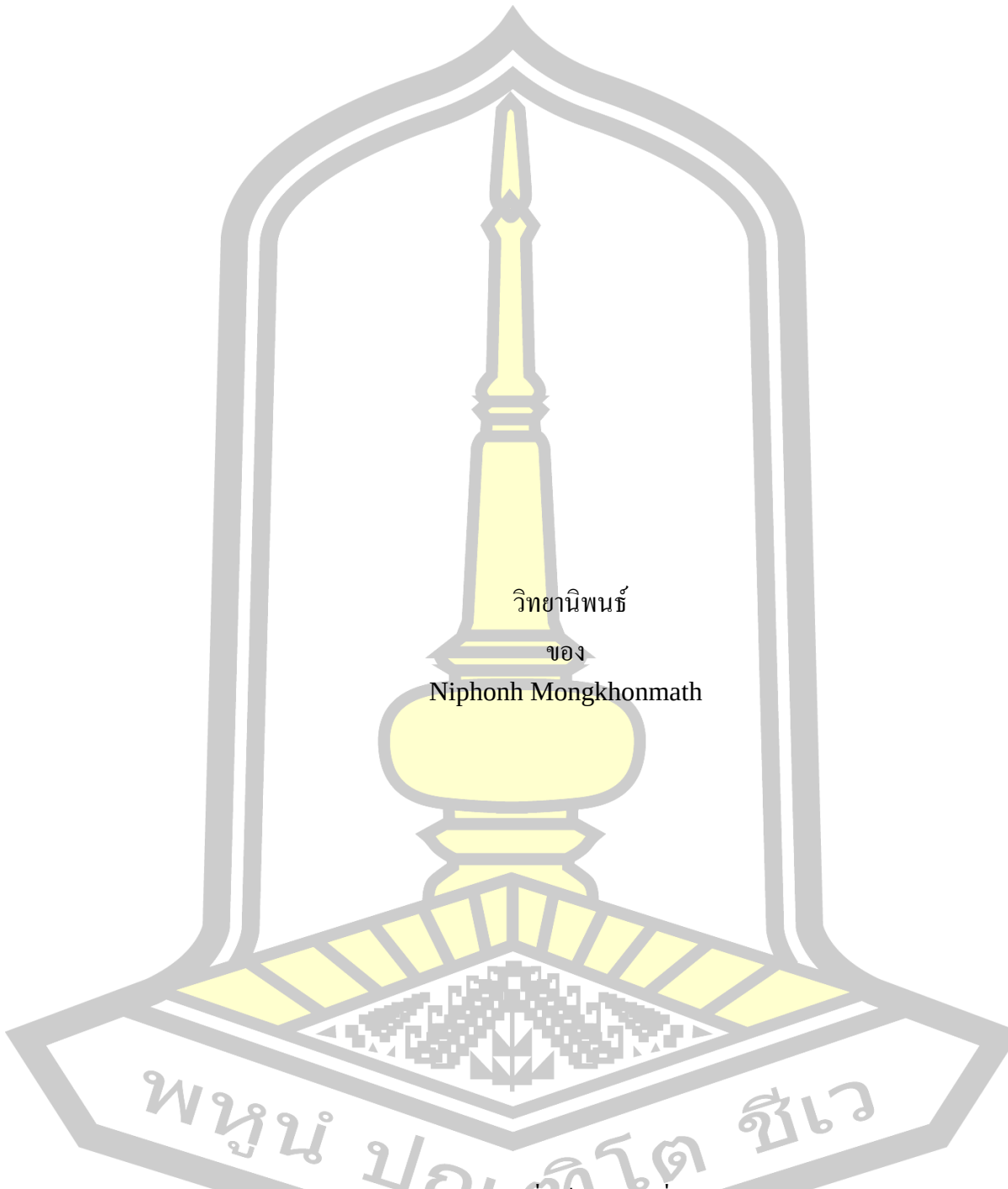

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ABSTRACT

Background: Adverse drug reactions (ADRs) are major global public health problems and one of the leading causes of morbidity, mortality, and hospitalization. ADRs will continue to pose a threat to public health as long as drugs are being used to treat various ailments. Pharmacovigilance (PV) is one of the main tools for monitoring patient's safety through detecting problems associated with medicines use and assessing their benefits and effectiveness to strike through maximize therapeutic outcomes. However, the under-reporting of ADRs is the main challenge of PV systems worldwide, especially in low/middle income countries (LMICs) including Lao PDR. This study aimed to determine the effectiveness of all available tools for enhancing ADRs reports, develop a modified TaWai mobile tool in Lao version, and evaluate effects of the modified TaWai in reporting ADRs in Lao PDR.

Methods: The methodology of this study was divided into 3 phases. Phase 1: A systematic review and meta-analysis was performed to determine effectiveness of available tools for enhancing ADR reports. Five databases were systematic searched from inception through September 2021. Two reviewers performed study selection, data extraction, and quality assessment independently. Data were evaluated and analyzed using a random-effects model. Heterogeneity was evaluated using I^2 and chi-squared tests. Phase 2: Tawai for health in Lao version was developed as chatbot by adapting the template of TaWai for health in Thai version. The situation match for Lao PDR, such as pharmacovigilance and the regulation of ADR report or law related to ADR report in Lao PDR, were used to develop the detail of each component of TaWai chatbot in Lao version. The Lao version was back-to-back-translated from the Thai version, and content validity was performed. Phase 3: A cluster- randomized controlled trial (RCT) was conducted to evaluate the effects of a modified Tawai mobile system for enhancing ADRs reports in Lao PDR from May to August 2022. The group of healthcare professionals (HCPs) in tertiary hospitals at Lao PDR were randomized to intervention or control group. Both groups were trained about ADRs and ADR reports but intervention group was received addition training on using modified TaWai mobile tool for ADR report. Outcomes of interest were rate and

quality of ADRs report, and satisfaction of HCPs.

Result: In phase 1 study, a total of 12 studies (9 RCTs and 3 Non-RCTs) with 24,298 participants were included but only eight studies were analyzed in meta-analysis. Interventions evaluated in included studies were educated of HCPs in different strategies used to improve ADR reporting including face to face workshop (n=9 studies), repeated telephone (n=2), and email or letter (n=2). Meta-analysis indicated that using all interventions increased number of overall ADRs report with risk ratio (RR) 4.80 (95% confidence interval (CI) 2.44 to 9.41, I^2=83%, n = 8). However, based on types of interventions, only educated HCPs by face to face workshop can increase ADRs report with risk ratio (RR) 4.39 (95%CI 2.81 to 6.81, I^2= 79 %, n = 6). In phase 2, the modified TaWai tool in Lao version was developed. The content validity test indicated that this tool is representative of the domain being assessed/ interest in ADR report. In phase 3, 16 and 18 HCPs were included in the intervention and control groups, respectively. Age, experience, and characteristics of HCPs in both groups were comparable. Rate of ADRs report in intervention group was higher than those in control group (28 vs. 3 report in 4 months). The number of high quality reports in the intervention group were also higher than those in the control group (28 vs 2 reports). One report in control group was judged as low quality report because there was no several key information including seriousness of the reaction, date to start/ stop of drug, date of the reaction start/stopped, comorbidity, dose of use, frequency, dosage form, route of administration, and the detail of reporter. In addition, the HCPs satisfied to used modified TaWai tool to report ADRs in hospital setting.

Conclusion: TaWai program intervention showed an improvement in ADRs report at the hospital and had a benefit for providers at PV center in collecting data. TaWai mobile App were reduced time, quickly to report ADRs, and it also gave a high satisfaction of HCPs to use TaWai mobile showed that is suitable appropriate to the context for HCPs report ADRs at the hospital in Lao PDR. In the future will do many department or difference hospital to support this TaWai tool.

Keyword : Adverse drug reaction reporting system, ADRs report promote tool, pharmacovigilance, adverse drug event, clinical controlled trial

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CHAPTER 1

Introduction

1.1 Background

Adverse drug reactions (ADRs) are major global public health problems and one of the leading causes of morbidity, mortality, and hospitalization. ADRs will continue to pose a threat to public health as long as drugs are being used to treat various ailments.(1) There are approximately 3-5% of the hospital admissions in France caused by ADRs (2), and one in 10 hospitalized patients has experienced ADRs in Europe. ADRs are one of the 10 leading causes of morbidity and mortality in the USA. It also caused to deaths approximately 197,000 persons/year in Europe.(3) Regarding to the health care system's burden at any certain point of time from a prospective study in UK, 800-bed hospitals may be occupied with ADRs patients admitted. The economic effects of the ADRs are significant; in the USA, the cost per ADR in the intensive care unit (ICU) and non-ICU wards has been estimated at USD 19,685 and USD 13,994, respectively.(4)

Pharmacovigilance (PV) is one of the main tools for monitoring patient's safety through detecting problems associated with medicines use and assessing their benefits and effectiveness to strike through maximize therapeutic outcomes. However, under-reporting of ADRs is the main challenge of pharmacovigilance systems worldwide, especially in spontaneous reporting systems. In previous study report that less than 10% of detected ADRs are effectively reported to medicine regulatory authorities.(5)

According to the under-reporting of ADRs, several studies examining the effects of tools or activities on promoting ADRs reports and detecting ADRs in healthcare institutions have been performed and implemented in practice.(2, 6, 7) In hospitalized patients, ADRs have been reported particularly serious events. The national pharmacovigilance programs direct more to patient self-reports of ADRs. These reports can be submitted online in many countries such as the USA, Canada, Australia, New Zealand, Kenya, and Malaysia.(6) The US Food and Drug Administration (FDA) has been gathering ADR reporting from both health care professionals (HCPs) and consumers since its inception in the 1960s. Reports can be submitted by phone or e-mail or uploaded directly online. The number of online reports has increased to 45%, especially by HCPs.(7)

Worldwide collections of ADRs on intensive medication are now collected via the internet and smartphone. The smartphone might become the leading technique in low and middle-income countries (2) where broad mobile phone service can

manage cheaper than internet communication. Internet-based methods to ensure drug safety and Pharmacovigilance are spreading rapidly. Pharmacovigilance agency websites are ever more welcoming of spontaneous ADR reporting. Meanwhile, new mobile apps are being developed to allow ADR reporting anywhere, anytime.(2) In Europe, some enterprises are developing user-friendly apps that enable everyone to use a smartphone or tablet to make spontaneous ADR reporting.(7)

"TaWai for Health" is a system of tools for reporting ADR and monitoring the safety of health products, including medications, herbal medicine, food supplement, and cosmetics. It cooperates between the public and private sectors to see the various problems. It has been developed and authorized by researchers from the Prince of Songkla University, Songkla, Thailand. This tool is composed of the report of ADRs, the suspect products, and exaggerated advertisements. The benefits of the TaWai for Health care system are helping monitor health products and reducing the problems from using of dangerous medicines that are illegally available in general stores. It improves the efficiency of medical uses and health products. Furthermore, it helps reduce the harm caused by the use of unnecessary medicines and reduces the government expenditures for detecting product hazards.(8)

In Lao PDR, the rate of ADR reporting to PV center is very low. According to previous data, only 22 spontaneous ADR reporting have been submitted to the PV center from 2016 to 2019.(9) Based on previous survey in Lao PDR, the low rate of ADR reporting is a lot of routine work and lack of time to report. There was no severe ADR, and the physicians feel that ADR reporting increase their workload, and there was no feedback after reporting. These reasons related to the common causes of low rate of ADR reporting from previous literature (10) , which the main problems of ADR reporting are a lot of usual workloads and lack of time, problems related to the organization and activities of the PV system, and problems related to potential conflicts.(10) Moreover, previous studies in the United Kingdom reported about factors related to underreporting of ADRs, including wants to keep the report or publish it as its work (ambition), not interested in the report (ignorance), lack of confidence in the report (diffidence), unsure if ADR or not, and often claimed that the barn and no time (lethargy).(11)

Although many tools and strategies are available for enhancing ADR reporting in several countries such as Thailand, Malaysia, USA, Canada(8), the studies evaluating and implementing these tools in Lao PDR are limited. In addition underreporting of ADRs is still a major problem of the pharmacovigilance system in Lao PDR. Therefore, this study was review the types, characteristics, and effectiveness of available tools for enhancing ADR reporting around the world. Then, good features of effectiveness tools appropriated outcomes and appropriated study designs for implementing and assessing tools was used to develop and implement a tool system for enhancing ADRs report at hospital in Lao PDR.

1.2 General objective

To evaluate the effects of modified TaWai mobile system for enhancing adverse drug reaction reports in Lao PDR.

Specific objectives:

2.1 To identify and assess types, characteristics, and effectiveness of available tools for enhancing ADR reporting by using systematic review and meta-analysis method

2.2 To develop a TaWai mobile tool in Lao version for reporting adverse drug reaction by modifying an available tool TaWai in Thai version.

2.3 To evaluate effects of the modified TaWai mobile for reporting adverse drug reaction in Lao PDR by using the cluster randomized controlled trial (cluster-RCT).

1.3 Research questions

How are the effects of modified TaWai mobile system in Lao PDR?

1.4 Definition of research

1.4.1 Modified TaWai mobile system is the TaWai for ADR reporting application in Lao version modified from TaWai for Health in the Thai version. This application is available on the mobile phone.

1.4.2 Adverse drug reaction is a response to a harmful, unintended medicine and occurs at doses normally used for the prophylaxis, diagnosis or therapy of disease. In this study, we use the ADR definition according to WHO definition.(12)

1.4.3 HCP in this study is doctors and pharmacists at Mahosot and Setthathilad hospital.

1.4.4 Effectiveness of tool is a tool that have a benefit and quality to report ADRs. It's measured by HCPS that used TaWai tool at hospital

1.4.5 Tertiary hospital in Lao PDR is a central hospital with three locations in Laos including Setthathirath, Mahosot, and Mittaphab Hospitals.

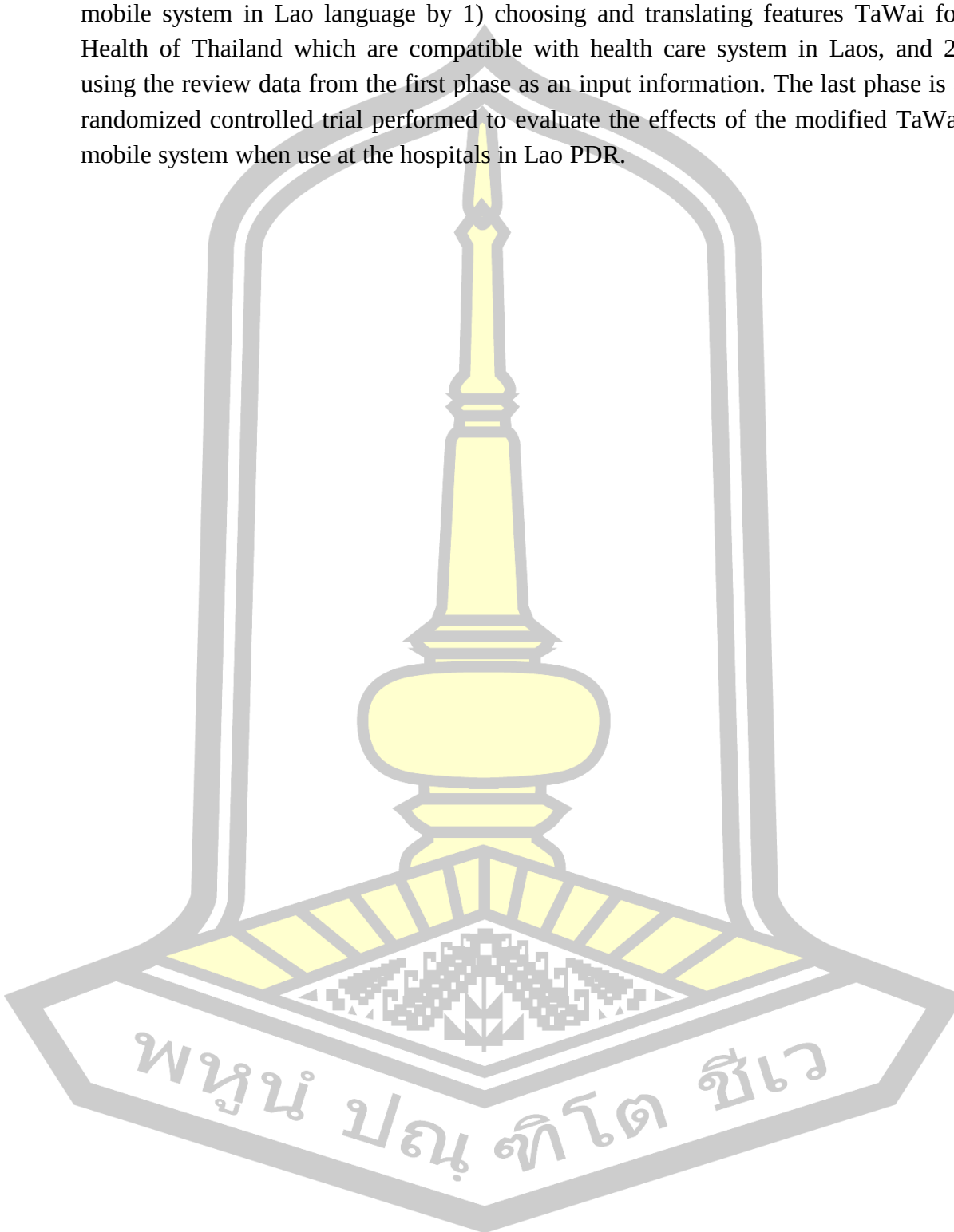
1.4.5 ADR rate is number of ADR report by HCPs at hospital in Lao PDR.

1.5 Scope of the research

There are 3 phases of the study, including 1) Review phases, 2) Tool development phase, and 3) Evaluation phase.

In this study, the first phase was a systematic review and meta-analysis performed to identify and assess types, characteristics, and effectiveness of available

tools for enhancing ADR reporting. The second phase is to develop a modified TaWai mobile system in Lao language by 1) choosing and translating features TaWai for Health of Thailand which are compatible with health care system in Laos, and 2) using the review data from the first phase as an input information. The last phase is a randomized controlled trial performed to evaluate the effects of the modified TaWai mobile system when use at the hospitals in Lao PDR.



1.6 Conceptual framework

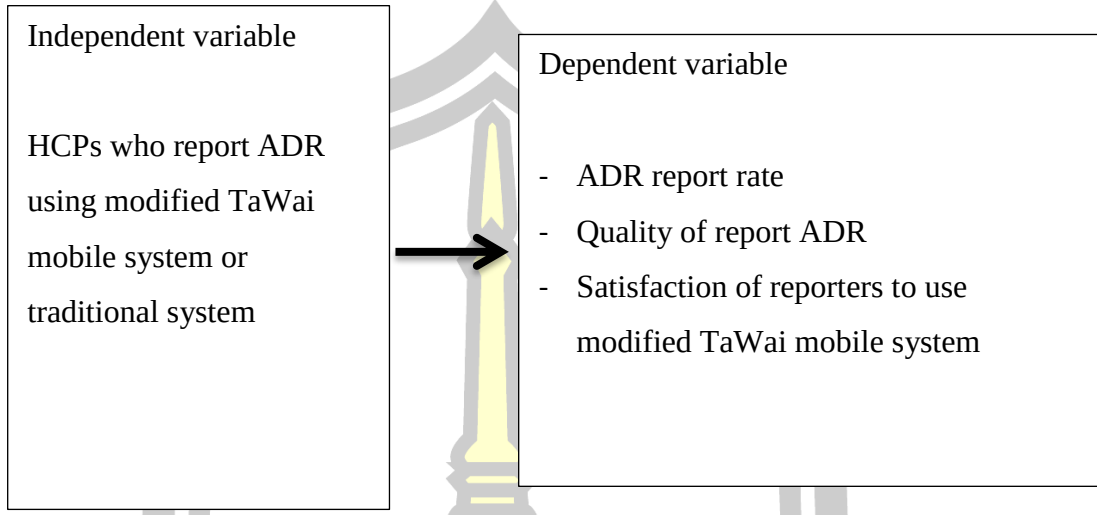


Figure 1: Conceptual framework of RCT

1.7 Expected Benefits

1.7.1 To be an input information for HCPs to aware of drug safety in the hospital in Lao PDR.

1.7.2 To be a model for developing the health system tool in pharmacovigilance in Lao PDR.

1.7.3 To get copyright of TaWai tool in Lao version for ADRs report at the hospital in Lao PDR (Lao version).

CHAPTER 2

Review Literature

2.1 Adverse drug reactions (ADRs)

2.1.1 Definition and epidemiology of ADRs

The World Health Organization (WHO) has defined adverse drug reaction (ADR) as “a noxious and unintended response to a drug which occurs at normal doses for the prophylaxis, diagnosis or treatment of a disease, or for modifications of physiological function”.(12) Adverse drug reactions (ADRs) are the most common public health problem worldwide and it is one of the leading causes of morbidity, mortality, and hospitalization.(13) The incidence of ADRs in each country is very different, because there were differences in the prescribing behavior, race, and genetics of the patients. In Europe, adverse drug reactions (ADRs) contribute to a considerable number of morbidity and mortality.(13) It has been estimated that approximately 5 % of all hospital admissions are caused by ADRs. There are approximately 3-5% of the hospital admissions in France caused by ADRs(2), and one in 10 hospitalized patients has experienced ADRs in Europe. ADRs are one of the 10 leading causes of morbidity and mortality in the USA. It also caused approximately 197,000 deaths in Europe.(3) The most recent data from the WHO European Hospital Morbidity Database reports that almost 419,000 people die from ADRs each year in Europe.(14)

Several studies report that the incidences of ADRs in hospitals are 10-30%.(14-16) In addition, 2.9-6.2% of patients with ADRs have to admit, and 1-11% of patients with ADRs have to stay in hospitals longer than those patients without ADRs.(17, 18) Problems related to ADRs affect healthcare costs by approximately $ 5.6 million per year.(19)

2.1.2 Types of Adverse Drug Reactions (ADRs)

ADRs can be categorized into several types depended on criteria for classification. However, the most common types are divided by characteristics or mechanisms of ADRs.(15, 16) Based on their characteristics or mechanisms, ADRs can be classified into 4 types as follows:

1) Type A (dose-related or Augmented) ADRs

Type A ADR is an ADR that can be predicted from the pharmacological action of the drug. The severity of this ADR type will be related to the dose of use. This type of ADRs can be prevented and corrected by reducing the dose, changing drug use, the combination of other drugs to reduce any adverse reactions from drugs, or changing the way of administering them. The incidence of type A ADRs is approximately 85-90% of all ADRs, but mortality from this type of ADR is low. Examples of this type of ADR include:

- Diazepam induced drowsiness
- Ototoxicity and Nephrotoxicity from Aminoglycosides
- Dry mouth, urinary retention from Antihistamine

2) Type B (non-dose related or Bizarre) ADRs

Type B ADR is not related to the pharmacological activity of the drug. It is independent of the dose. Therefore it is difficult to predict or prevent an event. Usually, an incidence of type B ADR is low (less than 20% or approximately 1: 10,000 or 1: 100,000). However, this type of ADRs result in more mortality rate than those in type A ADR. When ADR occurred, the drug had to be stopped immediately. Examples of this type of ADR include:

- Anaphylactic shock, urticaria from Penicillins
- Stevens-Johnson Syndrome from Sulfa drugs
- Agranulocytosis from Chloramphenicol

3) Type C (Continuous or Chronic) ADRs

Type C ADR is caused by prolonged drug use, unexpectedly, but there may be some predictable groups of drugs. Examples of this type of ADR include:

- Chloroquine induced retinopathy
- Drug addiction from Benzodiazepines

4) Type D (Delayed) ADRs

This type of ADR occurs after a long period of discontinuation of drug use. It is a long-latent type, such as cancer, early malformation in pregnant. Examples of this type of ADR include:

- Cervical cancer from Diethylstilbestrol
-Teratogenic effect from Thalidomide, Phenytoin

2.1.3 The severity of ADR symptoms

The severity of ADR symptoms presents in different manners including mild, moderate, and severe as shown below.

1) Mild or minor ADR is few ADR symptoms with no treatment needed. The drug may be stopped or not stopped.

2) Moderate ADR usually occurs on major organs. Patients with moderate ADR symptoms needs to be treated, hospitalization or stay in the hospital for at least 1 day.

3) Severe ADR is an ADR occurring with important organs, severe and death. This ADR is required hospital stay or intensive medical care such as Steven Johnson Syndrome (SJS), Toxic epidermal necrosis (TEN), Anaphylactic shock.

2.1.4 Methods for reporting ADR

In general, the country's ADR monitoring center has a platform or an ADR reporting forms to report the ADR occurring in hospital or healthcare setting. The healthcare professionals have a role to records or report ADRs using the form and sent ADR reporting to the PV center of each country. Reporting ADR by healthcare professionals may be required by law or a voluntary report depending on the policy of each country. For example, ADR was voluntarily reported to PV center in Lao PDR through electronic mail, post, and fax to the ADR center of the country directly.(20)

The suspected symptoms or adverse event occur during drug used may be related or not related to the drug. Therefore, the likelihood of adverse event should be analyzed and assessed based on several information including symptoms, drugs used, and patient data. The detail of each information should be provided in ADR reporting was shown below. (15, 20)

1) Patient information: patient identification number (HN), age, gender, patient health condition, etc.

2) Suspected symptoms: symptom characteristics, location of symptoms or events, time of occurrence, symptoms after discontinuation or when repeated drug (if any), laboratory results (if any), the severity of symptoms

3) Suspected drug: name of drug, lot number, the manufacture, dosage form, date of use and stop suspected drugs, indication of drug use

4) The concomitant drugs: this includes the patient's own medications, herbal medicines, and supplementary products: name of the drug, the manufacture, dosage form, indications for use, date of use and discontinuation of drug use.

5) Risk factors of the patient: history of the disease or comorbidity such as liver disease, kidney disease, drug allergy history etc.

The data obtained was used to assess the association of ADR with suspected drug by using the World Health Organization criteria (The WHO causality assessment of ADR reporting) (21) or by causality assessment tool for each country set. The popular tool is Naranjo's algorithm.

2.1.5 Naranjo's Algorithm (ADR probability scale Naranjo's Algorithm)

The ADR probability scale Naranjo's Algorithm consisted of 10 standard questions with a score for each question ranging from +2 to -1. The meaning of total score was shown below.

Total score <9 = Certain or Definite high probable

5-8 = Probable

1-4 = Possible

<0 = Not likely (Doubtful or Unlikely).

Table 1 Example of assessment the likelihood of adverse reactions from drug using of Naranjo's Algorithm

Standard question	Yes	No	Unknown	Score
1. ເຄີຍມີສະຫຼຸບ ຫຼື ລາຍງານປະຕິກິລິຍານີ້ກັບຢາທີ່ສົງໃສມາແລ້ວ 1. Have ever been concluded or reported this reaction to this drug of suspicion	+1	0	0	
2. ອາການບໍ່ພຶງປາດຖະໜາເກີດຂຶ້ນຫຼັງຈາກໄດ້ຮັບຢາທີ່ສົງໃສ 2. An adverse reaction occurred after the suspected drug was administered.	+2	-1	0	
3. ອາການບໍ່ພຶງປາດຖະໜາດີຂຶ້ນເມື່ອຢຸດຢາທີ່ສົງໃສ 3. Adverse reactions improved when discontinuation of the intended drug	+1	0	0	
4. ອາການບໍ່ພຶງປາດຖະໜາເກີດຂຶ້ນອີກເມື່ອເຈົ້າໃຫ້ຢາທີ່ສົງໃສຄືນ 4. Adverse reactions recur when reuse the drug	+2	-1	0	

Table 1 (continue)

Standard question	Yes	No	Unknown	Score
5. ປະຕິກິລິຍາທີ່ເກີດຂຶ້ນສາມາດເກີດຈາກສາເຫດອື່ນນອກຈາກຢາທີ່ສົງໃສ 5. The reaction can be caused by other drugs suspected	-1	+2	0	
6. ປະຕິກິລິຍາເກີດຂຶ້ນອີກເມື່ອໄດ້ຮັບຢາຫຼອກ 6. The reactions were repeated when the placebo was given	-1	+1	0	
8 ປະຕິກິລິຍາຮ້າຍແຮງເກີດຂຶ້ເມື່ອເພີ່ມຂະໜາດຢາ ຫຼື ຫຼຸດຂະໜາດຢາ 8. Severe reactions occur when the dose is increased or decreased	+1	0	0	
9. ຄົນເຈັບເຄີຍມີປະຕິກິລິຍາແພ້ຢາຄືກັນນີ້ມາແລ້ວເມື່ອໄດ້ຮັບຢາຄັ້ງກ່ອນ 9. The patient had a similar reaction to the previous dose	+1	0	0	
10. ອາການບໍ່ເຜິ່ງປາດຖະໜາຕາມີຫຼັກຖານໄດ້ຮັບການຍືນຍອມໂດຍວິທີ່ອື່ນທີ່ເໝາະສົມ 10. The adverse reaction has been evidenced by an appropriate method	+1	0	0	

2.1.6 Evaluation of health products against adverse drug reaction

1) Product reaction (ADR / Vaccine reaction) identify the probability level

Probability level is defined as the results of an assessment of the degree of suspected drug association with an adverse event classified into 5 levels as follows:

1.1) **Certain** is defined as clinical symptoms including laboratory abnormalities that have characteristic as follow

1. Occurred during the period consistent with the use of the suspected drug.

2. It cannot be described by existing disease or by other drugs or chemicals.

3. When you stop using the drug, you have a noticeable improvement in symptoms or recovery.

4. If there is a need to re-use the drug. Adverse events that can be described by pharmacological activity or as evident adverse events must occur clear.

1.2) **Probable** means a case of clinical symptoms including abnormal laboratory results that have characteristic as follow

1. Occurred during the period consistent with the suspected drug use, and

2. Not likely to be related to an existing disease or other drugs or chemicals, and

3. When the drug was stopped in question, symptoms improved or recover from that symptom, but

4. There is no information on the repeated use of the drug.

1.3) Possible means in cases clinical symptoms include laboratory abnormalities that have characteristic as follow

1. Occurred during the period consistent with the use of the drug in question, but

2. Can be described by existing diseases or other drugs or chemicals used in combinations.

3. No information about suspected or incomplete discontinuation of the drug

1.4) **Unlikely** means in cases of clinical symptom including abnormal laboratory results that have characteristic as follow

1. The duration of symptoms inconsistent with the duration of drug use; and

2. It can be clearly explained by existing disease or other drug or chemical combination.

1.5) Cannot be divided into level **(Unclassified)** it means no data to indicate the relevance of the health product to the occurrence of the adverse event, please specify the reasons.

2.2 Definition and importance of ADR monitoring

ADR monitoring is a process of continuously monitoring undesirable effects suspected to be associated with medicinal products. Usually, this process occurs after the medicine is launched in the market. ADR monitoring system is a system used for collecting, classifying, and analyzing new information of ADRs from reliable scientific resources, and then the content and any action were taken on specific drug based on the new information of ADRs. After that the information will be circulated or reported to all health sectors. ADR monitoring system is an important process in the healthcare system because ADRs data are limited and drug-drug interactions are frequently not identified in clinical studies. Therefore, post-marketing surveillance or ADRs monitoring system is performed for several objectives as follows.

1) To detect the nature and frequency of ADRs

2) To assist the Drug Regulatory Authority, Public Health Programs, Scientists and Consumer Society to minimize ADRs

3) To provide updated Drug Safety Information to Health Care Professionals

4) To upgrade package insert and design appropriated package insert information and dissemination of information for marketing

5) To disseminate safety information by designing proper education program to consumers

6) To identify risk factors that may predispose, induce or influence the development, severity and incidence of ADRs.(22)

2.3 Steps of ADRs monitoring

There are 4 important steps in ADRs monitoring. The concept of each step is shown below.

2.3.1 Identifying adverse drug reaction (ADR)

The first step of ADR monitoring is to identify ADRs. In this step definition of ADRs is important thus reporter should understand the ADR definition. Although several ADR definitions exist, the WHO definition is internationally accepted and most widely used. According to WHO definition, therapeutic failures, intentional and accidental poisonings, drug abuse, and adverse events due to errors in drug administration or noncompliance (taking more or less of a drug than the prescribed amount) are excluded. ADRs are mainly identified in the pre-marketing studies and in the post-marketing surveillance studies. Disadvantages of the pre-marketing studies are lack sufficient knowledge to extrapolate information collected from animal studies directly into risks in humans and very few numbers subjects (not more than 4000). Another major disadvantage is that clinical trials cannot be done in the rare group of subjects such as children, the elderly, and pregnant women. In addition, clinical or pre-marketing studies cannot generate information on long-term adverse effects. Therefore, only clinical or pre-marketing studies type A ADR is known during clinical or pre-marketing studies. So, all other types of ADRs can only be identified in post-marketing surveillance.(8) Nowadays, 3 methods are used for identifying adverse drug reactions of post-marketing surveillance.

1) Anecdotal reporting

The majority of the first reports of ADR come through anecdotal reports from individual doctors when a patient has suffered some peculiar effect. Such anecdotal reports need to be verified by further studies, and these sometimes fail to confirm the problem.

2) Intensive monitoring studies

Intensive monitoring studies provide a systematic and detailed collection of data from well-defined groups of inpatients. The surveillance is done by specially trained health care professionals who devote their full-time efforts towards recording all the drugs administered and all the events, which might conceivably be drug-induced. Subsequently, statistical screening for the drug-event association may lead to special studies.(8)

3) Spontaneous reporting system (SRS)

Spontaneous reporting system (SRS) is the principal method used for monitoring the safety of marketed drugs. In UK, USA, India, and Australia, the ADR monitoring programs in use are based on spontaneous reporting systems. In this system, clinicians are encouraged to report any reaction related to drug use. Usually, attention is focused on new drugs and serious ADRs. The rationale for SRS is to generate signals of potential drug problems, identify rare ADRs and theoretically monitor continuously all drug used in a variety of real conditions from the time they are first marketed.(21) The strengths of this method are simple, effective, inexpensive and continuous. In addition, ADRs from uncommonly used medicines or ADR rarely reported from other methods may be detected. However, the weakness of this method is under-reporting, vary of report rate, and clinical information supplied is limited.

2.3.2 Assessing causality between drug and suspected reaction

Causality assessment is the method to assess the relationship between a drug and a suspected reaction is established. There are 3 approaches to assess causality including opinion of an individual expert, the opinion of a panel of experts, and formal algorithms.(21)

For the opinion of an individual expert approach, an individual expert in the area of ADRs would evaluate the case. In the process of evaluation, the expert may consider and critically evaluate all the data obtained to assess whether the drug has caused the particular reaction. A panel of experts adopts a similar procedure to arrive at a collective opinion. Using formal algorithms, collected data is subjected and critically assessed by using one or more standard algorithms. Some of the important algorithms used are Naranjo, WHO, European ABO system, Kramer, Bayesian, and French imputation method.

There is no gold standard for the causality assessment method. The categorization of the causal relationship between a drug and suspected adverse reactions varies with the scale adopted. WHO scale categorizes the causality relationship into certain, probable, possible, unaccessible/unclassifiable, unlikely, conditional /unclassifiable. The Naranjo's scale categorizes the reaction as definite, probable, possible or unlikely. In general, the following 4 different basic points can be considered in attributing a clinical adverse event to the drug including temporal time relationship between suspected reaction and drug, de-challenge (cessation of drug), re-challenge, (reintroducing drugs), and likelihood of other possible causes.(21)

2.3.3 Documentation of ADR in patient's medical records

After identifying and assessing the causality of ADR, documentation of ADR in patient's medical records should be done. This process is used for alerting clinicians and other health care professionals to the possibility of a particular drug causing the suspected reaction.

2.3.4 Reporting serious ADRs to Pharmacovigilance centers /ADR regulating authorities

According to FDA, a serious reaction is classified as fatal, life-threatening, prolonging hospitalization, and causing a significant persistent disability, resulting in a congenital anomaly and requiring intervention to prevent permanent damage or resulting in death.

Hatwig SC et al, categorized ADRs into 7 levels as by their severity. Level 1 and 2 are categorized to mild ADR whereas level 3 and 4 are categorized to moderate ADR, and level 5, 6 and 7 are categorized to severe ADR.(23)

Karch and Lasanga classified severity into minor, moderate, severe and lethal.(24) In minor severity, there is no need for antidote, therapy or prolongation of hospitalization. To classify as moderate severity, a change in drug therapy, specific treatment, or increased in hospitalization by at least one day is required. Severe class includes all potentially life-threatening reactions causing permanent damage or requiring intensive medical care. Lethal reactions are the one which directly or indirectly contributes to the death of the patient. Different ADR regulatory authorities are - Committee on the safety of medicine (CSM), adverse drug reaction advisory committee (ADRAC), MEDWATCH, Vaccine Adverse Event Reporting System. WHO-UMC international database maintains all the data of ADRs.(21)

2.4 Component or information required for ADR reporting

There are 5 components or required information for ADR reporting.

1) Patient Information: name the patient, age, sex history of drug allergy etc.

2) ADRs Description: date of founding the symptom, level of symptom severity.

3) Information Related to Suspected Drug(s): Name of drug, company of manufacture, dosage, instructions for use, date of use and stop using drugs, indications of that drug

4) Information on Management of ADR

5) Information about the reporter: doctors, pharmacists, and nurses

2.5 ADRs monitoring and reporting system in Lao PDR

There is only one national pharmacovigilance (PV) center in Lao, PDR. This center was officially inaugurated in the year 2012. The PV center communicates all ADR reporting data to WHO –UMC for incorporating in the international database.

Spontaneous report system (SRS) is an approach process to monitor and report ADR at hospital in Lao PDR. In this system, doctors will identify patient's ADRs. The doctors will assess causality between drug and suspected reaction. After that, important component of ADR reporting will be reported to the pharmacist. The pharmacist will collect data and record ADR reporting form. Then the pharmacist will send the report to the PV center. After that, the PV center collect data, evaluates and synchronizes information to WHO- UMC.

Although Lao PDR has PV center and system to report ADR, currently the number of ADR reporting is very low when compared with other countries. For example, in Settathilad hospital, one of the tertiary hospital in Lao PDR where uses SRS approach to monitor and report ADRs, the number of ADR reporting is approximately 6 cases per year. Previous data indicated that there are only 5, 2, 3, and 15 cases of ADR reporting in years 2017, 2018, 2019, and 2020, respectively. Although underreporting of ADRs is a common problem in the SRS, there is no tool to enhance ADR reporting in Settathilad hospital in Lao PDR. In addition, there is no trial to evaluate factors related to low ADR reporting.

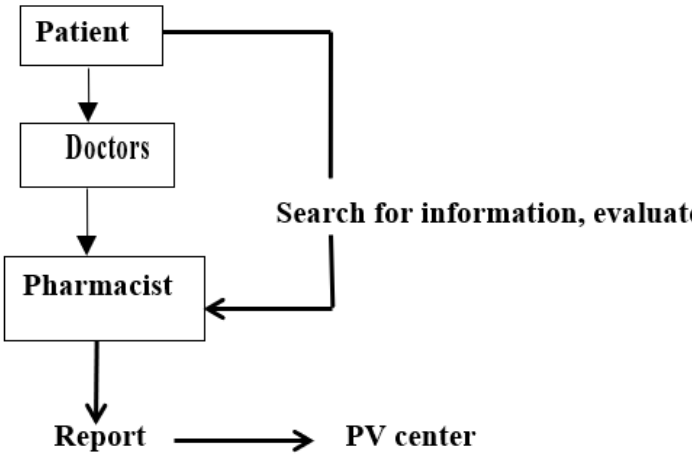


Figure 2: Procedures for ADR reporting of the Settathilad hospital

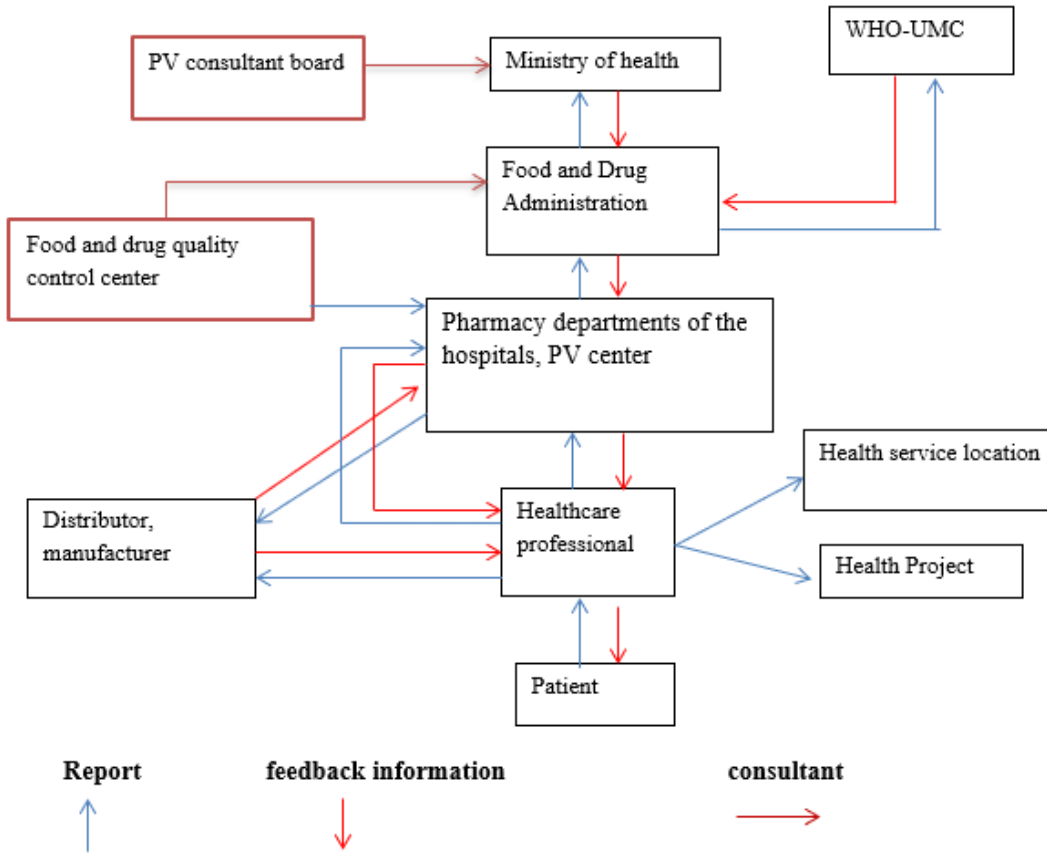
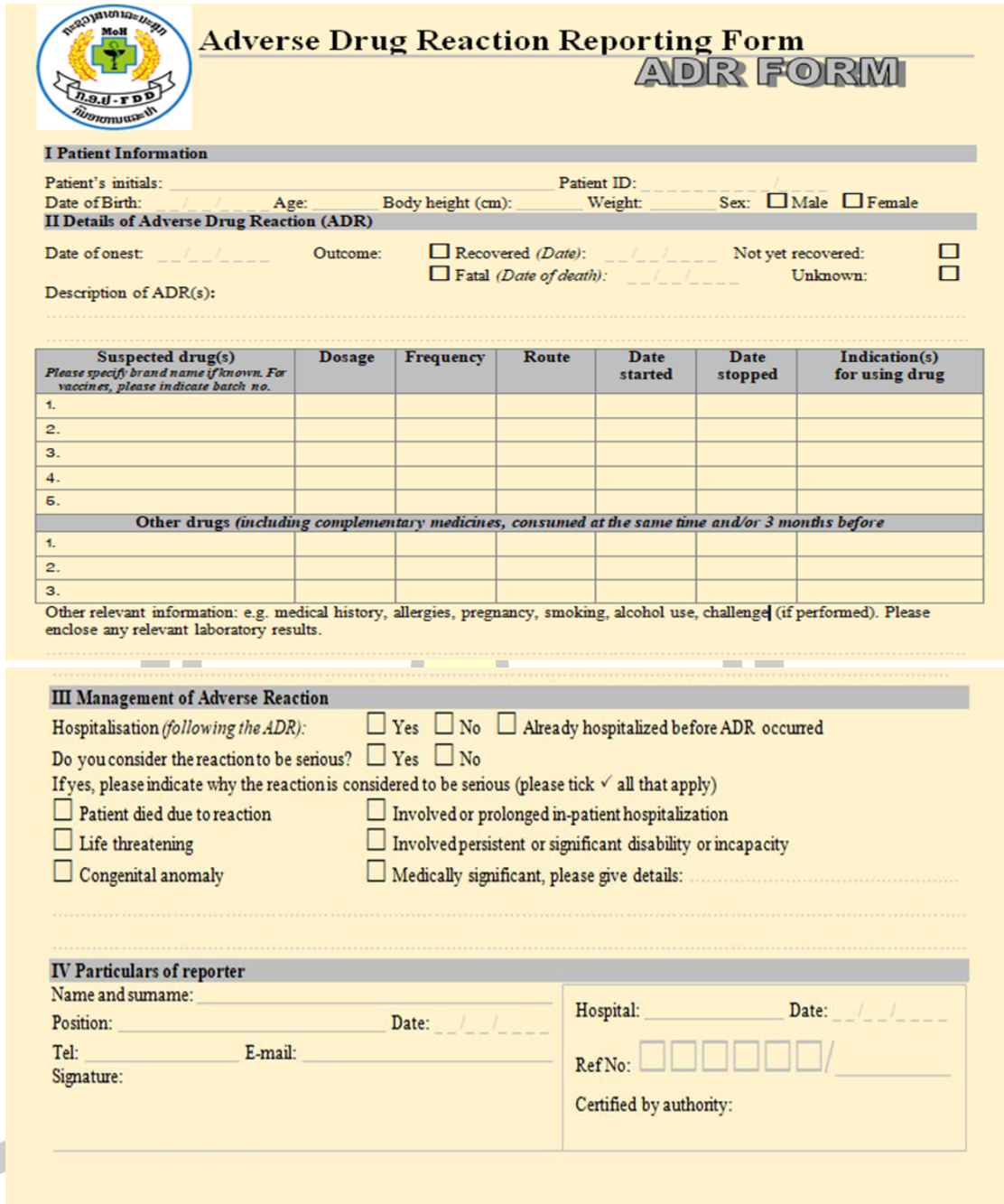


Figure 3: Procedures for ADR reporting of the national level in Lao PDR.(25)



Adverse Drug Reaction Reporting Form

ADR FORM

I Patient Information

Patient's initials: _____ Patient ID: _____

Date of Birth: __/__/____ Age: _____ Body height (cm): _____ Weight: _____ Sex: ☐ Male ☐ Female

II Details of Adverse Drug Reaction (ADR)

Date of onest: __/__/____ Outcome: ☐ Recovered *(Date)*: __/__/____ Not yet recovered: ☐

☐ Fatal *(Date of death)*: __/__/____ Unknown: ☐

Description of ADR(s):

Suspected drug(s) *Please specify brand name if known. For vaccines, please indicate batch no.*	Dosage	Frequency	Route	Date started	Date stopped	Indication(s) for using drug
1.						
2.						
3.						
4.						
5.						
Other drugs *(including complementary medicines, consumed at the same time and/or 3 months before*						
1.						
2.						
3.						

Other relevant information: e.g. medical history, allergies, pregnancy, smoking, alcohol use, challenge (if performed). Please enclose any relevant laboratory results.

III Management of Adverse Reaction

Hospitalisation *(following the ADR)*: ☐ Yes ☐ No ☐ Already hospitalized before ADR occurred

Do you consider the reaction to be serious? ☐ Yes ☐ No

If yes, please indicate why the reaction is considered to be serious (please tick ✓ all that apply)

☐ Patient died due to reaction ☐ Involved or prolonged in-patient hospitalization

☐ Life threatening ☐ Involved persistent or significant disability or incapacity

☐ Congenital anomaly ☐ Medically significant, please give details: .....

IV Particulars of reporter

Name and surname: _____

Position: _____ Date: __/__/____

Tel: _____ E-mail: _____

Signature:

Hospital: _____ Date: __/__/____

Ref No: ☐☐☐☐☐☐/_____

Certified by authority:

Figure 4: Spontaneous report ADRs form.(25)

2.6 Pharmacovigilance (PV) system in Lao PDR

The World Health Organization (WHO) defines PV as “the science and activities relating to the detection, collecting, researching, assessment, understanding, evaluating information from healthcare providers and patients on the adverse effect of medication, biological products, herbals, vaccines, medical device, traditional and complementary medicines with a view to identify new information about risk associated with products and prevention of adverse effects or any other possible drug-related problems that cause harm to patients”. According to the WHO Program for International Drug Monitoring (WHO PIDM), the purpose of PV program is to address patient safety in relation to the use of medicines globally. Many initiatives to support PV activities have been undertaken including the Strengthening Pharmaceutical Systems (SPS) Program in developing countries.(26, 27)

Lao PDR is a low to middle income country in the Asia region. The establishment of the PV system in Lao PDR follows the WHO Pharmacovigilance Drug Monitoring Program and covers the following 5 main parts of PV system including 1) Protection, policy, and law 2) Systems, structures and coordination of relevant parts 3) Signal type and protection information 4) Evaluation and risk assessment and 5) Control and risk communication.

Since PV system is important for patient safety, pharmacovigilance (PV) center in Lao PDR has been established for several reasons. The main purposes for the establishment of the PV Center in Lao PDR are:

1) To improve the treatment of patient health by collecting data, analysis and managing reports on health problems associated with the drug used, such as ADRs reports and medication error reports.

2) To reduce the errors in prescribing, dispensing and using of medicines by patients.

3) To monitor ADRs that is associated with poor quality medical products, which could be substandard and counterfeit.

4) To coordinate various activities related to data collection, ADR reporting from public health programs such as tuberculosis, HIV, and malaria.

5) To determine risk factors related to ADRs such as demographic, ethic, genetic factors, drug-drug interaction, drug and food factors.

6) To determine the mechanisms that could possibly induced ADRs.

7) To assess the benefits and risks of medical products and to avoid the risk associated with medicinal use.

8) To promote the rational use of the drug in Lao PDR.

9) To communicate and educate people about the risk associated with poor quality and unsafe pharmaceutical products or vaccines.

10) To maintain the national ADR database.

11) To alert the people or patients, policymakers, health care professionals, manufacturers/or distributors about the safety issues related to poor quality of health products.

12) To support the training of PV for university students, health care professionals and consumers.

2.6.1 Basic principle of the law of the Lao national policy and in the law on drug and medical product

According to WHO definition, Pharmacovigilance (PV) is the science and of detection, assessment, understanding and protection or problems associated with drug. Pharmacovigilance is mentioned in the Lao national policy and in the law on medicines in 2003. The center for PV and evaluation of ADRs must be established to provide all necessary information to the population and the Law on Consumer Protection, which promotes the protection of consumers with regard to dangerous and inferior products and protects the rights of consumers.

Depending on the national policy in Lao PDR code 7.7 mentions that the toxicology center must be established. This center focuses on monitoring of adverse effects of the use of prescribed drugs and self-medication and in cases of toxicity caused by drugs, chemicals and other health products.

In the law on medicines said that the toxicology center must collect data, evaluate and communicate on adverse reactions to health professionals, institutions and the population to raise their awareness.

2.6.2 Establishment practice and role of participatory in PV system in Lao PDR

The established procedures for reporting of PV activities (information sent to PV center) such as detection of signals, evaluation of risks, decisions for corrective action, and communication of information related to drug safety in each department in all health delivery systems are crucially essential. The following section provides the roles of each party in the PV reporting system in Lao PDR.

1) Roles of patients and consumers

Patients and consumers should be encouraged to report any suspected ADRs experienced in the course of their treatment immediately to their healthcare providers or directly to the national PV center. In case of children or malformation patients or elderly patients, their relatives or caregivers should be encouraged to report suspected ADRs too.

2) Roles of health service location

The directors and executives of health service locations are responsible for building the systems to promote the establishment of PV monitoring programs in their own institutions as shown below.

2.1) Health care professionals such as the doctors, pharmacists, nurses, other cadre of health workers including professional responsibility to monitor, detect, control, prevent and report any medication errors and to the persons responsible for PV monitoring in their own institutions.

2.2) Support the awareness about PV and drug information and to build a database for ADRs reports and poor quality products.

2.3) Develop training plans for employees to promote PV systems.

2.4) Health service institutions should promptly report any suspected case of ADRs and/or deaths cases related to the use of health products.

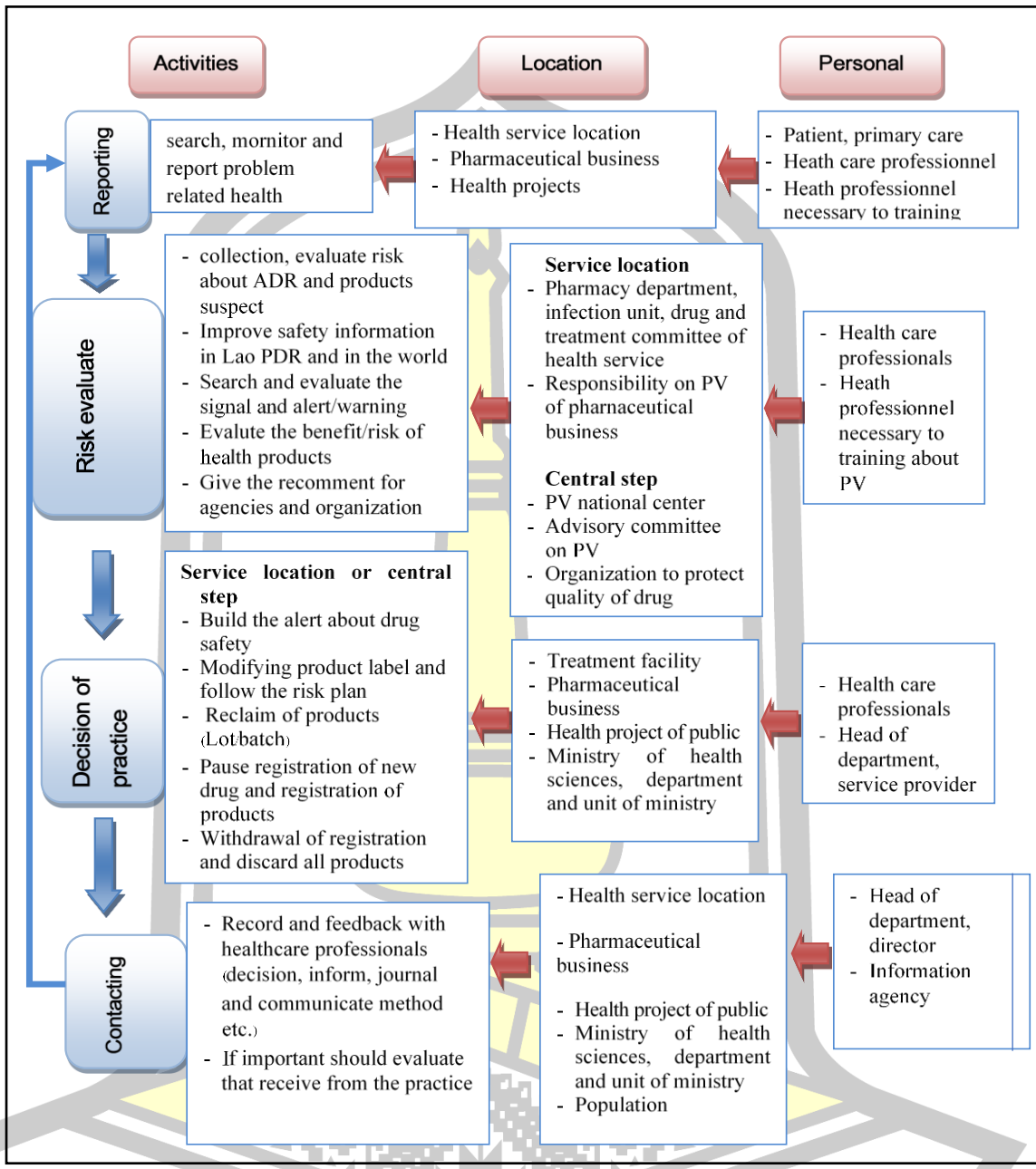


Figure 5: The performance of PV system in Lao PDR.(25)

3) Reporting of ADRs in Lao PDR

Doctors, pharmacist, nurses, midwives, and other health care professionals as well as patients can report ADRs. The reporters must ensure that all information of the patients, the suspected drugs, and the adverse events experienced are properly documented in the standard ADRs form(s) provided by the PV Center. In addition, the reporter should report every incident about the ADRs that happened in the process of treatment, including any suspected cases related to the drug, vaccine, a biologic product, or a traditional medicine. For reporting time, variations are depending on the severity of ADRs as shown below:

i. The ADRs reports should report immediately even if there is not enough information (initial report). This would give an opportunity for continuous monitoring and clinical investigation of the suspected cases.

ii. If reporting ADRs for hospitalized patients, adequate information and data of the patient should be collected and the patient's condition be continuously monitored.

iii. The ADR reporting should be sent to the National PV centre in an timely manner consistent with the established PV reporting system outlined below:

- Report ADRs in patient morbidity cases should be reported immediately within 7 days or of detecting or suspecting the ADR.
- ADRs of any case should be reported within 15 days of detecting the ADRs.
- Reports of ADRs in normal or mild cases can be collected and reported on the 5th day of every month.

4) Submitting ADRs reporting

- For health service locations with pharmacy services, health care professionals can submit ADR reporting to the hospitals' pharmacy departments for compilation and reporting to the hospitals management to be endorsed before submitting to the national PV centre. In urgent cases the reports should be sent directly to the National PV centre.
- For health service location that have no pharmacy services, healthcare workers should send ADRs reports directly to the National PV centre. All setting can submit ADR reporting to National PV center through 5 ways including postal, e-mail, online form, fax and telephone.

5) Step of evaluation and reply

- The National PV center would recheck and identify reported ADR to identify ADRs reporting to identify stages of the reports. If the ADRs are serious and life-threatening, then the pharmacovigilance center would immediately advise the responsible health service location directly with appropriate actions to be undertaken.

- In urgent cases, especially with serious ADRs, the National PV center should immediately collect and recheck information. Then advice the reporter and health service location on what necessary actions to implement.(20)

2.7 Tool for enhancing ADR reporting

2.7.1 Overview of tool for enhancing ADR reports and studies related to ADR reported tool

In Thailand, TaWai for health system is one of the tools for enhancing ADR reporting in patients even without the research to confirm. However, it has been tried out to use in the form of problem management in the community. The result founded that it can improve ADR management well. Furthermore, TaWai for Health is also ADR reporting in each year, ADRs reporting has increased every year from using this system.

Ines V et al, 2012 performed the study in Portugal to promoted spontaneous reporting of ADR by using hyperlink to enable online ADR reporting through the hospital's electronic patients record (EPRs). The result showed the median number of ADRs reporting per month significantly increased after using hyperlink access to EPRs. Furthermore, the serious ADR reporting increased by three fold and the non-previously reported ADR cases increased by four and half fold compared with the hospitals where the hyperlinks were not installed.(3)

Delphine A et al, 2014 performed study to assess, performances and effects of a new ADR reporting system via online. The characteristics of the online notifications including numbers of ADRs, ADRs reporting and file processing times, type of reporters, suspected drugs, "seriousness" and nature of ADRs were evaluated, and reported to the RPVC between 2010 to 2011. The results demonstrated a total of online 312 reports over a 18-month period. This showed a 45% increase in the number of reports from ambulatory healthcare professionals after implementing the new reporting tool. In addition, it is feasible to deploy an online ADR reporting system used by health professionals in current practice. Moreover, this has been the first published study demonstrating that an online reporting tool could help save time

on the ADR reporting period and file processing, which is essential to generate early safety.(6)

Ribeiro-vaz I and colleagues (2016), performed a systematic review and meta-analysis study (SR-MA) to evaluate the use of information systems in the promotion of adverse drug reactions reporting. The studies reported the data related to the number of ADRs before and after each intervention were implemented. The results of MA showed that using information system can increased the number of ADRs report by 1.2 fold.(1)

In Portugal, there was study implemented electronic health records to enhance ADR reporting in hospital. The result of this study indicated that electronic reporting interventions increased the number of ADR reporting by 2-fold. Therefore the establishment of electronic health records and ADR reporting systems would be an efficient method of increasing ADR reporting .(13)

De Vries ST et al (2017) performed a study to reveal the factors that may influence healthcare professionals (HCPs) and patients to use a mobile application for ADR reporting. The results showed that the factors that may influence the use of the mobile application were the types of feedback given on ADRs reports, access factors, ease of using the systems, social factor, type of language, the source of safety information being provided through the application and the security of the mobile application.(28)

AJ Avery et al (2015), performed study to evaluate the pharmacovigilance impact of patient reporting of ADRs by analyzing reports of suspected ADRs from the UK Yellow Card Scheme (UK YCS) and comparing reports from patients and HCPs, and also to elicit the views and experiences of patients and the public about patient reporting of ADRs. The result of this study indicated that Compared with HCPs, patient reports to the YCS contained a higher median number of suspected ADRs per report, and described reactions in more detail. The proportions of reports categorized as ‘serious’ were similar; the patterns of drugs and reactions reported differed. Patient reports were richer in their descriptions of reactions than those from HCPs, and more often noted the effects of ADRs on patients’ lives. Combining patient and HCP reports generated more potential signals than HCP reports alone; some potential signals in the ‘HCP-only’ data set were lost when combined with patient reports, but fewer than those gained; the addition of patient reports to HCP reports identified 47 new ‘serious’ reactions not previously included in ‘Summaries of Product Characteristics’. Most patient reporters found it fairly easy to make reports, although improvements to the scheme were suggested, including greater publicity and the redesign of web- and paper-based reporting systems. Among members of the public, 8.5% were aware of the YCS in 2009. In conclusions, the patient reporting of suspected ADRs has the potential to add value to pharmacovigilance by reporting types of drugs and reactions different from those reported by HCPs; generating new

potential signals; and describing suspected ADRs in enough detail to provide useful information on likely causality and impact on patients' lives.(29)

2.7.2 TaWai for health tool Thai version

TaWai for health is a tool for reporting and monitoring systems various health problems related to health products including the reporting of adverse reactions and suspect substandard and poor-quality health products. This system was designed and developed by research teams from Prince of Songkla University, Thailand to monitor public health safety and report various health problems. This system was designed to usable for patient and health care professional and apply in both hospital and community setting. The preliminary test to determine an effectiveness of this tool in Thailand indicated that established TaWai for health can improves the efficiency of drugs and health products used appropriately. Furthermore, it helps reduce government expenditures for detecting product hazards.(8) This tool composed of several part including ADRs report, report a suspect product and report an exaggerated as following:

1. Information on people affected by the product such as name the patient, age, sex and history of drug allergy, etc.
2. The detailed information of the symptom includes the date of founding the symptoms, level of symptom severity.
3. Type of product causing adverse reactions such as modern medicine, traditional medicine, supplementary medicine.
4. The source of products that induce ADR included public hospital, communities' health service center etc.

The study of Rungnapha Kongwong et al in Thailand (2020) aimed to determine the situation of using the TaWai for Health tool and improve the efficiency of using it in consumer protection by using two steps of operation. The first step was to analyze the report situation from the database by using data evaluation form and management situation by interviewing 2 TaWai system administrators. The second step was to increase the efficacy of TaWai for Health applications for consumer protection. The data from in-depth interviews from 6 experts and opinion hearing from 33 stakeholders were used to try out and develop the customer protection procedure using TaWai for Health application by the customer protection team at Ubon Ratchathani.(30)

The result from TaWai for Health database showed a total of 2,266 consumer protection problem reports in tree titles, including 1,366 illegal or harmful product reports, 611 adverse product reaction reports, and 289 illegal advertisement reports. Among these reports, only 636 reports were recorded as complete reports, which

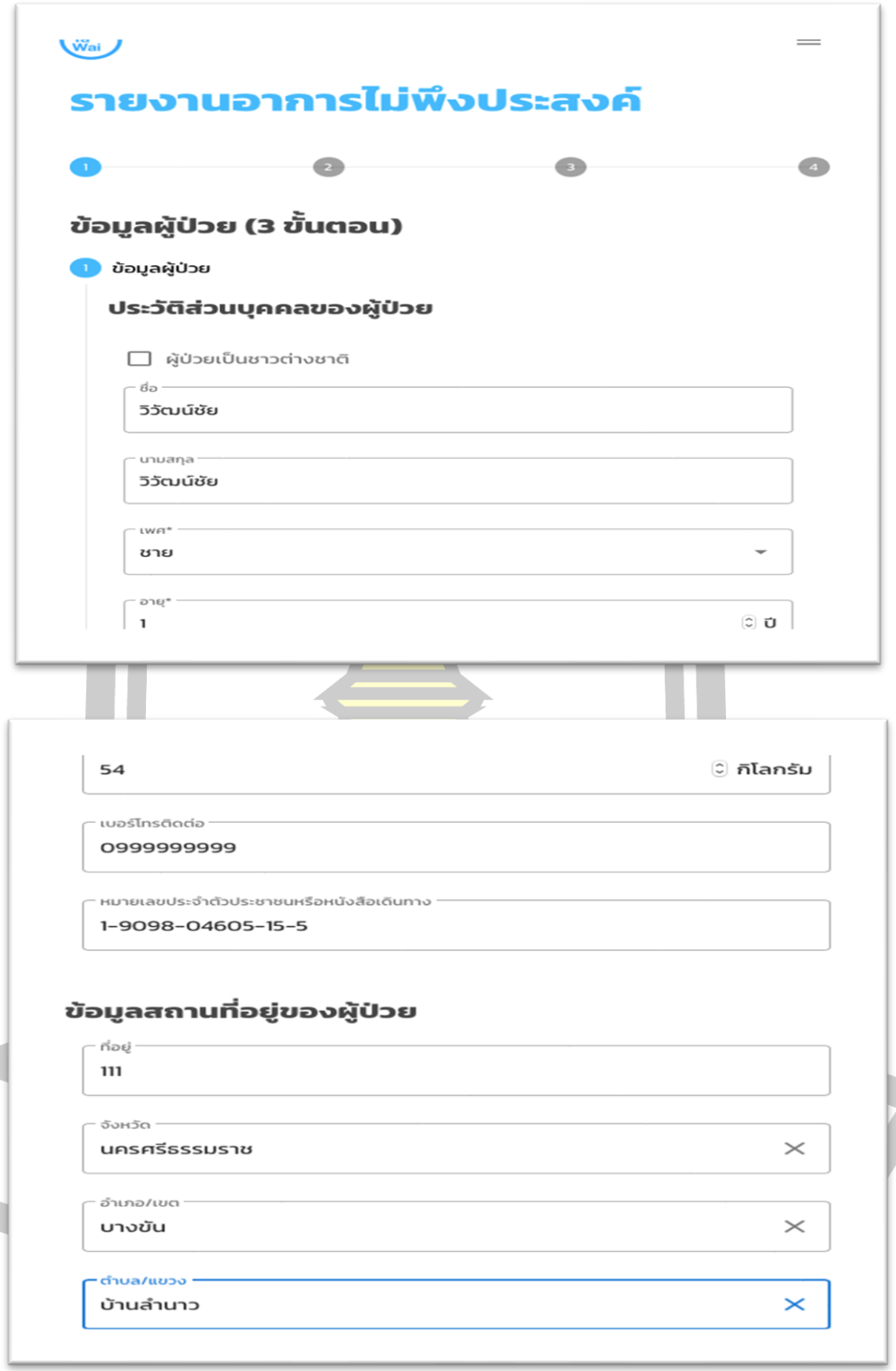
accounted for 28.06 % of the total. Data analysis showed that the low complete report rate due to irregular check and update the reports of case managers, lack of understanding of case management system, and vagueness of concrete management of daily reports. TaWai for Health networks needs the self-learning media for more understanding the application management and implementation.

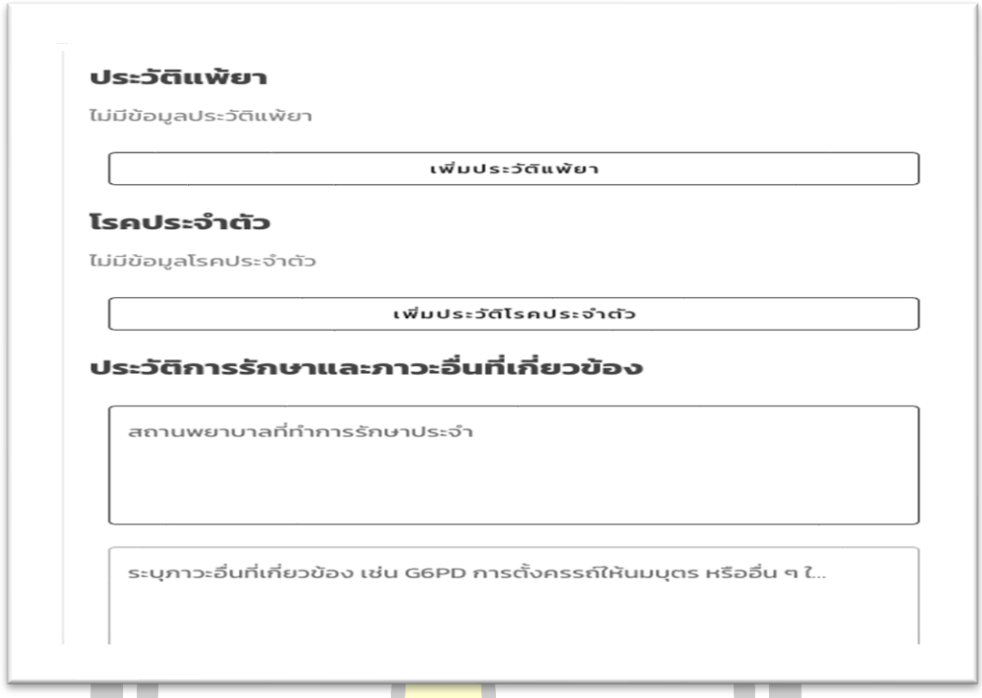
To develop the efficacy of the TaWai for Health application, the researchers created the practical management guideline applied from Surveillance and Rapid Response Time (SRRT) method. The experts and stakeholders proved the guideline before implementation. After four times of implementation and evaluation by TaWai for Health network in the study area, this procedure was practical and able to resolve the problem in time. The management guideline was including five steps. The first step was the problem report. The second step was to check and prioritize the report. The third step was problem management in order to the urgency of the problems. The fourth step is the case summary and updates of report status. The final step was the monitoring and evaluation.(30)

Furthermore, TaWai for health are also ADR reporting in each year, which demonstrated that ADRs reporting has increased from before without TaWai for health tool. The number of ADR reporting in 2019 and 2020 were 634 and 932 cases respectively.(31)

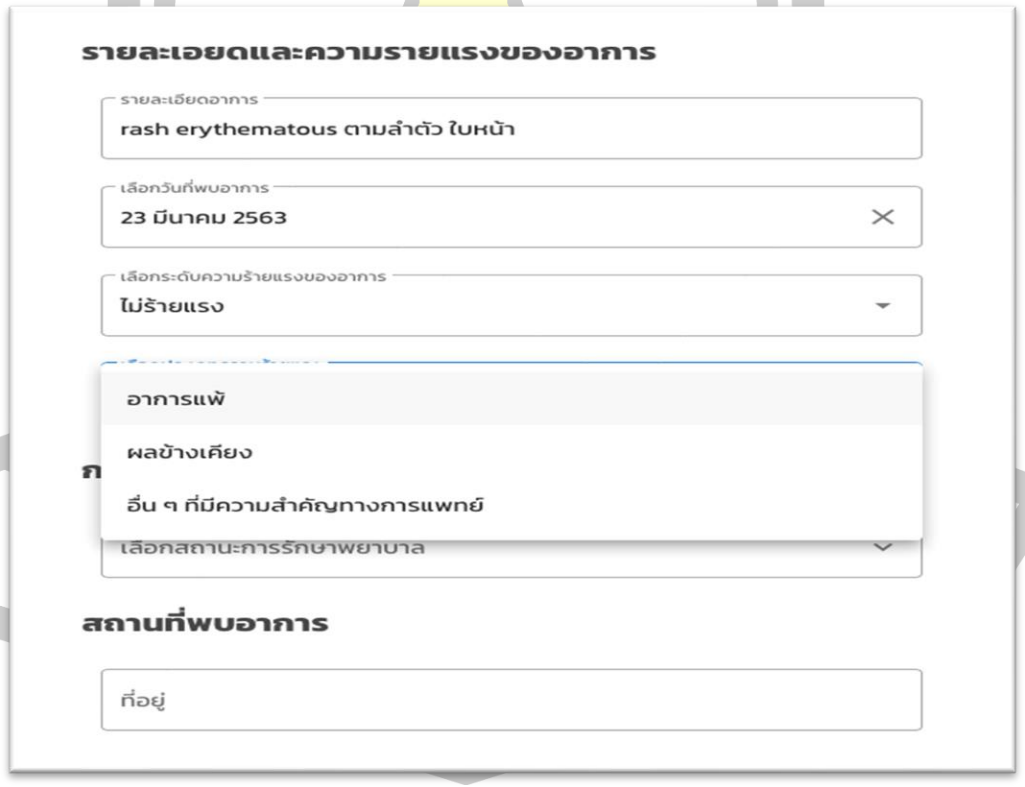
2.7.3 Example of procedure for reporting adverse reactions in TaWai system (TaWai Chatbot)

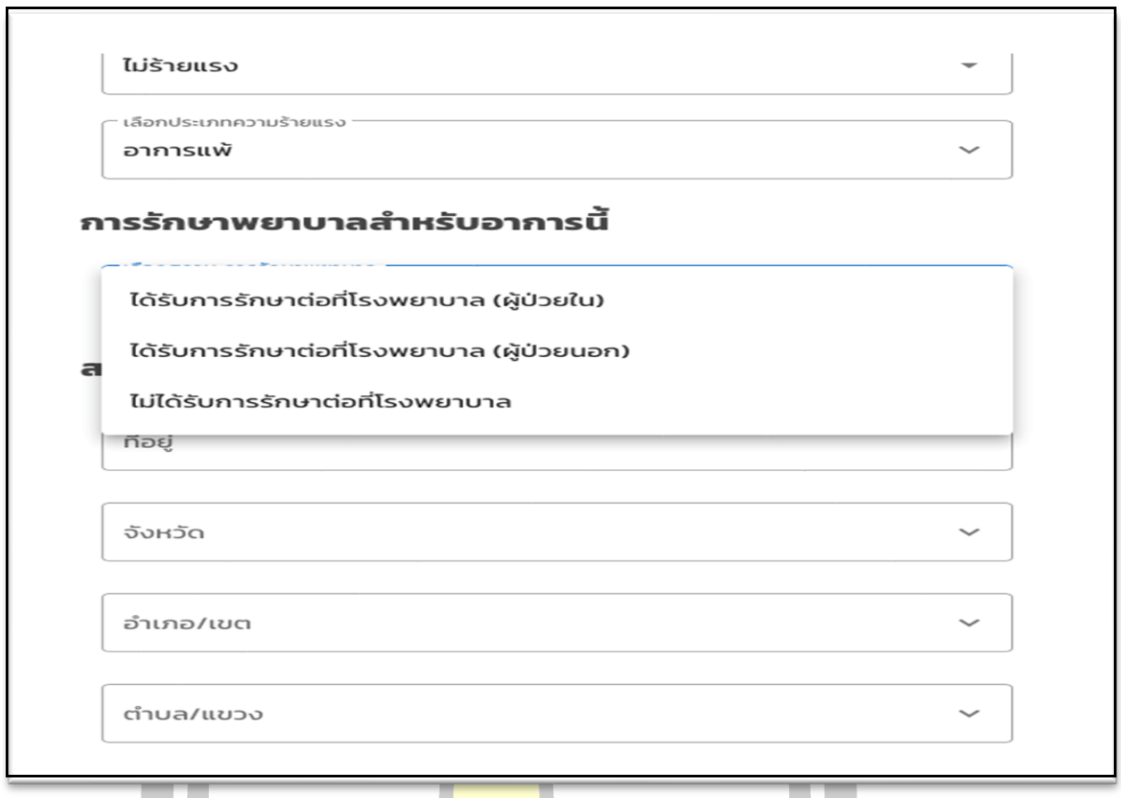
1) Information of patient



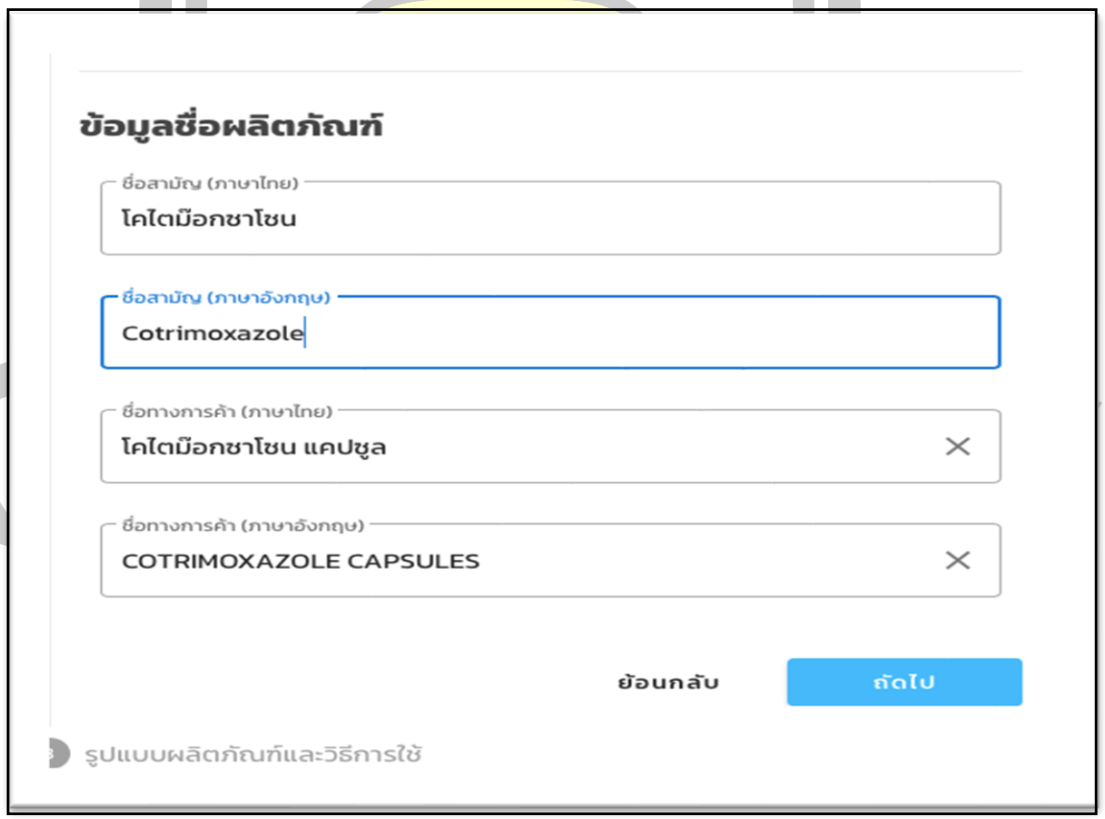


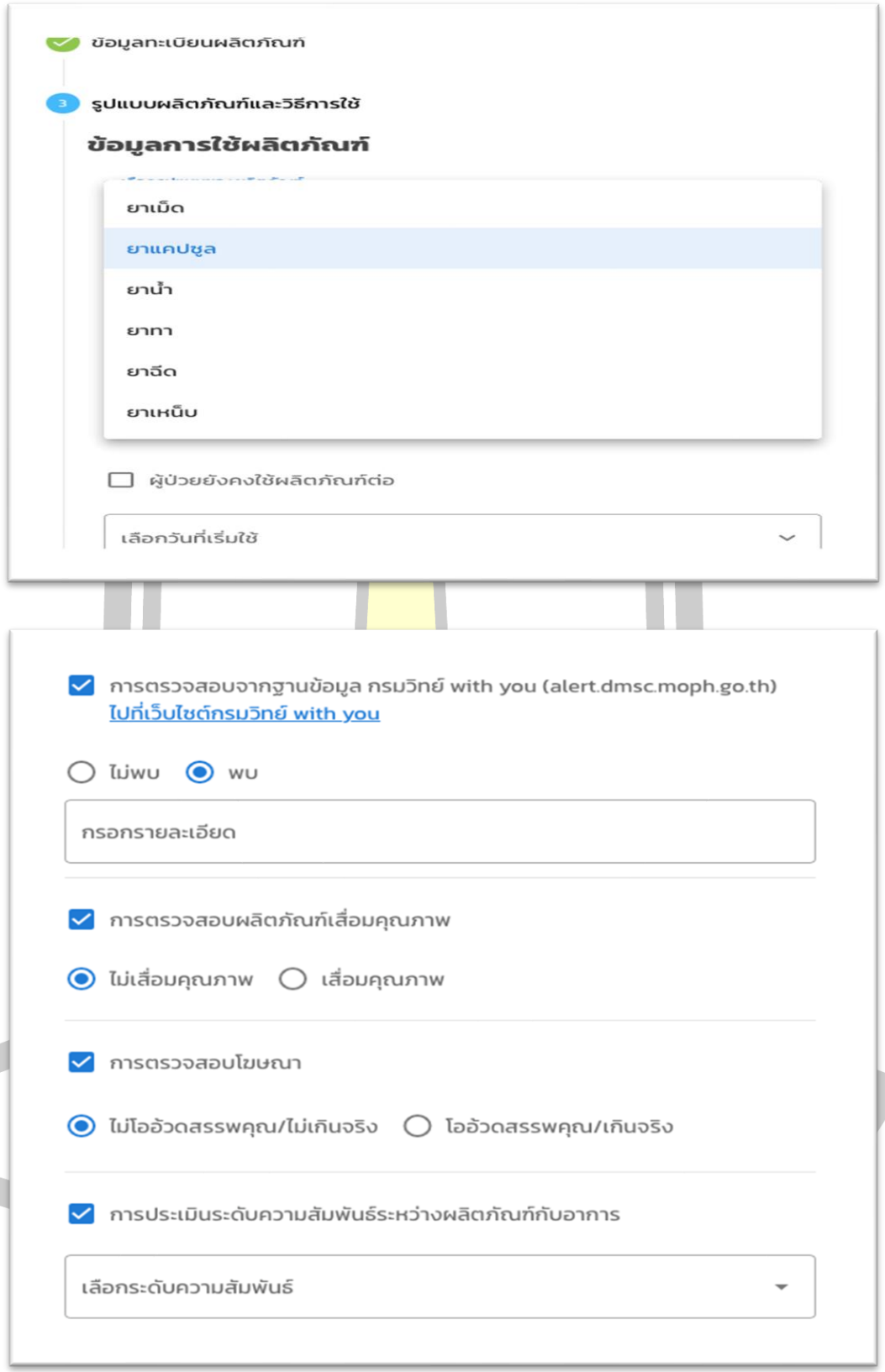
2) The detailed information of the symptom





3) Information of product induce ADR




ข้อมูลทะเบียนผลิตภัณฑ์
3 รูปแบบผลิตภัณฑ์และวิธีการใช้
ข้อมูลการใช้ผลิตภัณฑ์
ยาเม็ด
ยาแคปซูล
ยาน้ำ
ยาทา
ยาฉีด
ยาเหน็บ
ผู้ป่วยยังคงใช้ผลิตภัณฑ์ต่อ
เลือกวันที่เริ่มใช้
การตรวจสอบจากฐานข้อมูล กรมวิทย์ with you (alert.dmsc.moph.go.th)
ไปที่เว็บไซต์กรมวิทย์ with you
ไม่พบ
พบ
กรอกรายละเอียด
การตรวจสอบผลิตภัณฑ์เสื่อมคุณภาพ
ไม่เสื่อมคุณภาพ
เสื่อมคุณภาพ
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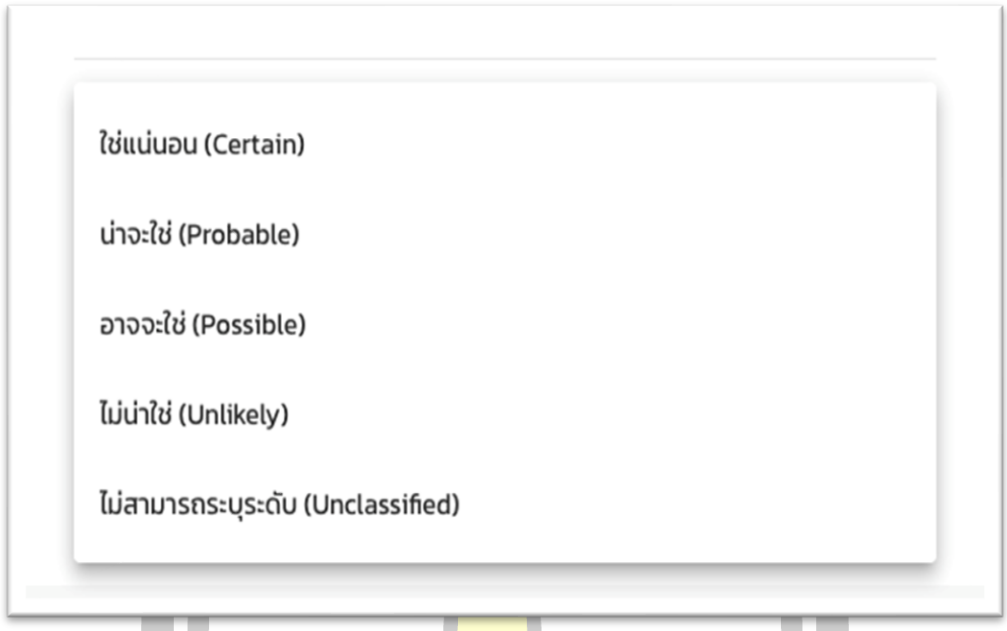
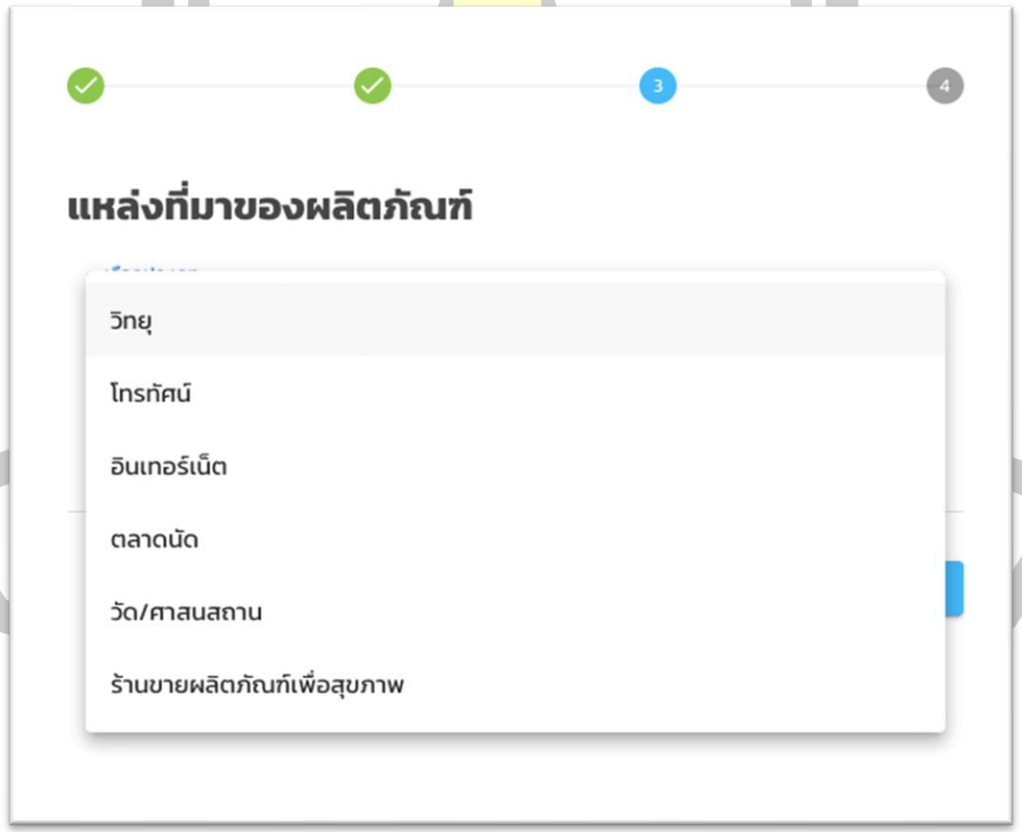
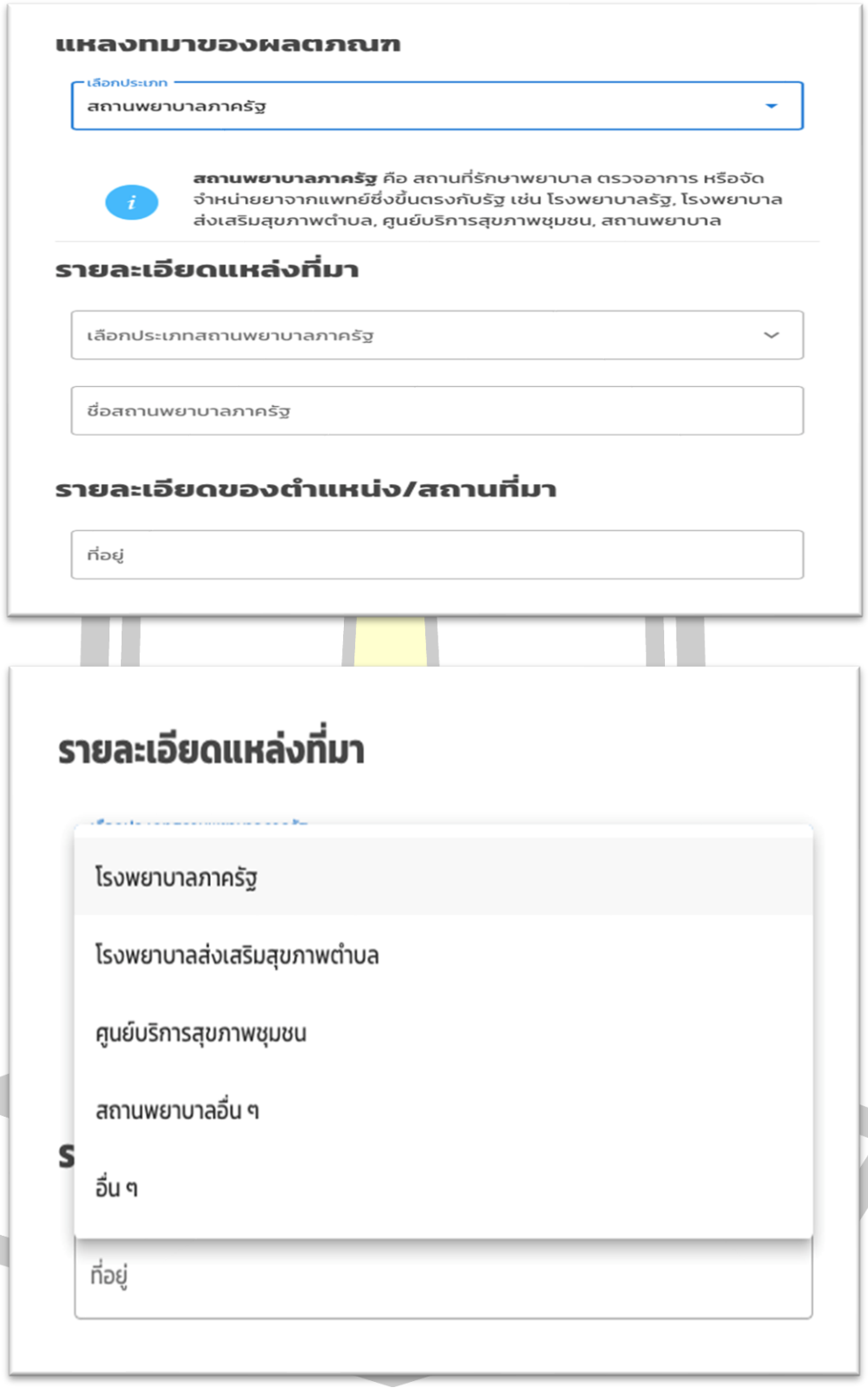
ไม่โออ้วดสรรพคุณ/ไม่เกินจริง
โออ้วดสรรพคุณ/เกินจริง
การประเมินระดับความสัมพันธ์ระหว่างผลิตภัณฑ์กับอาการ
เลือกระดับความสัมพันธ์

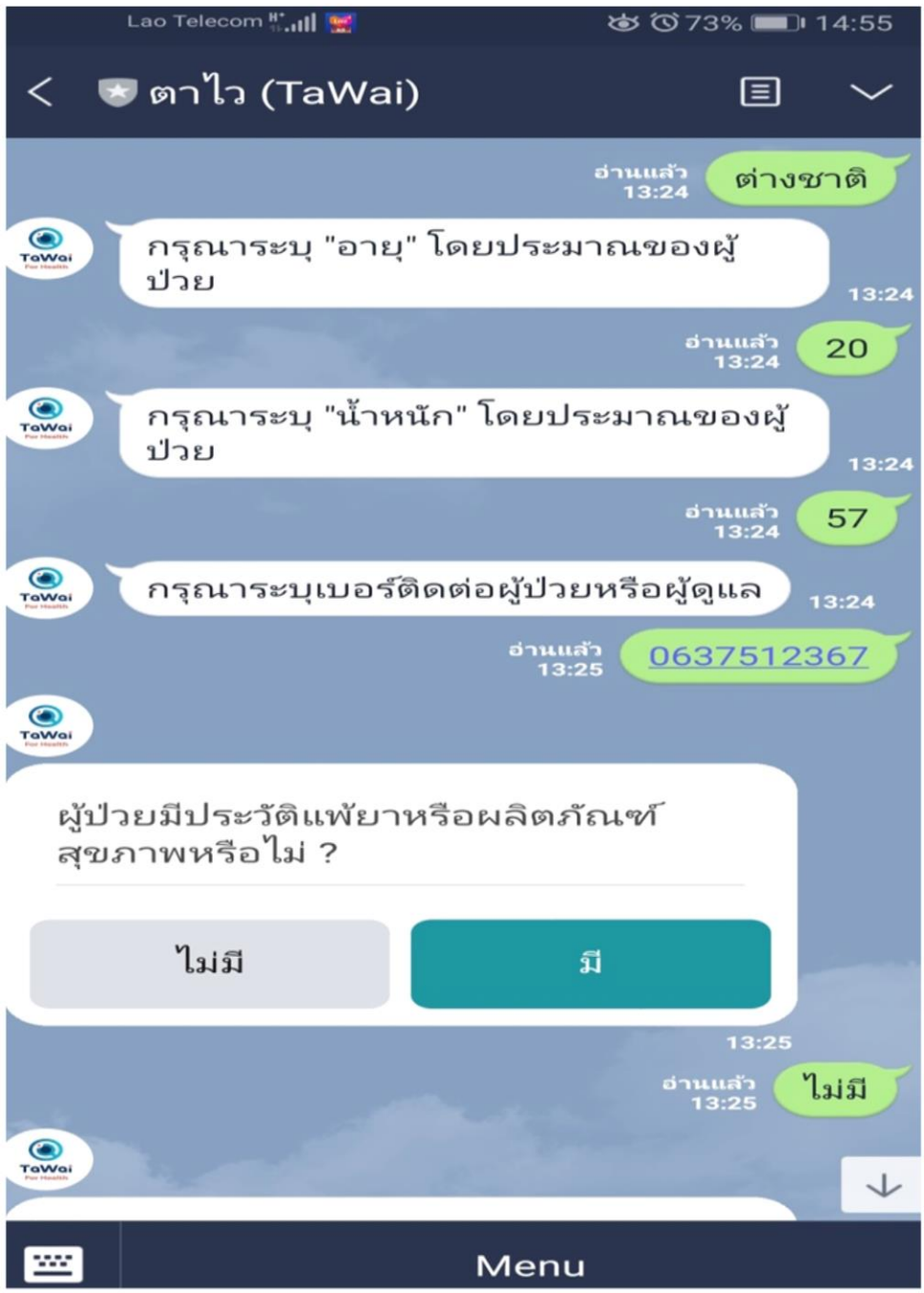


4) The source of products that induce ADR




แหล่งที่มาของผลตรวจ
เลือกประเภท
สถานพยาบาลภาครัฐ
สถานพยาบาลภาครัฐ คือ สถานที่รักษาพยาบาล ตรวจอาการ หรือจัดจำหน่ายยาจากแพทย์ซึ่งขึ้นตรงกับรัฐ เช่น โรงพยาบาลรัฐ, โรงพยาบาลส่งเสริมสุขภาพตำบล, ศูนย์บริการสุขภาพชุมชน, สถานพยาบาล
รายละเอียดแหล่งที่มา
เลือกประเภทสถานพยาบาลภาครัฐ
ชื่อสถานพยาบาลภาครัฐ
รายละเอียดของตำแหน่ง/สถานที่มา
ที่อยู่
รายละเอียดแหล่งที่มา
โรงพยาบาลภาครัฐ
โรงพยาบาลส่งเสริมสุขภาพตำบล
ศูนย์บริการสุขภาพชุมชน
สถานพยาบาลอื่น ๆ
อื่น ๆ
ที่อยู่

2.7.4 Example of procedure for reporting adverse reactions in Chatbot system


Lao Telecom
73%
14:55
ตาไว (TaWai)
อ่านแล้ว 13:24
ต่างชาติ
กรุณาระบุ "อายุ" โดยประมาณของผู้ป่วย
13:24
อ่านแล้ว 13:24
20
กรุณาระบุ "น้ำหนัก" โดยประมาณของผู้ป่วย
13:24
อ่านแล้ว 13:24
57
กรุณาระบุเบอร์ติดต่อผู้ป่วยหรือผู้ดูแล
13:24
อ่านแล้ว 13:25
0637512367
ผู้ป่วยมีประวัติแพ้ยาหรือผลิตภัณฑ์สุขภาพหรือไม่ ?
ไม่มี
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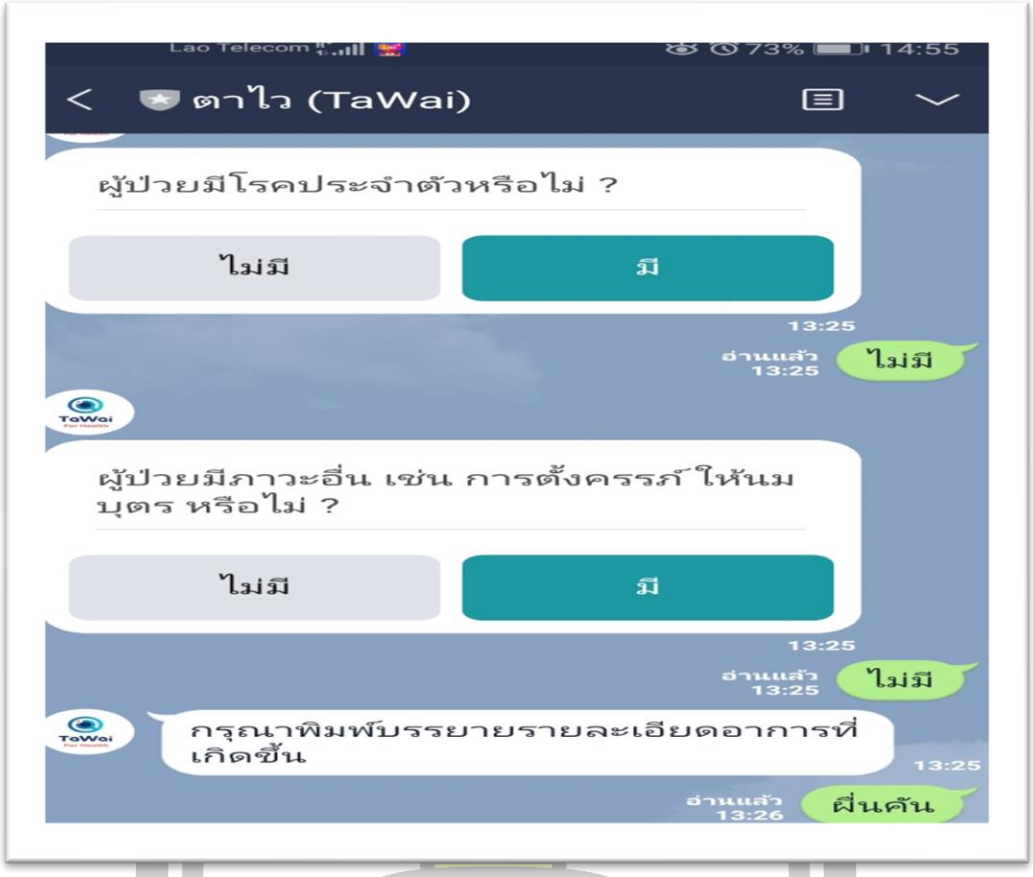
13:25
อ่านแล้ว 13:25
ไม่มี
Menu


Lao Telecom
73%
14:55
ตาไว (TaWai)
ผู้ป่วยมีโรคประจำตัวหรือไม่ ?
ไม่มี
มี
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อ่านแล้ว 13:25
ไม่มี
ผู้ป่วยมีภาวะอื่น เช่น การตั้งครรภ์ ให้นมบุตร หรือไม่ ?
ไม่มี
มี
13:25
อ่านแล้ว 13:25
ไม่มี
กรุณาพิมพ์บรรยายรายละเอียดอาการที่เกิดขึ้น
13:25
อ่านแล้ว 13:26
ผื่นคัน


ตาไว (TaWai)
13:26
ผื่นคัน
ท่านมีรูปอาการหรือความผิดปกติของผู้ป่วยหรือไม่ ?
ไม่มี
มี
13:26
อ่านแล้ว 13:26
ไม่มี
กรุณาระบุ "ช่วงเวลาที่เกิดอาการดังกล่าว" โดยประมาณ
13:26
อ่านแล้ว 13:27
บ่ายโมง
กรุณาระบุสถานที่พบอาการความผิดปกติของผู้ป่วย :
กรอกข้อมูล

2.7.5 Advantage and weakness of tool between TaWai system and Chat bot

1) Web TaWai

Advantage	Weakness
- A lot of detail - Can enter very detail information	- Expensive - A lot of time to report

2) Chat Bot

Advantage	Weakness
- Easy to report - Short time, quick	- Cheap - Limited detail information

2.8 Clinical trial

2.8.1 Overview of clinical trials

The randomized controlled trial is the principal method for obtaining a reliable evaluation of effect because a properly planned and executed clinical trial is a powerful experimental technique for assessing the effectiveness of an intervention.
A clinical trial is defined as a prospective study comparing the effect and value of intervention(s) against a control in human.(32) At baseline, the control group must be similar in relevant respects to the intervention group to ensure that differences in outcome come from an action of the intervention. The clinical trial is also called a clinical study. It is often classified into four phases of study. The details of each phase are given below.

1. Phase I trials are the first trials in humans and usually conducted in a small number (No more than 50 -100 subjects) of healthy volunteers and limited to a single dose or a few repeated doses. It is also called pharmacology and toxicity trials. The objective of this phase is to define initial safety, identifies toxicity of drugs or product in human, and also to establish pharmacokinetic and pharmacodynamic profiles of the drug.

2. Phase II trials are also called initial clinical investigation for treatment effect trials. The objective of this phase is to evaluate the efficacy and short-term safety in prime clinical conditions in selected populations and to establish efficacy, side effect, clinical toxicities of the drug. Usually, studies in this phase provide the information of optimal dose or therapeutic dose range of drug or product.

3. Phase III trials are sometime called full-scale evaluation of treatment trials. This phase is a large-scale pivotal study that is designed to evaluate both the efficacy and safety of an intervention. It is conducted in specific subject populations for which the drug is intended and conducted before regulatory submission and provides most of the information required for labeling.

4. Phase IV trials or post-marketing surveillance trials are conducted after local regulatory approval or after the product available on the market. Trials in this phase are designed to differentiate the drug from others in its class, compare its efficacy against similar marketed compounds, and demonstrate health economic benefits in “real world” settings.

2.8.2 Types of clinical controlled trial

In general, randomized controlled trials designed are classified into two types including parallel design, and crossover design trials.

A fundamental requirement for the use of the crossover design is that the condition being studied must be stable, so that it will return to the baseline state when a test or intervention is stopped, allowing subsequent assessment of the intervention under the same conditions. This design is defined that the study is permitted the comparison of different intervention in the same subject (Figure6) while in parallel design each patient receives only one intervention (Figure7). The problems of parallel design are many inter-subject variations and a large number of patients required while the subject variation between groups is eliminated and a few numbers of required patients are advantages of crossover design. One problem of crossover design is that the administration of the first intervention may influence the response to the second, called carry-over effect (32, 33), however it can be minimized by designing the trials with a suitable wash-out period between intervention or conduction the within patient design.

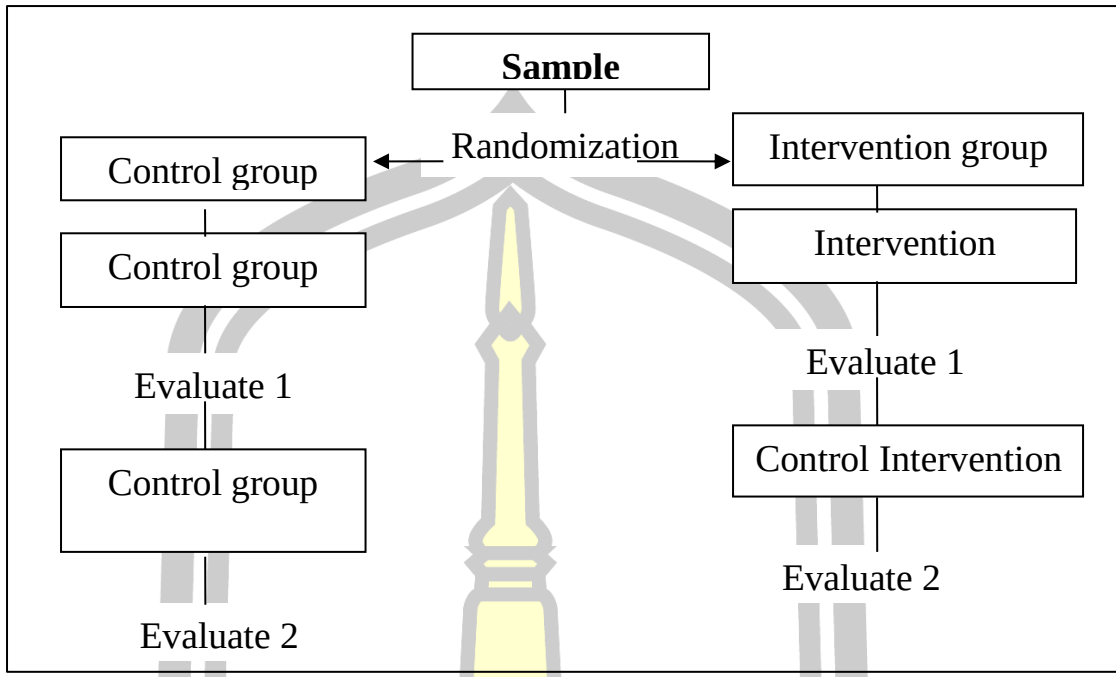


Figure 6: The crossover design

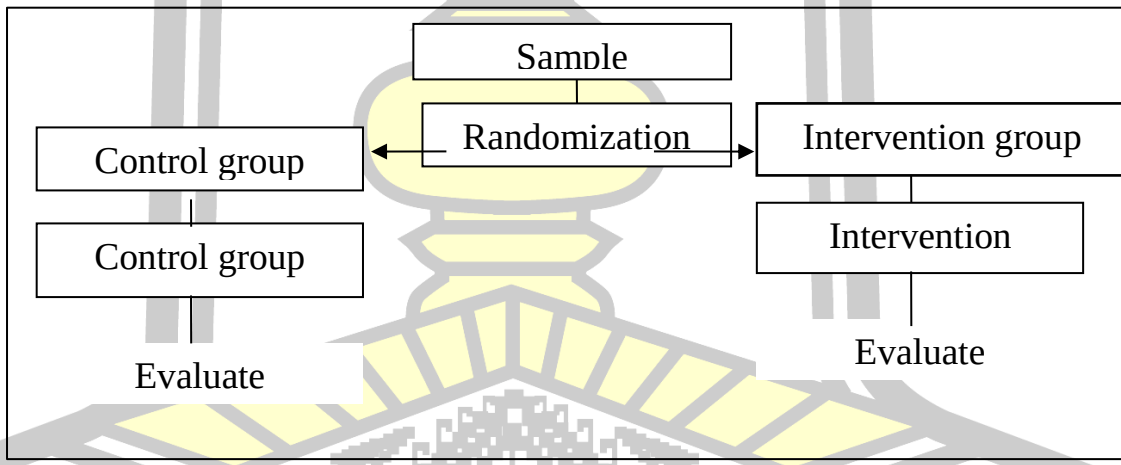


Figure 7: The parallel design

2.8.3 Randomization in clinical trial

Randomization is the process of assigning trials subjects to either intervention or control groups by chance to reduce potential bias. Therefore, the randomization should be performed to reduce the selection bias of each site and balance all prognostic factors and other characteristics of each study area.(34) Whatever the randomization process is used, the report of the trial should contain a brief but clear description of randomization method. The report of the trial should

clearly indicate the type of randomization method and how the randomization is implemented.(35)

Generally, there are two types of randomization method including fixed allocation randomization and adaptive randomization procedures. Fixed allocation randomization assign the intervention to subjects with a pre-specified probability, and this probability is not altered as the study progress. In contrast, the adaptive randomization procedures will be change the allocation probability as the study progress. In this study, five methods of fixed randomization including cluster, simple, blocked, and stratified randomization, and overall of adaptive randomization are reviewed.

1) Cluster randomization

Cluster randomization is a sampling population as a whole group not the individual. Usually group of population was randomized based on the needed area without the need to make a list of the population and sampling the population. For example, physicians or group practices in hospital, health plans, or even geographic regions (counties or states) can be defined as clusters. Therefore, cluster randomized trials (CRTs) will be involved randomization of groups (clusters) of individuals to control or intervention conditions. This type of design is commonly used to evaluate non-drug interventions, such as policy and service delivery interventions. In our study, we aim to determine effectiveness of TaWai tool in Lao version which is non-drug intervention. Thus, we performed a cluster randomized trial design for our study.

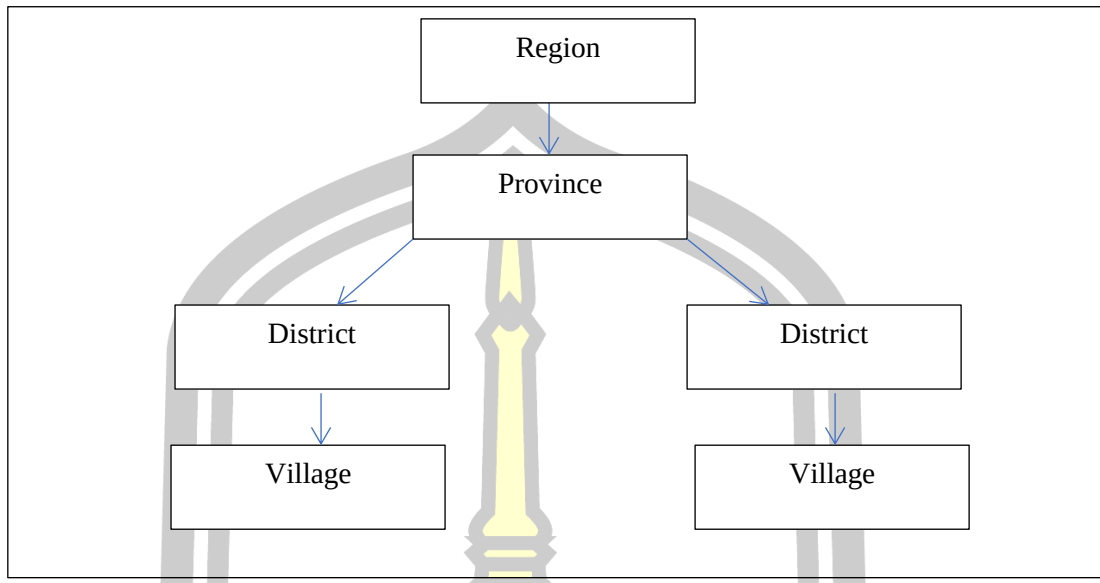


Figure 8: The cluster randomized

2) Simple randomization

Simple randomization is a simple and the most basic method of random treatment assignment. The classic technique of this method is the tossing an unbiased coin for each trial participant. In practice, for small studies, instead of tossing a coin to generate a randomization schedule, a random digit table on which the quality likely digits 0 to 9 are arranged by rows and columns is usually used to accomplish simple randomization. The advantage of this method is easy to practice. However, there are important limitations including risk of imbalance number of subject and imbalance prognosis between groups, especially for small sample size.

3) Blocked randomization

This method is also called permuted block randomization. It is used to avoid serious imbalance in the number of participants assigned to each group as could occur in simple randomization. The problem of this method is that assignment to the last person in each block can be known if the treatment was not blind. However, this problem can be solved by randomly varying block size. The detail of this method is provided below.

"Blocks" having equal numbers of As and Bs (A = intervention and B = control, for example) are used, with the order of treatments within the block being randomly permuted. This process is repeated for consecutive blocks of participants until all participants are randomized.(36) For example, a block of four has six different possible arrangements of two As and two Bs (Figure 9). A random number sequence is used to choose a particular block, which sets the allocation order for the first four subjects. Similarly, treatment group is allocated to the next four patients in the order specified by the next randomly selected block.

1. ABAB	2. BABA	3. AABB	4. BBAA	5. ABBA	6. BAAB

Figure 9: The example of block of four

4) Stratified randomization

Stratification can add to the credibility of a trial, as it ensures treatment balance on these known prognostic factors, allowing easy interpretation of outcomes without adjustment. Stratified randomization requires that the prognostic factors be measured either before or at the time of randomization. For example, in a trial of chemotherapy for breast cancer, suitable stratification factors might be menopausal status and estrogen-receptor status. Each factor was divided into two groups or strata (i.e., premenopausal or postmenopausal). Within each stratum, the randomization process itself could be simple randomization, but in practice most clinical trials use some blocked randomization strategy. As an example of stratified randomization with a block size of four, suppose an investigator wants to stratify on estrogen receptor status (ER+ or ER-) and menopausal status (premenopausal or postmenopausal). Thus, the design has 2x2 = 4 strata. The randomization for this example appears in table 3.

Table 2: Stratified randomization with block size of four

Strata	estrogen receptor status	menopausal status	Group of assignment
1	ER-	+	ABBA, BABA, …
2.	ER+	+	BABA, BBAA, …
3.	ER-	-	AABB, AABB, …
4.	ER+	-	Etc.

Where ER+ and ER- are estrogen receptor positive-and negative, respectively, + and - are pre- and postmenopausal, respectively.

5) Adaptive randomization

Adaptive randomization method is divided into two types including baseline adaptive, and response adaptive randomization.

Baseline adaptive randomization uses the differences in number of participants, which are greater than pre-specified value to adjust the probability of assigned participants. This method is being used especially in clinical trials of cancer where several prognostic factor need to be balanced. The advantage of this method is protection of a severe baseline imbalance for important prognostic factors. Response adaptive randomization uses information on participant response to intervention during course of the trial to determine the allocation of the next participant. This method is not commonly used because it is complicated and many clinical trials do not have an immediately occurring response variable.

Allocation concealments are methods used to implement the random allocation sequence, clarifying the sequence were concealed until interventions were assigned. They are important methods to avoid both conscious and unconscious selections of patients into the study. That means the advantages of randomized process still remain if the allocation concealment was conducted. Typically, “Allocation concealment” is the term used to describe this process and underpins successful randomization strategies.(37) There are several methods to concealment such as envelopes, numbered containers or central telephone etc.

2.8.5 Outcome assessment

Outcome assessment is a key step in clinical trial. The evaluation of each intervention progress after the start of the study needs to be done in an objective, accurate and consistent manner so that the study as a whole provides a meaningful assessment of the intervention's relative merits. The methods for assessing and recording intervention progress need precise definition in the study protocol.(37)

For clinical trials intervention, selection of the proper outcome and the appropriate test method for evaluation intervention depends on objective to development and study design.

2.9 Studies related to ADRs monitoring and reporting system

Lao PDR has monitored the ADR using the SRS system since 2012. However, ADR reporting in Lao PDR has always been a problem with low reporting rates. Due to less cooperation from HCPs, there was an effort to determine the cause of various factors that make HCPs do not report ADRs such as In the United States, in Rhod Island (38), and Cape Town (39). Previous studies in the United Kingdom reported that there are 7 factors related to underreporting of ADRs including: Complacency, Fear of litigation, feel guilty for causing the patient suffering (guilt), wants to keep the report or publish it as its work (ambition), not interested in the report (ignorance), lack of confidence in the report (diffidence), unsure if ADR or not, and often claimed that the barn and no time (lethargy).(11)

According to previous study in Thailand, the reasons for underreport of ADRs in Thailand is similar to United States and United Kingdom studies, but there are some differences reasons such as unknown of ADR reporting system, unknown of ADR reporting process, difficulty of reporting forms, most common and mild ADRs that are already known and not severe.(40) In addition, several studies have been performed to identify pattern and method for encouraging HCPs to report ADRs. The summary of those previous studies is provided below in table 1.

Table 3: Extracts information

Author	Year	Study design	Tool	Increase in report(fold)
Linder et al (41)	2010	Quasi experimental	Electronic ADR reporting	36.17
Chang et al (42)	2017	Ecological time series	Electronic ADR reporting	22.96
Rebeiro-Vaz et al (13)	2011	Cluster-RCT	Education + Telephone intervention	3.22
Herdeiro et al (43)	2012	Cluster-RCT	Telephone+ Education intervention	4
Raymond Li et al (44)	2019	Systematic review	- Telephone intervention - Electronic ADR reporting	9.26 13.69
Johansson M et al (45)	2011	RCT	Reminders	1.52
Lopez E et al(46)	2015	Cluster-RCT	Education	2.31
Figueiras A et al(47)	2006	Cluster-RCT	Education outreach	10
Shchory M et al (48)	2019	Cluster-RCT	Education	3

Li and colleagues (2019) conducted a systematic review to assess the impact of various strategies to improve ADR reporting published in the last decade by comparing with the strategies identified in the previous systematic reviews. A total of 10,021 articles were selected and screened. Of these 13 articles met the most common inclusion criteria which were the provision of educational session such as a presentation or workshop (31.6%). While using an electronic reporting tool has been noted to improve ADR reporting 26.3%, using telephone intervention also improves the reporting by 10.5% and feedbacks of reported ADRs improved by 5.3%. These results showed that all intervention utilized were effective in increasing the number of ADRs reports or the proportion and efficiency of ADRs reporting. The multifaceted strategies resulted in a point estimate increase in ADR reporting by 9.26-fold (−2.21–17.11, 95% CI) compared to 7.19-fold (−5.29–32.68, 95% CI) for single interventions (p=0.42). The electronic reporting tools were identified as the common interventional strategy with a point estimate increase of 13.69-fold (−5.29–32.68, 95%CI) compared to 4.42-fold (0.66–8.19, 95% CI) for traditional educational methods.(44)

The use of electronic reporting tools was more commonly identified as an interventional strategy, and also demonstrates an important advance in utilizing digital technology to facilitate the reporting of ADRs. For example, Linder et al captured electronic health records using an application to trigger an ADR reporting when a clinician discontinued medication due to the ADR.(41) It took the clinicians a mean of 53 seconds to send each report and this resulted in a 36-fold increase in reporting rates. Furthermore in Chang et al, 2017 increased 22.96 fold.(42)

In Rebeiro-Vaz et al (2012) conducted a cluster randomized controlled to evaluate of an intervention to improve the number and relevance of report ADRs. The result demonstrate that the intervention increased the rate of spontaneous reporting of ADR three times (RR = 3.22; 95% CI 1.33;7.80), when compared to the control group. The relevance of reporting, with an increase in severe adverse reactions by approximately four times (RR = 3.87; 95% CI 1.29; 11.61) and in unexpected adverse reactions by five times (RR = 5.02; 95% CI 1.33;18.93), compared to the control group. During a period of up to four months, educational interventions significantly increased the number and relevance of spontaneous reporting of adverse drug reactions by pharmacists in Northern Portugal.(13) Furthermore, in Herdeiro et al 2012, it similar method with Rebeiro-Vaz et al on evaluate the result of intervention to improve the quantity of ADR reporting by physician. The result shown that the education intervention plus telephone interview increased the ADR reporting rate of 4-fold (RR: 3.97; 95% CI 3.86, 4.08; $p < 0.001$) when comparison with the control group.(4, 49)

Furthermore, patients can play a major role in identifying, describing, and preventing ADRs. The studies by Berrewaerts J et al. (2016) highlighted the benefits of different methods as present below for collecting pharmacovigilance data from both HCPs and patients.

Firstly, Web-based spontaneous reporting of adverse drug reactions which was an online reporting. Through this online program, the number of reports increased. However, each country has used its own ADR reporting system, and not all countries have the same data. There was a need to harmonize ADR reporting forms between countries. Free-text comments in patient reporting forms can be valuable for pharmacovigilance, and can provide important information on how medicines can affect individuals and their lives. This information has been found to be useful in improving drug surveillance. But few patients are aware that they can submit their own adverse drug reaction reports. In order to increase consumer participation, the main reasons for patient reporting were the desire to share their experience, the seriousness of the adverse reaction, concerns about their own situation, and the lack of warning information in the patient information leaflet.

Secondly, web-based intensive monitoring that uses a specific inclusion point, such as an eligibility criterion whereby patients use a drug for the first time. Patients are tracked over time using online questionnaires to collect information on drug use and adverse drug reactions. This type of intensive monitoring can be useful for post-marketing surveillance. This method will provide quantified data and information on the time to onset of the adverse reaction and its evolution over time. The main reason for participation was altruism, while adverse drug reactions or negative drug experiences were generally less important.

Thirty, analysis of online forum postings were considered an appropriate source of observational information to supplement data from randomized clinical trials. From the posted messages, they identified a number of drug-related problems that were otherwise largely invisible. Analyses of data from websites can provide useful additional information. Using a similar approach, personal health messages from online communities have shown that trends in people's positive and negative feelings about certain medications can be tracked over time.

Finally, mobile phone systems use to monitor drug effects. Cell phones have proven to be a useful tool for collecting information on drug safety, particularly in developing countries. This technology offers a low-cost means and is accessible worldwide. It could be analyzed and transmit data and alerts in real-time. However, reactions tend to diminish over time, hampering long-term monitoring.(45)

The previous studies demonstrated that the telephone intervention, telephone intervention plus education or only education, electronic ADR reporting method, mobile phone system can increase rate of ADR reporting. For Lao PDR, there is no mobile tool model and method to increase ADR reporting. Therefore, implementation study to determine effect of developed tools for enhancing ADR reporting in Lao PDR should be conducted.

CHAPTER 3

Methodology

Overview:

This research consisted of three phases including 1) Review phases 2) Tool development phase, and 3) Evaluation phase.

The first phase (review phase) was the systematic review and meta-analysis to identify and assess types, characteristics, and effectiveness of available tools for enhancing ADR reporting. The second phase was the tool developing phase. The aim of this phase was to develop tool for enhancing ADRs report in Lao PDR by modifying the TaWai mobile system in Thai to Lao version. The last phase was tool evaluation phase. This phase was performed to evaluate the effects of using modified TaWai mobile system in Lao version which developed from phase 2. The detail of each phase was shown below.

3.1 Phase 1: Systematic review and meta-analysis (SR-MA) for evaluating the effectiveness of available tools for enhancing ADR reporting

This systematic review and meta-analysis was performed to determine the effectiveness of available tools for enhancing ADR reporting. The systematic review methodology was conducted according to the Cochrane guidelines (50), and the PRISMA Statement was followed in reporting the results (appendix 1).(51) A protocol was prepared following Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) and registered on the PROSPERO website number CRD42021277137.

3.1.1 Search strategy

International databases including PubMed, Sciences direct, Web of sciences, Embase and Scopus were searched from inception to September 2021 without language restrictions. Search terms including (“promote tool” OR “tool for Pharmacovigilance”) AND (“adverse drug reaction report” OR “ADR reporting”) AND “Pharmacovigilance system” OR “vigilance report” AND (“ADE’’ OR “adverse event’’ OR “AE”) AND (Clinical trial) were used for searching in each database.

We aim to determine effect of available tools therefore we selected to include only experimental study with controlled group. We excluded pre-post study, review or effect of real word use of program in one group.

3.1.2 Study selection

The articles were included if they are clinical controlled trial or randomized controlled to mention the key concept of using information systems or tools for enhancing ADR reporting in vigilance system, regardless of the length, and language of study. Two reviewers (Niphonh MONGKHONMATH and Ratree Sawangjit; NM and RS) were independently screened the study titles and abstracts. Then, the full texts were evaluated and the articles were excluded based on the following criteria: 1) Letter to the editor or expert opinion; 2) ADR reporting during clinical trials; 3) Not related to pharmacovigilance system; and 4) Review article. In cases of disagreement, a consensus meeting was held with the third reviewer (Panupong Puttarak or Phayom Sookaneknun Olson; PP or PSO) to decide whether the article should be selected.

3.1.3 Data extraction

Two reviewers (NM and RS) systematically extracted data regarding from each study publication year, study design, the area covered by the studies (i.e., region, country, or hospital), type of software (i.e., web-based or mobile), type of institution (i.e., regulatory authority or universities), target (healthcare professionals or patients),type of medicine (all, vaccines, chemotherapy, or others), type of ADR (all/serious ADRs based on the World Health Organization seriousness criteria). Discrepancies were resolved by discussion between the two reviewers or by consultation with the third arbitration (PP, PSO).

Table 4 Table of example of data extraction

ID	Author	year	Country	Study design	Setting (Universities, regulatory authority,hospital)	population (HCPs, pharmacist, nurse etc)	Sample size	number of group (no. in each group; I/C)	Number of intervention group	Control group	measurement time (month)	follow up time month)	Study outcome	Type of ADR	Type of products
1	Ribeiro-Vaz	2011	Portugal	Cluster RCT	Hospital and community pharmacist	Pharmacist	1467	3 (261/103/1103)	364	1103	4	20	Number and quality of report ADR	Overall, Serious, unexpected and probable	Medi-cines
2	Johansson	2011	Sweden	RCT	Primary health care unit	GPs and nurse	151	2 (77/74)	77	74	12	12	Number and quality of report ADR	Overall,Serious, unexpected and new drug	Medic-ines

3.1.4 Quality assessment of included studies

Quality assessment of included studies were independently assessed by two reviewers (NM and RS) using Cochrane Risk of Bias (ROB) tool version 2.0 for RCT.(52) We assessed bias over the following domains: selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of researchers conducting outcome assessments), and attrition bias (incomplete outcome data), and reporting bias (selective reporting), and other sources of bias.

A judgment of 'low risk' of bias, 'high risk' or bias, or 'some concern' of bias was provided for each domain. Example of ROB assessment was showed in below

No.	Author	Year	Random sequence generation	Allocation concealment	Binding of participant and personnel	Binding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias	Overall Bias
1	Ribeiro-Vaz	2011								
2	Johansan	2011								
3	Herdeiro	2012								
4	Lopez-Gonzalez	2015								

Low risk Unclear High risk

Any disagreements were resolved by discussion or by involving a third reviewer until consensus was reached.

3.1.5 Outcome measures and data analysis

1) Outcome measure

The outcome of interest was the efficacy of tools for enhancing ADRs reports. The efficacy in this review was represented by the number of ADRs reported before and after each intervention.

2) Statistical analysis

For each study with available data, the rate of increased ADR reporting and the respective 95% confidence intervals (95%CI) were calculated. The pooled effect size was calculated with the inverse variance method using a random-effects model, and a forest plot was presented.

In case, the means were reported without standard deviations, we calculated the standard deviation from the information report such as p-values, confidence intervals.

3) Assessment of heterogeneity

Between-study heterogeneity was assessed using the I^2- statistic which described the percentage of variation across studies due to heterogeneity rather than chance. Rules of thumb for interpretation of this statistic suggested that $I^2 < 30\%$ equates to no heterogeneity, $I^2 > 30\%$ equates to moderate heterogeneity, $I^2 > 50\%$ equates to substantial heterogeneity and $I^2 > 75\%$ equates to considerable heterogeneity. For all I^2 values above 50%, we investigated potential sources of heterogeneity.(53)

4) Assessment of publication bias

We assessed publication bias used funnel plots and Eager's test. If non-significant or p-value more than 0.5, that means there was no publication bias but p-value less than 0.5 means there was publication bias.

3.2 Phase 2: Developing and validating modified TaWai in Lao version.

3.2.1 Step of development TaWai application

We developed a tool for enhancing ADR reporting in Lao PDR by modifying TaWai for health in Thai version with information from phase 1 to comply with health care system in Lao PDR. The detail of step for development TaWai application were shown below.

1) Consulted with expert of TaWai application for report ADR.

2) Modified Tawai in Lao version was developed as chatbot by adapted the template of TaWai for health in Thai version. The TaWai in Lao version was back-to-back-translated from the Thai version.

3) The information from phase 1 and situation of health care system in Lao PDR such as pharmacovigilance (PV) and the regulations or laws related to ADR reporting in Lao PDR were used to develop each component of TaWai chatbot in Lao version. Information from phase 1, the criteria of a national guideline for PV, the situation of health care and ADR report in Lao PDR, and the regulation of ADR reporting or law related to ADR reporting in Lao PDR.The example of information used for develop each component was shown below.

(1) The criteria for reporting ADR following WHO guidelines used in TaWai Thai and Lao PDR versions was showed in table below.

Items	Thai version	Lao version
1. The patient information	✓	✓
2. The detail of ADRs	✓	✓
3. The management of ADR	✓	✓
4. The reporter information	✓	✓

(2) Most of the comparative issues or assessments of TaWai's reportable issues criteria in Thailand and Lao PDR are the same or not different because both are built in instruments and reported according to WHO criteria.

(3) Situations and problems of ADR reporting in Lao PDR

Based on previous survey in Lao PDR, the low rate of ADR reports is a lot of routine work and lack of time to report. There was no severe ADR, and the physicians feel that ADR reporting increase their workload, and there was no feedback after reporting. These reasons related to the common causes of low rate of ADR report from previous literature, which the main problems of ADR report are a lot of usual workloads and lack of time, problems related to the organization and activities of the PV system (10).

(4) Regular and situation of PV system in Lao PDR

Persons who play a role in the reporting of ADRs in Laos were the doctors, pharmacist, nurses, midwives, and other health care professional as well as patients can report ADRs. The reporters must ensure that all information of the patients, the suspected drugs, and the adverse events experienced are properly documented in the standard ADRs form(s) provided by the PV Center, but in reality the doctors was identify patient's ADRs. The doctors was assessed causality between drug and suspected reaction. After that, important component of ADR reporting was reported to the pharmacist. The pharmacist was collected data and record ADR reporting form. Then the pharmacist will send the report to the PV center. After that, the PV center collect data, evaluated and synchronizes information to WHO- UMC, which before in Lao PDR never had issued drug allergy cards to the patient. Its causes the patients to use the same medicine because the patent doesn't remember what medicine allergy before, which this reason, it cause the repeated medicine allergy. So, the problem of the lack of drug allergy card issuance in Laos, which leads to the research design and assessment in Part 3.

4) The components of modified TaWai system in Lao version were conducted based on information mentioned above. The main components were classified into 4 parts including (1) the patient information, (2) the detail of ADRs, (3) the management of ADRs, and (4) reporter information.

(1) The patient information such as name and surname, HN, OPD or IPD, date of birth, age, body height (cm), weight and sexes were included in the first component of the tool.

(2) The details of ADRs such as date of onset, duration, sign and symptom, severity, date and time to recovered, suspected drug data including dosage form, route and frequency of administration, starting and stopping date, the indication of suspected drug, other concomitant medicine, and additional patients' data such as the history of food-drug allergy, pregnancy or breastfeeding, the social history of patients were included in the second component of the tool

(3) The management of ADRs such as hospitalization due to ADR, treatment regimen or management plan for suspected ADR, duration of treatment were included in the third component tool.

(4) The reporter information such as name and surname, position, date of report, telephone number, e-mail or contact information were included in the fourth component of the tool.

There are four major components in the system, but may be located separately as appropriate when actual use.

5) Questions and details of response for all components were drafted in Lao and the content validity was tested paper card before construct into the chatbot program. The detail of content validity was provided in the quality testing of research tool. An example of questions and responses were provided in appendix 2.

6) The programmer constructed the chatbot of TaWai for Health in Lao version following the draft related situation in Lao PDR (appendix 3). The example of the draft for construction the chatbot was shown below

7) Then, the pre-final version test was performed and the result of this test was used to edit the developed tool before the validity test of the final tool.

(1) The pre-final version was tested by 5 health care professionals (HCPs) (4) who work at Settathilad hospital including doctors, pharmacists, who was invited to participate in the study. Those HCPS were trained about TaWai for Health system and completed the questionnaires. The data of missing answers were recorded.

(2) The HCPs were asked to explain the problems encountered in answering the items and the reasons for missing items, and comment on the wording, comprehensiveness, and relevance of the items. The Lao version of TaWai for Health was finalized after consideration of the results of the pre-testing.

8) After completing the final version of TaWai for Health in Lao, we performed a preliminary test to validate the developed tool. This stage is like the pilot study, we assigned 5 HCPs at the different departments to use the modified tool for 1 week to validate the developed tool.(4)

3.2.2 Step of quality testing of research tool

Quality of modified TaWai in Lao version was examined using content validity test. The objectives were the content validity or OIC test were the assessment of whether the content measure or test were relevant to the research objective or not. The detail of each test was provided below

1) Validity test

Validity is one of the most important properties of research tools. In this study, we performed the content validity test to determine the quality of modified TaWai in Lao version because content validity can demonstrate the level of instrument accuracy in measuring what it is intended to measure and provides information on the representativeness. The contents of each component of the modified TaWai in Lao version were validated by three experts including Dr. Phoutsathaphone Sibounheuang, Prof. Soulivanh Keokinnaly, and Assist. Prof. Dr. Ratree Sawangjit. The qualification of each expert was provided below.

- Dr. Phoutsathaphone Sibounheuang, lecturer at University of health sciences in Lao PDR, Doctor of Philosophy (Pharmacy), Faculty of Pharmacy at Mahasarakham University, Thailand.

- Prof. Soulivanh Keokinnaly, Head of the pharmacovigilance center at the ministry of health in Lao PDR, Master of Public Health at University of health sciences in Lao PDR.

- Assist. Prof. Dr. Ratree Sawangjit, Assistant Professor at Mahasarakham University, Doctor of Philosophy (Biological Pharmacy), International Program, Faculty of Pharmacy at Mahidol University.

Three experts were asked to evaluate each item by giving the item a rating of +1 = consistent, -1 = not consistent, or 0 = don't know for each objective. Then the Item Objective Congruence (IOC) scores of each item were calculated as formula (1).(20) If scores less than 0.5 we excluded that item from the component.

Formula $IOC = \frac{\sum R}{N}$ ..... (1)

IOC = Conformity Index (Index of Item Objective Congruence)

R = Expert opinion score for each question

N = Number of experts

In which the points are given by experts as follows:

+1: indicates the question is consistent with the research objective or the operational definition.

-1: means the question is not consistent with the research purpose or operating definition

0: indicates unsure whether the question is consistent with the research objective or the operational definition.

The interpretation criteria

IOC ≥ 0.5 means that the question is relevant to the research objective.

IOC <0.5 means the question does not relevant the research objective.

2) Usability test

The usability test is the method makes us bring our tool to a group of people who are to be target users to try by setting goals for them to achieve the question. Then watched and observed how users think, make decisions, use our tool to accomplish that goal. We performed a usability test to validate the developed tool. This stage we assigned 5 HCPs to use the modified tool for 1 week to validate the developed tool. Each person has to fill out one report.

3.3 Phase 3: Evaluating TaWai mobile system in Lao

A cluster randomized controlled trial was conducted to evaluate the effects of the TaWai mobile system in Lao version. The detail of study design was shown below. **Overview of design**

The design of this study was a cluster randomized controlled trial (cluster RCT). The group of healthcare professionals (HCPs) in tertiary hospitals at Lao PDR were randomized to intervention or control group. Both groups were trained about ADRs and ADR reporting but intervention group was assigned to have addition training on using modified TaWai mobile tool for ADR report and use TaWai tool to report ADRs. Outcomes of interest were rate and quality of ADRs reporting, and satisfaction of HCPs. This study was conducted in compliance with the principles of good clinical practice (GCP) and in accordance with the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Mahasarakham University, Thailand and Lao National Ethics Committee for Health Research, Lao PDR. Written informed consent was obtained from all participants before enrollment. The study is reported in accordance with CONSORT recommendations for randomized controlled trials (54) and the study protocol is registered at www.clinicaltrials.in.th (TCTR2020607002).

3.3.1 Ethical approval and consent to participate

This study was conducted in compliance with the principles of good clinical practice (GCP) and in accordance with the Declaration of Helsinki. The study protocol consent forms, and tools were approved by the Ethics Committee of Mahasarakham University, Thailand (ID: 115-074/2022) and Lao National Ethics Committee for Health Research, Lao PDR (ID: 2021.35). The certificate of approval is in the appendix 9. Written informed consent was obtained from all participants before enrollment

3.3.2 Participants

The recruitment was through invitations by researcher via head of service department in a target cluster of tertiary hospital in Lao PDR (Tuberculosis (TB) and HIV departments of Setthathilad and Mahosot hospitals). The recruitment period was July, 2021, to December, 2021. The study was conducted in May 2022, to August 2022.

Participant eligibility criteria:

Inclusion criteria

1) HCPs who have at least 6 months of experience in the hospital
2) HCPs who have a role in report ADR of patient
3) HCPs who are willing to participate
4) More than 18 years of age

Exclusion criteria

1) HCPs who refuse to participate in this study
2) Nurse

3.3.3. Randomization

All tertiary hospitals in Lao PDR including Mahosot, Setthathirad and Mittapab hospitals were set as a cluster of targeted setting for this study because these setting have more items of medicines that may cause a lot of ADRs. Therefore, there are 3 clusters of tertiary hospitals in Lao PDR. Simple random process was used to sampling the 2 of 3 tertiary hospitals as a target cluster for study (Setthathilad and Mahosot hospitals). Based on simple random sampling, Setthathilad and Mahosot hospitals were assigned as target cluster for this study. These 2 hospitals were randomized into intervention and control group. Based on cluster randomization concept, all department in Setthathilad and Mahosot hospitals should be assigned into the intervention and control group following the randomization code of hospital (HCP cluster of hospital). However, only HCPs in tuberculosis (TB) and HIV departments

willing to participate in this study. Therefore, healthcare professionals (HCPs) in the TB and HIV departments of each hospital who met inclusion-exclusion criteria as mentioned above were recruited into this study.

3.3.4 Intervention and duration of study

The HCPs in control group was given ADR education plus usual practice while the HCPs in the intervention group was given ADR education plus TaWai tool for report ADR in their hospital.

Description of interventions

There were two different types of interventions used in this study including education program of ADR, and modified TaWai mobile tool. Education program of ADR was used as control or standard intervention for this study. This program consisted of a training about the overview of ADRs, ADR monitoring and reporting, common ADRs of medicines used in TB and HIV patients, and management of those ADRs. All HCPs in TB and HIV departments of all randomized hospitals were trained the program by lecturer in Lao PDR in 1 hour for 2 days. The modified TaWai mobile app for Health in Lao version was used as additional tool for reporting ADR in the intervention group whereas the control group used a conventional form which commonly used to report ADR in Lao PDR. In the intervention group, HCPs were trained how to use TaWai for Health in 30 minutes before starting the study. The duration of study and follow up time for each group was 4 months.

3.3.5 The procedure of the study

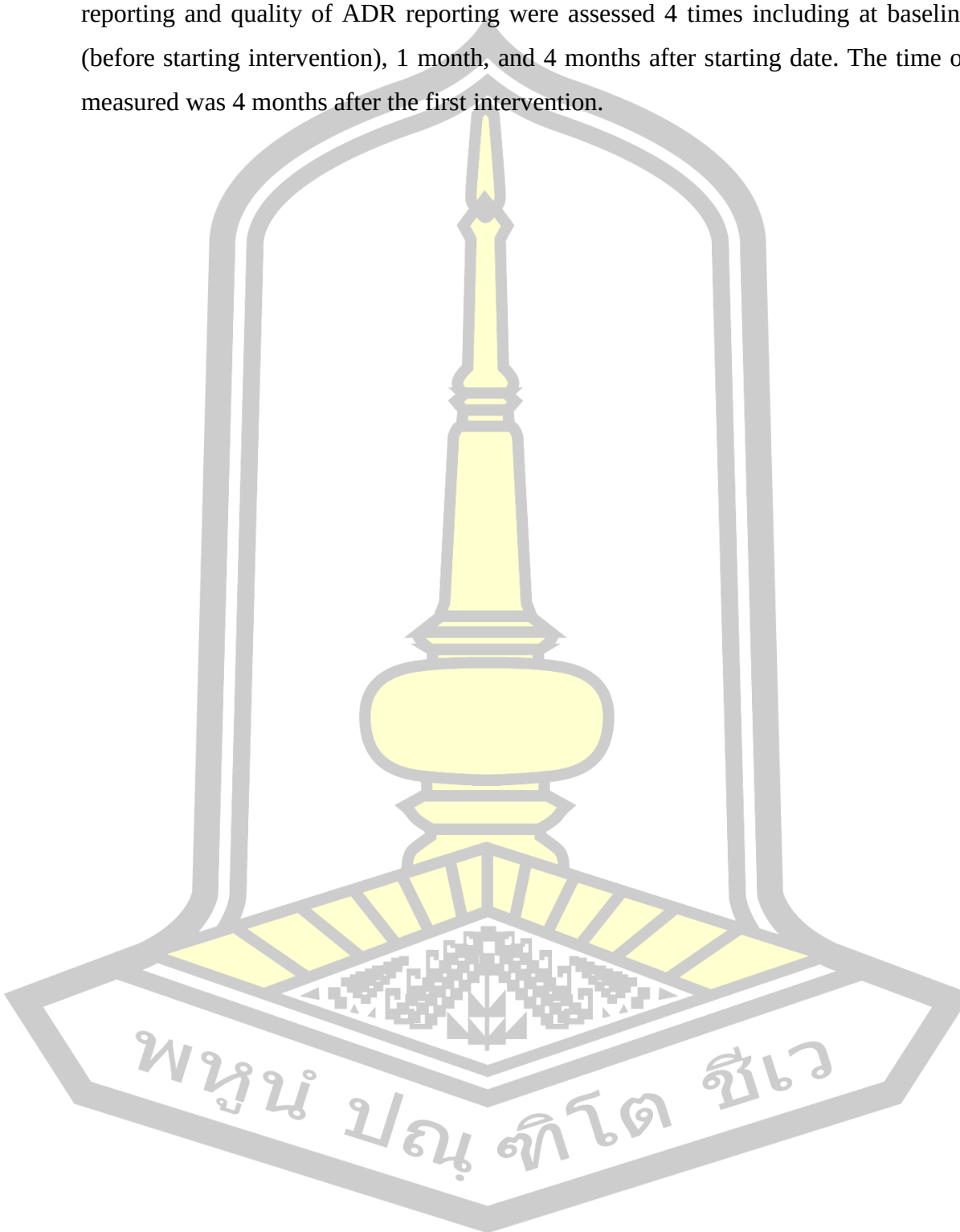
The method of study

1) The researcher submitted the study protocol to the ethics committee (EC) of Mahasarakham University, Thailand and Lao National Ethics Committee for Health Research, Lao PDR.

2) All participants were asked to give a written informed consent form before participating in the study.

3) The expert lecturer in Lao PDR trained education program of ADRs for all HCPs in TB and HIV department of targeted hospitals in 1 hour/day for 2 days. In addition, the researcher trained how to use modified TaWai mobile app for HCPs in the intervention group for 30 minutes. Then researcher advised them to use this tool for reporting ADR during 4 months of study period

4) During the study, target outcomes including the number or rate of ADR reporting and quality of ADR reporting were assessed 4 times including at baseline (before starting intervention), 1 month, and 4 months after starting date. The time of measured was 4 months after the first intervention.



3.3.6 The framework of the study

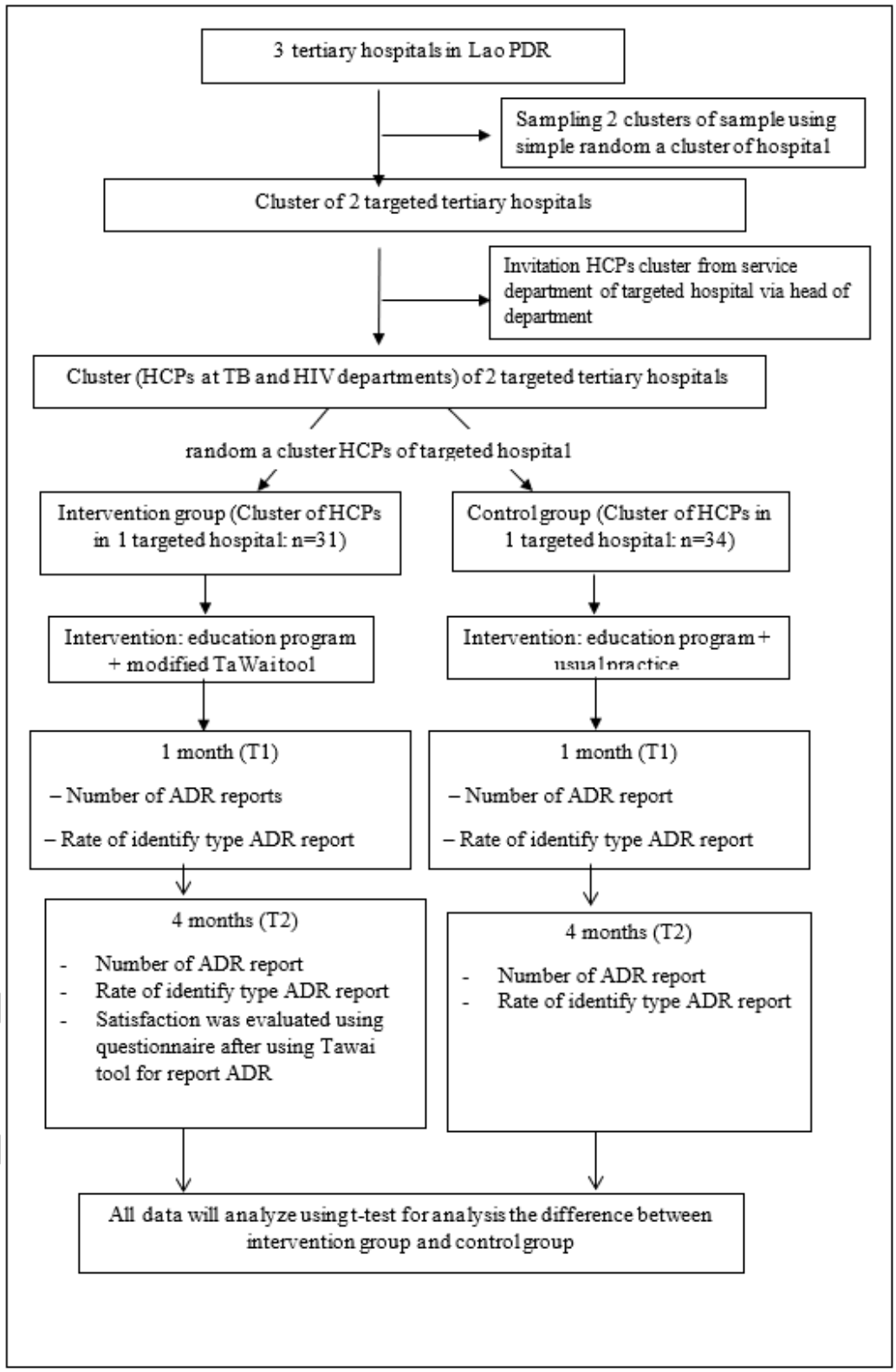


Figure 10 The framework of the study

3.3.7 Outcome assessment

We assessed the efficacy of the intervention such as the number of ADR reporting, percent of ADR reporting and report for quality of the tool. Furthermore, the satisfaction and knowledge of the reporters were evaluated following in appendix 4 and 5.

3.3.8 Data analysis

Statistical analysis was performed using STATA. The statistical significance was considered as $p<0.05$.

1) The statistics was shown as percentages, means with standard deviations for continuous variables and frequencies with percent for categorical variables.

2) Categorical variables were presented as numbers and percentages. gender, age of patients, history of the disease, types of ADR.

3) For categorical variables, a Chi-square method was used to compare between the groups, with the Fisher's exact test performed when the sample size is small.

4) Continuous variables were presented as mean ± SD when data is the normal distribution. A T-test for independent samples were used to compare the mean values between groups

CHAPTER 4

Results

The results of this study were divided into three phases:

Phase 1: Systematic review and meta-analysis of effectiveness of tools for enhancing adverse drug reaction reports

Phase 2: Developing and validating of modified TaWai mobile app in Lao version

Phases 3: Evaluating effects of the modified TaWai in reporting adverse drug reaction in Lao PDR by using the cluster-RCT

4.1 Phase 1: Systematic review and meta-analysis of effectiveness of tools for enhancing adverse drug reaction reports

The PRISMA flow diagram of study selection is shown in Figure 6. The 1,492 related articles were identified through database searching and other sources. After duplication removal, 1,370 articles were eligible for screening. Eighty-nine articles were selected for full-text review based on the title and abstract screening. A total of 78 articles were excluded after full text review because they have no control group. Therefore, 12 articles were included in this study, but only 8 RCTs were included in meta-analysis. The characteristics of included studies were summarized in Table 3. Twelve studies with 24,129 participants were included. Among all studies, there were 10 studies conducted in Europe and 2 studies conducted in Asia. Periods of study ranged from 2004 to 2020. Follow-up durations, and measurement time were three months to three years. All trials indicated that the number of ADR reporting were increased after using tool or program for enhancing ADR reporting. Nine of the studies were randomized controlled design (6 cluster RCTs, 3 RCTs) and three studies were non-randomized controlled trial (non-RCT). Most of included studies (9 of 12) were two-arm design. Characteristics of all interventions were presented in Table 5. Interventions evaluated in the included studies were educated of HCPs using different strategies including face to face workshop (n=9 studies), repeated telephone (n=2), email or letter (n=2), and reward (n=1). The duration of intervention was one month to three months. The most common comparators were usual practice.

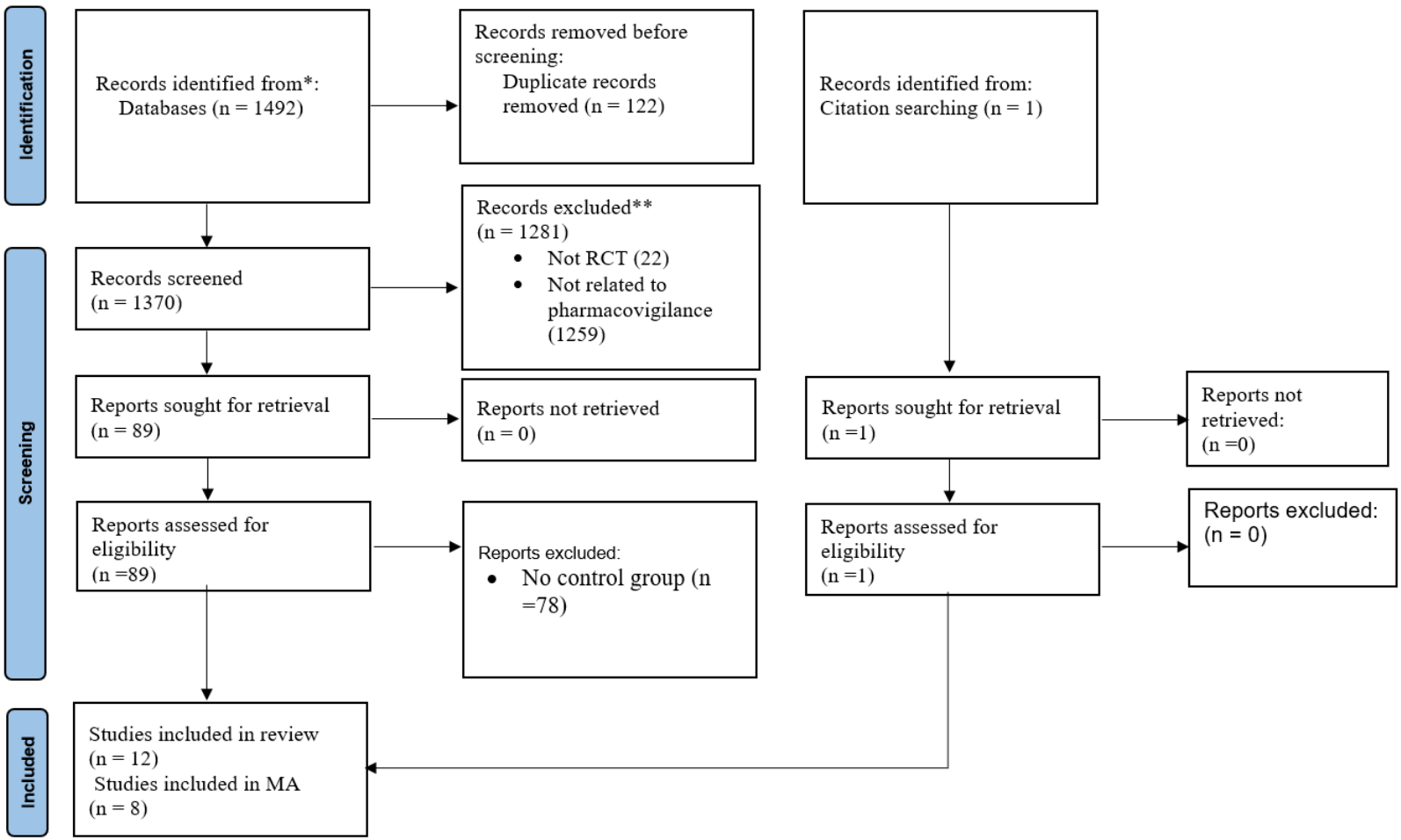


Figure 11: PRISMA flow chart of study selection. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis

Table 5: Characteristic of included studies

Author, year	Country	Study design	Setting	Population	Sample size	Number of group (no. in each group; I/C)	Number of intervention group	Control group	Measure time (month)	Follow up time (month)	Study outcome	Type of ADRs	Type of products
Ribeiro-Vaz et al,2011	Portugal	Cluster RCT	Hospital and community pharmacist	Pharmacist	1467	3 (261/103/1103)	364	1103	4	20	Number of report ADRs	Overall, Serious, unexpected and probable	Medicines
Johansson et al,2011	Sweden	RCT	Primary health care unit	GPs and nurse	151	2 (77/74)	77	74	12	12	Number and quality of report ADRs	Overall, Serious, unexpected and new drug	Medicines
Herdeiro et al,2012	Portugal	Cluster RCT	Hospital	Physicians and primary care	6579	3 (1034/438/5107)	1472	5107	4	20	Number of reporting	Overall, Serious, unexpected and probable	Medicines
Lopez-Gonsalez et al,2015	Spain	Cluster RCT	Hospital and primary care centre	Physicians	7498	2 (2120/3614)	2120	3614	4	8	Number of reports ADRs	Overall, Serious, unexpected and probable	Medicines
Figueiras et al,2016	Portugal	Cluster RCT	Hospital	Physicians	6451	2 (1388/5063)	1388	5063	4	16	Number of reporting	Overall, Serious, unexpected and new drug	Medicines
Shochory et al, 2020	Isarael	cluster RCT	Medical center	Physicians and nurse	433	2 (207/226)	207	226	5	17	percentage and number of ADRs report,	Overall of ADR et	Medicines
Herdeiro et al,2008	Portugal	Cluster RCT	Hospital and community pharmacist	Pharmacist	1433	2 (342/1091)	342	1091	4	16	Total number of report	Overall, Serious and unexpected and new drug	Medicines
Johansson et al,2009	Sweden	RCT	Primary health care unit	head of primary care unit	117	2 (59/58)	59	58	12	12	Number and quality of report ADRs	Overall, Serious and unexpected	Medicines
Bracchi et al,2005	England	Prospective	GP, community pharmacies	GP and Pharmacist	3784	NR	Pharmacist	Northern region of England	12	12	Number of ADRs report	Overall of ADRs	Medicines
Gony et al,2010	France	longitudinal	Non-university hospital	doctors and nurses	NR	NR	All HCPs two regions	All HCPs one regions	36	36	number of ADRs report	Serious ADRs	Medicines
Backstrom et al, 2006	Sweden	Prospective	Hospital and primary care center	GPs and physician	NR	NR	Unclear	Unclear	6	6	number of ADRs report	Overall Serious and suspected ADRs	Medicines
Desai C et al,2014	India	RCT	Tertiary care teaching hospital	Prescribers	169	2(84/85)	Prescribers	Prescribers	3	3	Rate and quality of ADR reporting	Overall of serious ADR	Medicines

Abbreviation: *GPs: general practitioners; RCT: randomized controlled trial; NR: not report; ADR: adverse drug reaction

Table 6 Characteristics of interventions

Author, year	Control group	Tools/platforms of intervention group	Detail of interventions	Types of communication	Intensity/dosage regimen	Frequency/ month	Provider
Ribeiro-Vaz et al,2011	Usual practice	1. Education by face to face workshop 2. Education by telephone	**Education:** 1 h about 1. Introduction about problem of ADR, 2. Impact on public health 3. A spontaneous report of ADR. Some of attitude and Knowledge. **Telephone:** The script was found to be efficient, enabling conversation between interviewer and pharmacist. 4-12 min	Two-way communication	1. 1 h, 2 times per week for 1 month 2. 4-12 min, 2 times per week for one month	8	Pharmacist
Johansson et al,2011	Usual practice	Education by letter	The Information letters: consisted of (i) the heading “ADR Information Letter”, (ii) a current case report of an ADR and (iii) instructions on what and how to report. The letters were sent in January, May, and September	One- way communication	1 time per month for3 occasion	3	Pharmacist
Herdeiro et al,2012	Usual practice	1. Education by face to face workshop 2. Education by telephone	**Telephone:** 3–8 min, depending on the degree of physician participation. A total of three attempts were made to call each physician by telephone, after which he/she was deemed impossible to contact. During the interview, physicians were asked whether (i) they had ever had any suspicion of ADRs; (ii) they had experienced any difficulty in reporting; (iii) they remembered the different methods that could be used for reporting purposes (telephone, fax, email or internet); (iv) they attached importance to the individual physician’s role in reporting; (v) they remembered any cases of an alert (such as cyclooxygenase-2 inhibitors and statins cases) in which reporting had played a vital role; and finally (vi) they had any questions	Two-way communication	1. 1 h, 2 times per week for 1 month 2. 3-8 min, 2 times per week for one month	8	Physician

Table 6 (continue)

Author, year	Control group	Tools/platforms of intervention group	Detail of interventions	Types of communication	Intensity/dosage regimen	Frequency/ month	Provider
			concerning the reporting system. Following the telephone interview, each participant was sent support material, which included one letter of acknowledgment, one ADR spontaneous report form and one NPC presentation folder to the desired address. **Workshops**, on the other hand, consisted of a brief presentation lasting approximately 1 hour, including definitions of pharmacovigilance, ADRs and their impact on public health, followed by a more in-depth approach to spontaneous ADR reporting and physicians' attitudes to and knowledge of the practice.				
Lopez-Gonsalez et al,2015	Usual practice	Education by face to face workshop	**The education about**: 1. Importance of reporting ADR, 2. Explain in term morbidity, mortality and cost. 3. on limitation of clinical trial for detection of ADR and advantage about spontaneous report	One-way communication	25 min, 1 time per week for 1 month	4	Pharmacist
Figueiras et al,2016	Usual practice	Education by face to face workshop	Identify attitude about probability of ADR reporting 1.present definition about PV and ADR.2. Review if International studies on drug related morbidity, mortality, hospital admission and cost	One-way communication	1 h per week for 1month	4	Physician
Shochory et al,2020	Usual practice	Education by face to face workshop	1. Poster for raising the aware about ADR 2. 45 min for lecture about ADR and pharmacovigilance, explain about importance of ADR, information about the relationship between ADE and morbidity, mortality, incidence and prevalence of ADR during hospitalization and the cost of ADRs.	One-way communication	45 min, 1 time and Visit department 2 time per week	8	Physician

Table 6 (continue)

Author, year	Control group	Tools/platforms of intervention group	Detail of interventions	Types of communication	Intensity/dosage regimen	Frequency/ month	Provider
			3. Program promotion: Visit department 2 time/week for talking with medical staff for discus about mobile phone ,homepage sending text message				
Herdeiro et al,2008	Usual practice	Education by face to face workshop	The intervention took the form of 1-hour long educational outreach visits tailored to training needs detected in a previous study	One-way communication	1 h per month	1	Pharmacist
Johansson et al,2009	Usual practice	Education by email	The intervention consisted of e-mails with attachments sent out to each of the 117 heads in January, May and September 2007. These e-mails included (1) the heading “Every ADR reporting is important”, (2) a current case report of an ADR and (3) instructions on how to report. The number of reports from each primary health care unit run by the same head was registered, as was the quality of the report. The quality was defined as high if the ADR was (1) serious, (2) unexpected or (3) related to the use of new drugs and not labeled as common in the summary of product characteristics	One-way communication	1 time per month for 3 occasion	3	Pharmacist
Bracchi et al,2005	Usual practice	Education by face to face workshop	Not report	One-way communication	Not report	Not report	Physician
Gony et al,2005	Usual practice	Education by face to face workshop	Not report	One-way communication	Not report	Not report	Physician
Backstrom et al,2006	Usual practice	Reward	The information given was the same, except the additional information only to the physicians in the IA that they would receive two lottery tickets with a value of around 5 euros, in	One-way communication	Not report	Not report	Physician

Table 6 (continue)

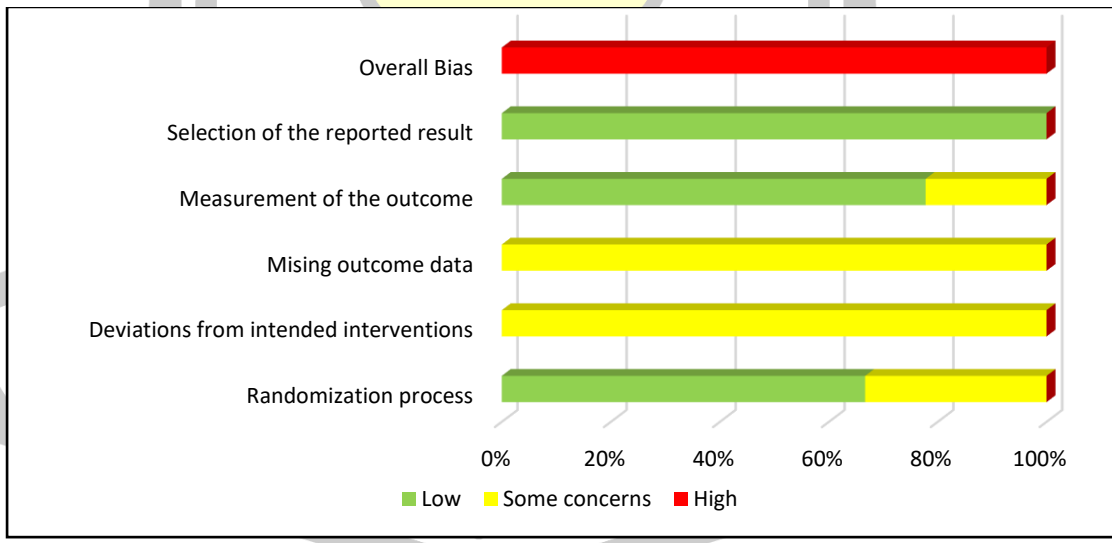
Author, year	Control group	Tools/platforms of intervention group	Detail of interventions	Types of communication	Intensity/dosage regimen	Frequency/ month	Provider
			addition to the usual feedback in connection to each ADR reporting during a period of 6 months.				
Desai C et al,2014	Usual practices	Education by face to face	Study tools included a pre-validated knowledge, attitude and practice (KAP) questionnaire, ADR Reporting Forms and Educational Interventions (EI). Data was collected in pre- intervention (Pre-IP), intervention I and II (IP-I, IP-II) and post- intervention (Post-IP) phases, each of 3 months. Both groups were educated through a Pharmacovigilance Awareness Program and posters. Additionally, Group A (n = 84) also received SMS alerts (IP-I) and personal briefings (IP-II) while Group B (n = 85) received e- mails (IP-I) and information leaflets (IPII).	One-way communication	Not report	3	Pharmacist

4.1.1 Quality assessment for RCT and non-RCT

For 9 RCTs included in this study, 100% (9/9) overall bias were rated high risk of bias. The major reason for the judgment of high risk of bias was blinding of participants and personnel (performance bias) was not discussed sufficiently (Figure7). However, ROBIN-I was used for quality assessment for non-RCT founded moderate to serious risk of bias (Figure 12).

No.	Author	Year	Random sequence generation	Allocation cocealment	Binding of participant and personnel	Binding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias	Overall Bias
1	Ribeiro-Vaz	2011								
2	Johansan	2011								
3	Herdeiro	2012								
4	Lopez-Gonzalez	2015								
5	Figueiras	2016								
6	Shchory	2020								
7	Herdeiro	2008								
8	Johanson	2009								
9	Desai C	2014								

11A: ROB individual assessment



11B: Overall ROB assessment

Figure 12: Risk of bias assessment of the included randomized controlled trial

Author, Year	Baseline confounding	Selection of participants	Classification of intervention	Missing data	Measurement of outcomes	Selection of reported results	Overall risk of bias
Bracchi et al,2005	Moderate	Low	NI	NI	Moderate	Moderate	Moderate
Gony et al,2010	Low	Low	NI	Serious	Moderate	Moderate	Serious
Backstrom et al, 2006	Moderate	Low	NI	NI	Moderate	Moderate	Serious

Abbreviation: *NI: No information

Figure 13: Risk of bias assessment of the included non-randomized controlled trials

4.1.2. Effects of interventions on ADR reporting

The meta-analysis indicated that educated HCPs by all strategies showed a statistically significant 4.5 folds increase in overall ADR reporting (RR=4.53, 95% CI; 2.59-7.92; n=10, I^2=84.4%) compared to the control group (figure 13). In addition, educated HCPs can increase reports of serious, and high level of probability ADRs (Figure 13). Subgroup analysis by types of intervention indicated that educated HCPs by face to face workshop resulted in a significant increase of overall ADRs reporting with a risk ratio (RR) of 4.37 (95%CI: 2.81-6.81; n=6; I^2=79%) when compared with usual method. In addition, this strategy also significantly increased reports of serious, high level of probability, and new drug related ADRs (Figure 14.1). However, educated HCPs by educated by repeated telephone and, email or letter did not increase rate of ADR reporting (Figure 14.2, 14.3). In terms of quality of report, the number of high-quality ADR reporting in intervention group was statistically significant increased with RR 1.36 (95%CI: 1.14, 1.62; n=3; I^2=0%) compared with the control group.

For publication bias tests using funnel plot and egger tests indicated that there was no evidence of small study effect (p-value = 0.163) as showed in figure 16.

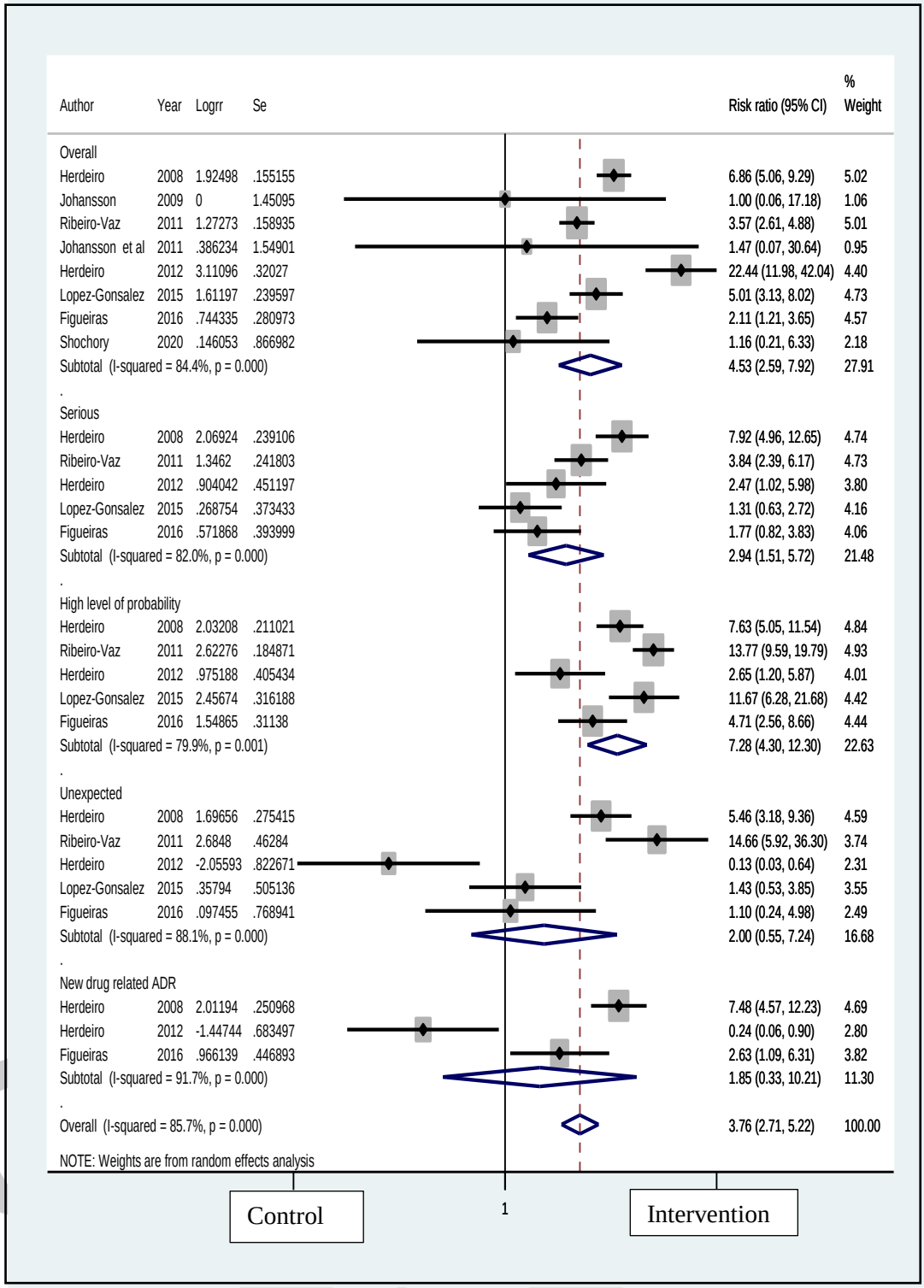


Figure 14: Meta-analysis of all intervention for any type of ADR reporting

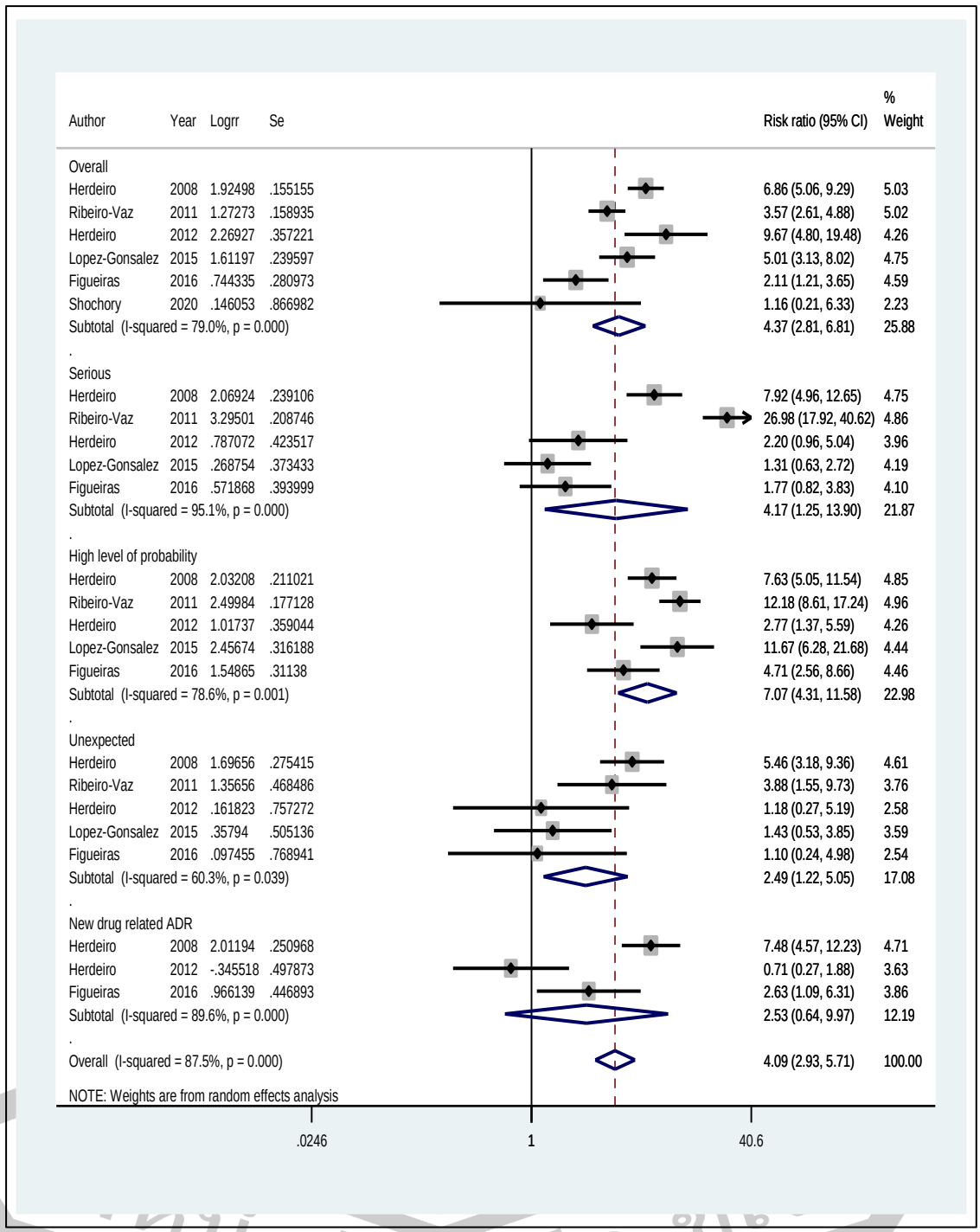


Figure 15 Meta-analysis results separated by types of interventions: educated by face to face

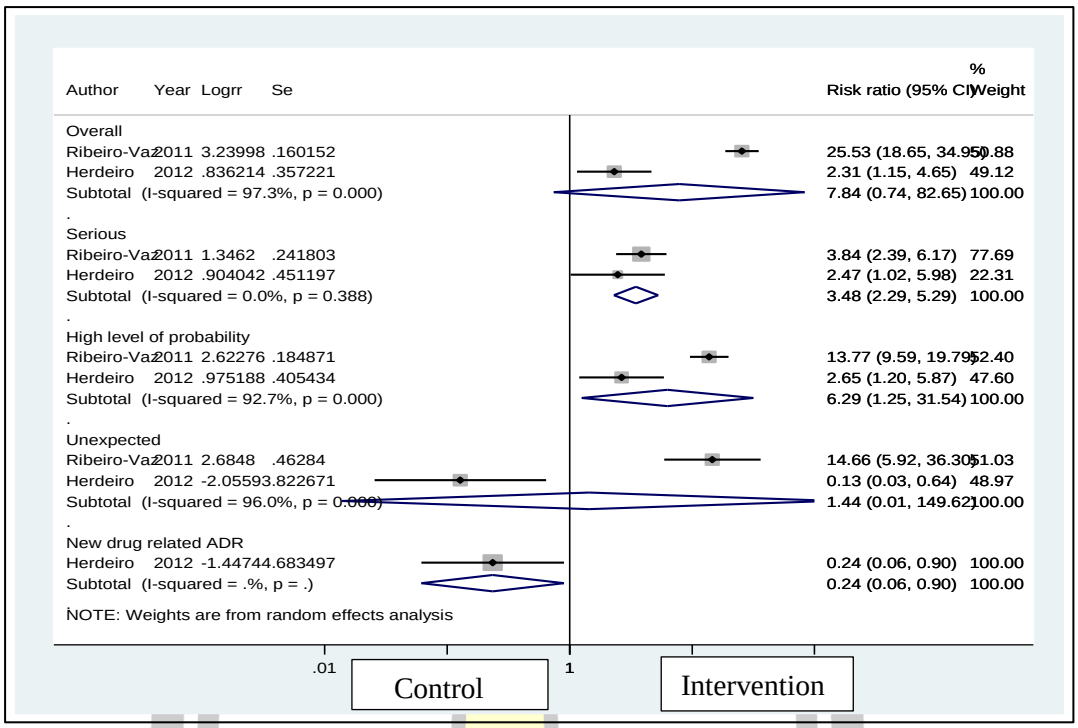


Figure 16 Meta-analysis results separated by types of interventions: educated by repeated telephone

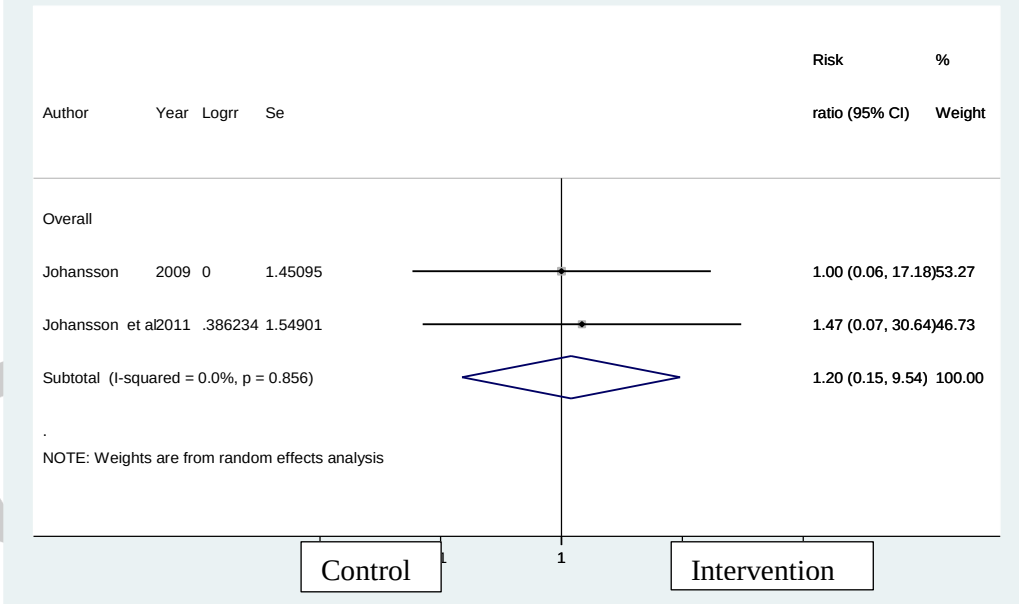


Figure 17 Meta-analysis results separated by types of interventions: educated by email or letter

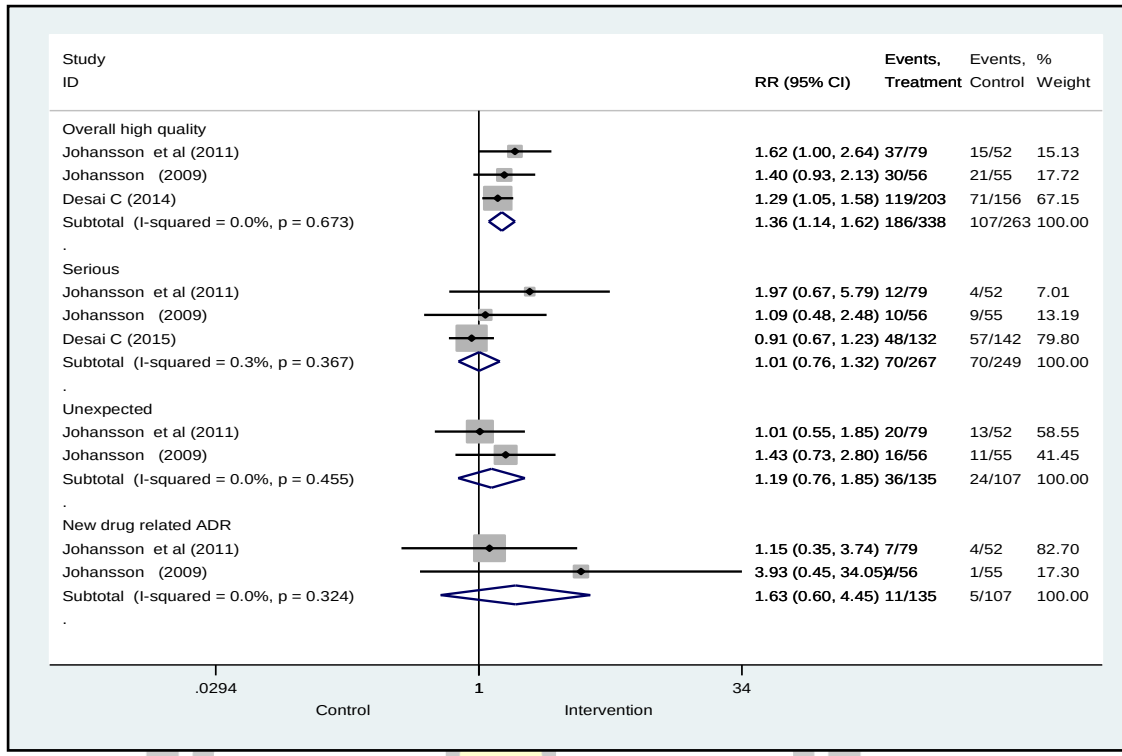


Figure 18 Meta-analysis of high-quality report outcome

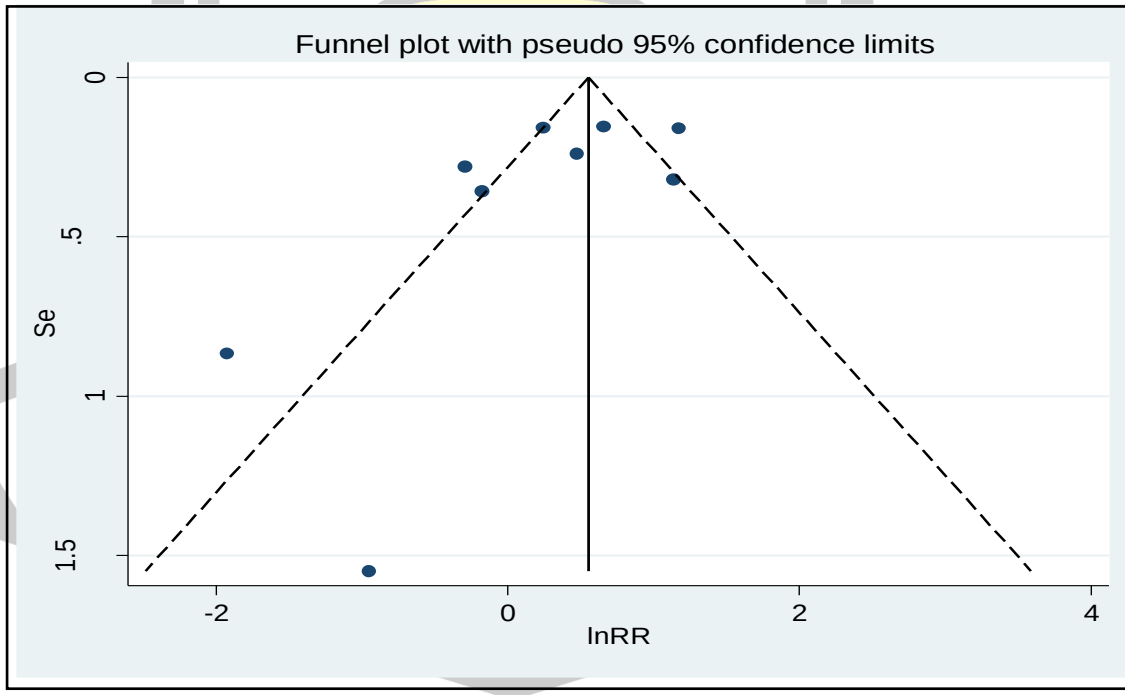


Figure 19 Publication bias for overall ADR reporting

4.2 Phase 2: Developing and validating of modified TaWai in Lao version

1. Modified Tawai in Lao version was developed as a draft for developing chatbot on app for using with mobile phone. Items for applying in this version were developed from Thai version incorporated with situation of Lao PDR, national guideline of pharmacovigilance, the regulation of ADR reporting, and law related to ADR reporting in Lao PDR. Important information of ADR reporting needed for WHO was also applied in this version.

2. Quality testing of research tool

Quality of modified TaWai in Lao version was examined using validity test. The content validity test of each component of the modified TaWai in Lao version was approved by three experts included Dr. Phoutsathaphone Sibounheuang (Vice-head of pharmaceutical care department) Dr. Khamloun Choumlyvong (Head of TB Unit), and Dr. Soulyvanh Keokinnaly (Head of PV center). The assessor's qualifications are the people who understand Lao language, and working related with PV or report case ADR, and graduated with a bachelor degree. The result of almost every question of the content validity test of IOC were equal 1, it demonstrated that these questions were available. It showed that every question was consistent or means that the questions is relevant to the research objective. The question for the content validity assessment were following the detail below.

Table 7 The content validity test of each component of the modified TaWai in Lao version

N°	Content assessment	Score comment of expert			Total score	IOC	Result
		Expert 1	Expert 2	Expert 3			
Patient information							
A1	Name-surname of patient	+1	+1	+1	3	1	Available
A2	Gender	+1	+1	+1	3	1	Available
A3	National	+1	+1	+1	3	1	Available
A4	Age	+1	+1	+1	3	1	Available
A5	Weigh (kg)	+1	+1	+1	3	1	Available
A6	High deceit (cm)	+1	+1	+1	3	1	Available
A7	HN	+1	+1	+1	3	1	Available
A8	History of drug allergy or health product	+1	+1	+1	3	1	Available
A9	co-morbidity	+1	+1	+1	3	1	Available
A10	Other such as pregnancy, breast feeding	+1	+1	+1	3	1	Available
A11	Patient smoking or drink alcohol or not	+1	+1	+1	3	1	Available
Detail of ADR							
B1	Write a description of the adverse reactions that occur.	+1	+1	+1	3	1	Available
B2	Do you have pictures of the patient's symptoms or abnormalities??	+1	+1	+1	3	1	Available
B3	Date of ADR occur	+1	+1	+1	3	1	Available
B4	Department of ADR occur	+1	+1	+1	3	1	Available
B5	For the symptoms that occur it severe or not?	+1	+1	+1	3	1	Available
B6	For the symptoms that occurred this time. Has the patient been admitted to the hospital or not?	+1	+1	+1	3	1	Available
Detail of drug suspect							
C1	Please specify the name of the product in question.	+1	+1	+1	3	1	Available
C2	Choose a product type	+1	+1	+1	3	1	Available

Table 7 (continue)

N°	Content assessment	Score comment of expert			Total score	IOC	Result
		Expert 1	Expert 2	Expert 3			
C3	product form	+1	+1	+1	3	1	Available
C5	ท่านมีรูปผลิตภัณฑ์ ดั่งกล่าว หรือไม่ ? Do you have a picture of the product or not?	+1	+1	+1	3	1	Available
C6	ท่านหราบเลขทะเบียนผลิตภัณฑ์ หรือ เลขทะเบียน อย ของผลิตภัณ ดั่งกล่าวหรือไม่? Do you know the product registration number or FDA registration number of this products?	+1	+1	+1	3	1	Available
C7	กรุณาระบุผลิตภัณฑ์ หรือ ยาแรกที่คิดว่าเป็นสาเหตทำให้เกิดอาการไม่พึ่งประสง Please specify the first product or drug that is thought to cause unintended symptoms.	+1	+1	+1	3	1	Available
C8	กรุณาระบุปริมาณการใช้ผลิตภัณฑ์ ของผู้ป่วย (ต่อครั้ง/ต่อวัน) Please specify the amount of use of the patient's product (per time/per day).	+1	+1	+1	3	1	Available
C9	Please specify the purpose of the patient using the product.	+1	+1	+1	3	1	Available
C10	กรุณาระบุ ช่วงเวลาที่เริ่มใช้ผลิตภัณฑ์Please specify when the product starts.	+1	+1	+1	3	1	Available
C11	กรุณาระบุ ช่วงเวลาที่อยุดใช้ผลิตภัณฑ์Please specify the period when you stop using the product.	+1	+1	+1	3	1	Available

Table 7 (continue)

N°	Content assessment	Score comment of expert			Total score	IOC	Result
		Expert 1	Expert 2	Expert 3			
C12	กรุณาระบุข้อสงสัยเพิ่มเติมที่เกี่ยวข้องกับผลิตภัณฑ์ นี้ Please indicate any additional inquiries related to this product.	+1	+1	+1	3	1	Available
C13	กรุณาเลือก หรือ ระบุแหล่งที่มาของผลิตภัณฑ์ นี้ Please select or specify the origin of this product.	+1	+1	+1	3	1	Available
C14	หากประเมินตาม Category Naranjo ความเป็นไปได้ของอาการไม่เพิ่งประสงที่เกิดขึ้นนี้ ท่านให้คะแนนท่าไร? If assessed by Naranjo category, the possibility of Category ADR assessment	+1	+1	+1	3	1	Available
Reporter information							
D1	The reporter such as name and surname, position, date of report, telephone number, e-mail or contact information	+1	+1	+1	3	1	Available

3. Use case scenario

After assessed the validity test, the pre-final tool test (use case scenario**)** was performed, five HCPs were asked use this modified TaWai app for report ADR from case studies prepared by researcher. Then the problem or misunderstanding of item or information in app was reported. This test indicated that most question were available, but there had some minor revisions to Lao language in part of suspected medications and had a minor problem about category of ADR evaluated by Naranjo algorithm.

4. After revision the problem of draft for chabot development, the programmer constructed the chatbot of TaWai for Health in Lao version on the mobile app following the draft in Appendix 2.

5. A pilot testing

After completing the final version of TaWai for Health in Lao, we performed a preliminary test to validate the developed tool. 5 HCPs from the different departments were asked to use this modified TaWai app to report ADRs for 1 week. The result showed that all 5 HCPs answer the question almost correct and right. After that, the researcher interviewed all HCPs to find the problems of the chabot. The problems were consulted with the programmer to construct the final version of modified TaWai app in Lao version as show in figure below or Link https://lin.ee/MTrkJ9b.

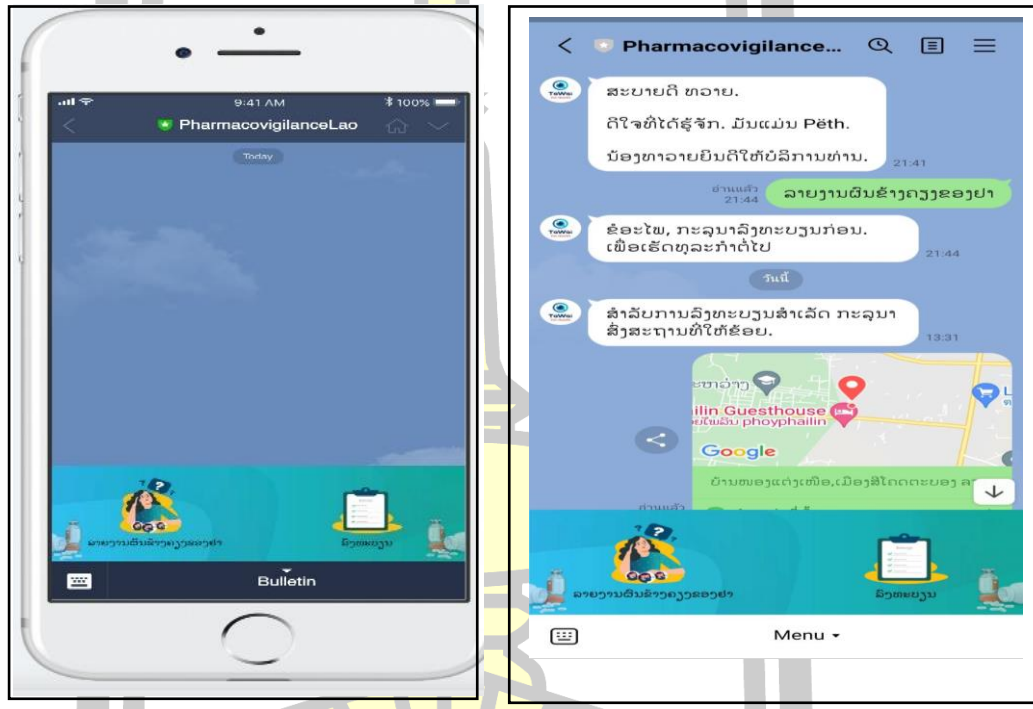


Figure of registration in TaWai app

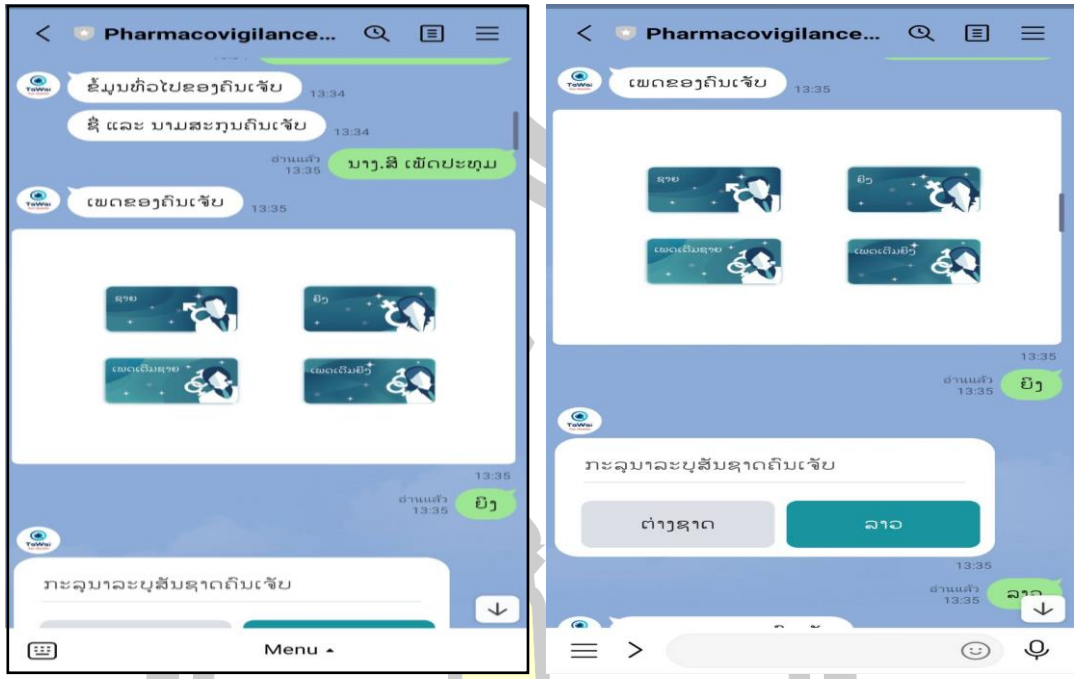


Figure of Patients information

Figure of suspect medicine or product information

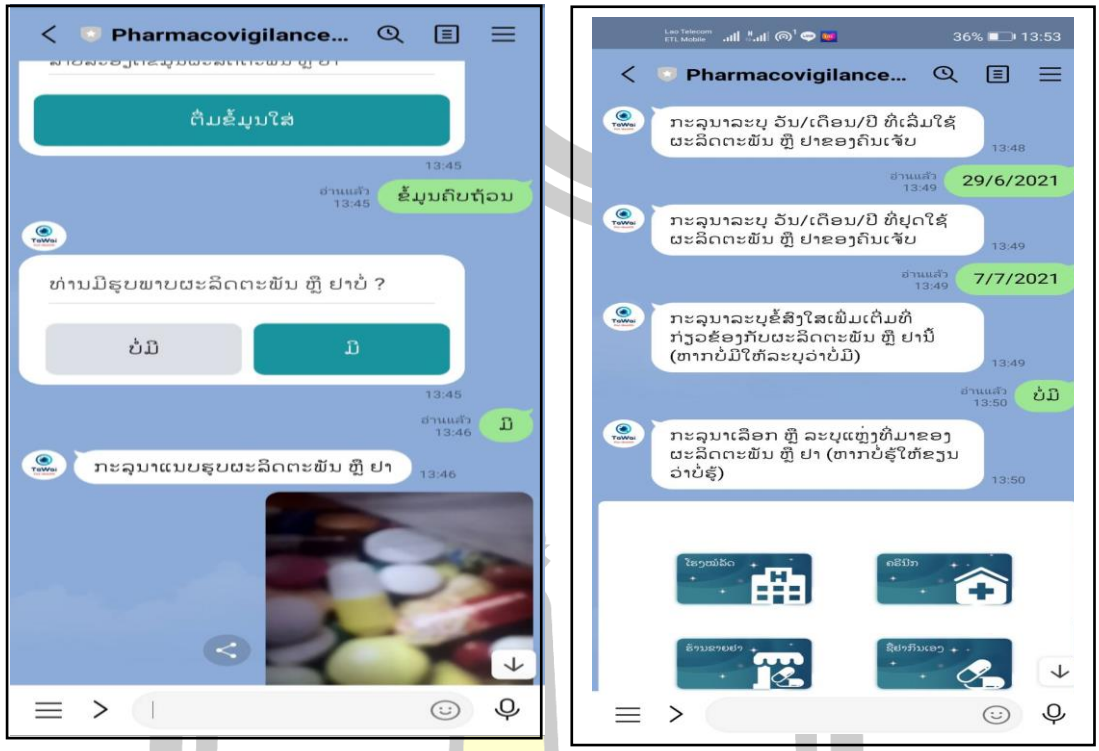


Figure of detail of medicine or product suspect

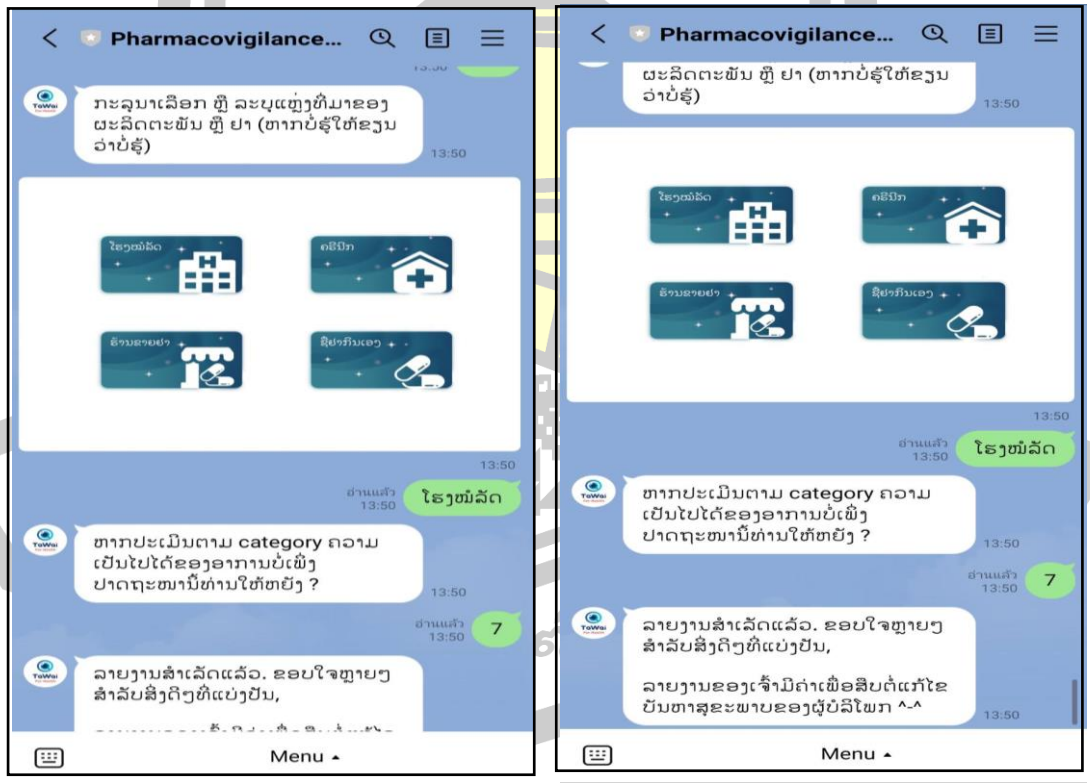


Figure of product or medicine source

4.3 Phase 3: Evaluating TaWai mobile system in Lao

A cluster-RCT was performed to evaluate the developed TaWai mobile system in Lao. The two of tree tertiary in Lao PDR were randomized to control and intervention groups. Based on simple random sampling, Setthathilad and Mahosot hospitals were assigned as target cluster for this study. These 2 hospitals were randomized into intervention and control group. Then, all healthcare professionals (HCPs) work at these hospitals were assigned into the intervention and control group following the randomization code of hospital (HCP cluster of hospital). The HCPs in the control group was given ADR education plus usual practice while the HCPs in the intervention group was given ADR education plus TaWai tool for report ADR in their hospital. Overall, 34 HCPs with average age of 37.94 (SD: 8.83) years were enrolled and participated in ADR education program training of this study. Characteristics of all included HCPs in this study were reported in Table 7. Most of them were females (65%). Work experience in hospital of HCPs in the intervention and control group was approximately 12 and 13 years, respectively. All characteristics including gender, age, occupation, education, marital status, duration of work, and experience of work at hospital between 2 groups were similar (Table 9).

Table 8: Characteristics of included healthcare professionals

Characteristics	All participants (n=34)	Intervention group (n=16)	Control group (n=18)	P-value
Gender, n (%)				
- Male	12 (35.29)	4 (25)	8 (44.44)	0.23[a]
- Female	22 (64.71)	12 (75)	10 (55.56)	
Age (year), Mean ± SD	37.94±8.83	37.75 ± 9.08	38.11±8.87	0.52[b]
Range	26-59	28-58	26-59	
Occupation, n (%)				0.54[a]
- Doctor	27 (79.41)	12 (68.75)	15 (83.33)	
- Pharmacist	7(20.59)	4 (31.25)	3 (16.67)	
Education, n (%)				0.61[a]
- Bachelor	22 (64.71)	12 (68.75)	11 (61.11)	
- Master	11 (32.35)	4 (31.25)	6 (33.33)	
- Phd	1 (2.94)	0 (0.00)	1 (5.56)	
Marital status, n (%)				0.53[a]
- Single	8 (3.53)	4 (25)	4 (22.22)	
- Married	25 (73.53)	11 (68.75)	14 (77.78)	
- Widow	1 (2.94)	1 (6.25)	0	
Duration of work (year), Mean ± SD	12.64 ± 7.92	12.12 ± 7.43	13.11 ± 8.13	0.81[b]
Range	2-32	3-32	2-32	
Experience of work at hospital (year), Mean ± SD	12.41 ± 7.78	11.68 ± 7.01	13.05 ± 8.57	0.64[b]
Range	2-32	3-32	2-32	

a= Fisher's exact test, b= independent t-test

4.3.1 Knowledge of HCPs on adverse drug reaction (ADR) and pharmacovigilance (PV).

To ensure the similarity of knowledge on ADR and PV between 2 groups, all included HCPs were participated in ADR education program training and questionnaire on this topic was used to evaluate their knowledge before and after training. The result indicated that knowledge on ADR and PV of HCPs between intervention and control groups was comparable (Table 8). The criteria of evaluated their knowledge by theory Bloom 1971 et all, it divided in three levels were the high knowledge score ≥ 80 % (37 scores), the moderate knowledge score 60-79% (28-36 scores) and low of knowledge ≤ 60% (≤ 28 scores).

Table 9: Knowledge of HCPs between intervention and control groups

Outcome	**Intervention (n=16)**	**Control (n=18)**	**P-value**
Score of knowledge assessed by questionnaires (Total score=46)			
Pre-test	36.33 ± 3.25	36.22 ±1.71	0.97
Post-test	37.44 ± 3.23	40.66 ± 2.12	0.45

a=independent t-test

4.3.2 Effect of intervention on ADR reporting

The number and detail of ADR reporting in intervention and control groups were reported in Table 9. The number of ADR reporting in intervention and control groups were 28 and 3 cases, respectively. The number of ADR reporting classified by reporters were 78% in the intervention and 66% in the control groups. The most characteristics of patients who have ADRs were males and Lao national with average age of 44.21 (SD: 10.00) years and 33.66 (SD: 8.50) years respectively. However, the most patient had no history of allergy and the patient had smoking and drink alcohol in two groups. Furthermore, the detail of patient allergy in intervention and control groups were rash 36% and 33% respectively and rash+ short of breathiness (SOB) with or without itchy were 11% and 67% respectively. The most severity of ADR were non serious and for the suspected medications were Bactrim and anti-TB. In addition, the most indication of medicine were HIV and TB patients. For three cases in control group had been reporting to pharmacist and sent to PV center, we double-check to ensure the data in PV center.

Table 10 Number and characteristics of ADRs report in intervention and control group

Characteristics of patients who have ADRs	Intervention group, n (%)	Control group, n (%)
Number of ADR reporting classified by reporters		
▪ Doctor	22 (78.57)	0 (0.00)
▪ Pharmacist	6 (21.43)	2 (66.67)
▪ Unknown		1 (33.33)
Gender of patient		
▪ Male	18 (64.29)	2(66.67)
▪ Female	10 (35.71)	1 (33.33)
National, n (%)		
▪ Lao	27 (96.43)	3 (100)
▪ Foreigner	1 (3.57)	0 (0.00
Age (year), Mean ± SD	44.21±10.00	33.66±8.50
Range	24-70	25-42
History of drug allergy, n (%)		
▪ No	24 (85.71)	2 (66.67)
▪ Yes: Occurring of rash	4 (14.9)	0 (0.00)
▪ Pyrazinamine	2 (7.14)	0 (0.00)
▪ 4FDC	1 (3.57)	0 (0.00)
▪ Bactrim	1 (3.57)	0 (0.00)
▪ Unknown		1 (33.33)
Comorbidity, n (%)		
▪ No	15 (53.57)	2 (66.67)
▪ Yes:	13 (46.43)	0 (0.00)
▪ Hypertension	6 (21.43)	0 (0.00)
▪ Gout	6 (21.43)	0 (0.00)
▪ Diabetic	1 (3.57)	0 (0.00)
▪ Unknown		1 (33.33)
Social history: smoke or alcohol drinking, n (%)		
▪ No	13 (46.43)	
▪ Yes	16 (53.57)	2 (66.67)
▪ Unknown		1 (33.33)
Department found ADR, n (%)		
▪ TB	9 (32.14)	3 (100)
▪ HIV	19 (67.87)	0 (0.00)

Table 10 (continue)

Characteristics of patients who have ADRs	Intervention group, n (%)	Control group, n (%)
Detail of patient allergy, n (%)		
1) Type B ADR (Drug allergy)		
▪ Total Rash		
- Rash	10 (35.71)	1 (33.33)
- Rash with itchy	9 (32.14)	2 (66.67)
- Rash+ SOB with or without itchy	3 (10.73)	0 (0.00)
- Rash + fever with or without itchy/ SOB	2 (7.14)	0 (0.00)
- Edema	1 (3.57)	0 (0.00)
2) Type A ADR (true ADR)		
- Renal toxicity	2 (7.14)	0 (0.00)
- Hepatotoxicity	1 (3.57)	0 (0.00)
Severity of ADR, n (%)		
▪ Serious	6 (21.43)	0 (0.00)
▪ Non serious	22 (78.57)	2 (66.67)
▪ Unknown		1 (33.33)
Suspected medications, n (%)		
▪ Bactrim	9 (32.17)	0 (0.00)
▪ Anti-TB drug	6(21.42)	3 (100)
▪ Anti-viral	3(10.71)	0 (0.00)
▪ Analgesic	3(10.71)	0 (0.00)
▪ Fixed combination of Tenofovir/Lamivudine/Dolutegravir	3(10.71)	0 (0.00)
▪ NSIADS	1(3.57)	0 (0.00)
▪ combination of linezolid, bedaquidine, levofloxacin, and clofazamine (alternative regimen for TB treatment)	1(3.57)	0 (0.00)
▪ Other: amphotericin B, azithromycine	2 (7.14)	0 (0.00)
Dosage form and administration route of medicine, n (%)		
▪ Tablet (oral)		
▪ Unknown	28 (100)	2 (66.67)
		1 (33.33)
Medication approval from Lao FDA, n (%)		
▪ No	6 (21.43)	0 (0.00)
▪ Yes	22 (78.57)	2 (66.67)
▪ Unknown		1 (33.33)

Table 10 (continue)

Characteristics of patients who have ADRs	Intervention group, n (%)	Control group, n (%)
Indication of medicine, n (%)		
▪ HIV	11 (39.29)	
▪ TB	6 (21.43)	
▪ Fever	3 (10.71)	3 (100)
▪ Pneumonia	3 (10.71)	
▪ Back pain	1 (3.57)	
▪ MDR-TB	1 (3.57)	
▪ Meningitis	1 (3.57)	
▪ Prophylaxis	1 (3.57)	
▪ Toxoplasma	1 (3.57)	
Source of medicine, n (%)		
▪ Tertiary hospital	25 (89.29)	3 (100)
▪ Pharmacy	3 (10.71)	0 (0.00)
Category of ADR evaluated by Naranjo algorithm		
▪ Definite		
▪ Probable	2 (7.14)	0 (0.00)
▪ Unknown	26 (92.86)	2 (66.67)
		1 (33.33)
Quality of ADR reporting		
▪ High quality	28	2
▪ Low	0	1

4.3.3 Quality of ADR reporting

The quality of report in this study was assessed using WHO criteria. The report was rated as high quality if it consists of all important items following WHO criteria. The criteria of low quality of the reports was critical for appropriate evaluation of the relationship between the product and adverse reactions, thus good case reports include the following elements 1) Description of the adverse reaction or disease experience, including time to onset of signs or symptoms and the seriousness of the reaction/s; 2) Suspected and concomitant medicines details (i.e., name, dose, dosage form, rout of administration, indication for use, duration of use& batch number especially for vaccines), including over-the-counter medications, dietary

supplements, and recently discontinued medications; 3) Patient characteristics, including the name or initials, age, sex, weight, and baseline medical condition prior to product therapy, co-morbid conditions, use of concomitant medications, relevant family history of disease, and presence of other risk factors; 4) Documentation of the diagnosis of the reactions, including methods used to make the diagnosis; 5) Clinical course of the reaction and patient outcomes (e.g., hospitalization or death). When one or more of these information are missing, it considered a low quality of report. In this study, 30 of 31 reports were rated as high quality report (table 9). The number of high quality reports were higher in intervention group than those in control group (28 vs. 2 reports). One ADR reporting was rated as low quality report because there were missing of several items including seriousness of the reaction, date to start and stop of drug, date the reaction start, stopped, comorbidity, dose of used, frequency, dosage form, route of administration, and detail of the reporter.

4.3.4 Management of ADRs

The management of ADRs in intervention and control groups indicated that the most ever seen ADRs before and the experience on management ADR was not different. However, the self-assessment of their knowledge and skill for management and report ADRs were high to very high as showed in Table 11.

Table 11 The management of ADRs

Items of assessment	Intervention group, n (%)	Control group, n (%)
Experience and knowledge of included HCPs		
Previous experience (ever seen ADR before) on ADR		
▪ No	1 (6.25)	0 (0.00)
▪ Yes	15 (93.75)	18 (100)
Previous experience on management ADR		
▪ Stop drug and treat with Hydrocortisone or Dexamethasone	14 (33.33)	16 (38.08)
▪ Monitor and evaluate patient can reuse the drug	9 (21.42)	9 (21.42)
▪ Find the cause of allergy, what drug, what type of ADR	6 (14.28)	7 (16.66)
▪ Change drug	5 (11.90)	7 (16.66)
▪ Notify the doctor	4 (9.55)	1 (2.38)
▪ treat with adrenaline (if severe case)	1 (2.38)	1 (2.38)
▪ treat with antihistamine such as chlorpheniramine	1 (2.38)	1 (2.38)
▪ If severe case, split patient for monitor	1 (2.38)	1 (2.38)
▪ Report ADR to PV center using ADR reporting form for serious AE within 7 days	1 (2.38)	4 (9.52)
Self-assessment of their knowledge and skill for management and report ADR		
Knowledge levels, n (%)		
▪ Very low	0 (0.00)	0 (0.00)
▪ Low	0 (0.00)	0 (0.00)
▪ Moderate	8 (50.00)	7 (38.89)
▪ High	7 (43.75)	9 (50.00)
▪ Very high	1 (6.25)	2 (11.11)
Skill of report, n (%)		
▪ Very low	0 (0.00)	0 (0.00)
▪ Low	0 (0.00)	0 (0.00)
▪ Moderate	6 (37.5)	5 (27.78)
▪ High	10 (62.5)	10 (55.56)
▪ Very high	0 (0.00)	3 (16.67)

4.3.5 Satisfaction of TaWai in intervention group

Sixteen HCPs in the intervention group used modified TaWai tool in Lao version for report ADRs in the hospital. Their satisfactions of using this tool were assessed at the end of study. The results in part of satisfaction of TaWai tool for HCPs in intervention group our study found that HCPs had satisfaction to used TaWai program to report ADRs at hospital were very high 82.55% as showed in Table 12.

Table 12 HCPs on using of the modified TaWai tool application

Items of assessment (N=16)	Intervention group
Tawai tool easy to access, n (%)	
▪ Very low	0 (0.00)
▪ Low	0 (0.00)
▪ Moderate	1 (6.25)
▪ High	9 (56.25)
▪ Very high	6 (37.50)
Easy access to work, n (%)	
▪ Very low	0 (0.00)
▪ Low	0 (0.00)
▪ Moderate	0 (0.00)
▪ High	10 (62.50)
▪ Very high	6 (37.50)
Can access anytime and anywhere, n (%)	
▪ Very low	0 (0.00)
▪ Low	0 (0.00)
▪ Moderate	1 (6.25)
▪ High	8 (50.00)
▪ Very high	7 (43.75)
Characteristic and size of letters is beautiful, n (%)	
▪ Very low	0 (0.00)
▪ Low	0 (0.00)
▪ Moderate	1 (6.25)
▪ High	12 (75.0)
▪ Very high	3 (10.75)
Suitability of characteristic and letters, n (%)	
▪ Very low	0 (0.00)
▪ Low	0(0.00)
▪ Moderate	0 (0.00)
▪ High	13 (81.25)
▪ Very high	3 (18.75)
Times to access not so long, n (%)	
▪ Very low	0 (0.00)
▪ Low	0 (0.00)

Table 12 (continue)

Items of assessment (N=16)	Intervention group
▪ Moderate	2 (12.50)
▪ High	9 (56.25)
▪ Very high	3 (31.25)
Easy to use, n (%)	
▪ Very low	0 (0.00)
▪ Low	0 (0.00)
▪ Moderate	1 (6.25)
▪ High	9 (56.25)
▪ Very high	6 (37.50)
Convenient to use, n (%)	
▪ Very low	0 (0.00)
▪ Low	0 (0.00)
▪ Moderate	1 (6.25)
▪ High	5 (31.25)
▪ Very high	10(62.50)
Complication to use, n (%)	
▪ Very low	6 (37.50)
▪ Low	7 (43.75)
▪ Moderate	3 (18.75)
▪ High	0 (0.00)
▪ Very high	0 (0.00)
Reduce time for report ADRs, n (%)	
▪ Very low	0 (0.00)
▪ Low	0 (0.00)
▪ Moderate	2 (12.50)
▪ High	9 (56.25)
▪ Very high	5 (31.25)
Reduce the difficulty for report ADRs, n (%)	
▪ Very low	0 (0.00)
▪ Low	0 (0.00)
▪ Moderate	1 (6.25)
▪ High	10 (62.50)
▪ Very high	5 (31.25)
Questionnaire on TaWai tool are consist with real work practice, n (%)	
▪ Very low	0 (0.00)
▪ Low	0 (0.00)
▪ Moderate	0 (0.00)
▪ High	10 (62.50)
▪ Very high	6 (37.50)
Tools are very useful for patients, n (%)	
▪ Very low	0 (0.00)
▪ Low	0 (0.00)

Table 12 (continue)

Items of assessment (N=16)	Intervention group
▪ Moderate	0 (0.00)
▪ High	7 (43.75)
▪ Very high	9 (56.25)
Tools are very useful for HCPs, n (%)	
▪ Very low	0 (0.00)
▪ Low	0 (0.00)
▪ Moderate	0 (0.00)
▪ High	9 (56.25)
▪ Very high	7 (43.75)
Tools are appropriate for the hospital, n (%)	
▪ Very low	0 (0.00)
▪ Low	0 (0.00)
▪ Moderate	0 (0.00)
▪ High	6 (37.50)
▪ Very high	10 (62.50)
Tool are appropriate for the context of Laos, n (%)	
▪ Very low	0 (0.00)
▪ Low	0 (0.00)
▪ Moderate	0 (0.00)
▪ High	10 (62.50)
▪ Very high	6 (37.50)
Right use of tool in hospital, n (%)	
▪ Very low	0 (0.00)
▪ Low	0 (0.00)
▪ Moderate	0 (0.00)
▪ High	9 (56.25)
▪ Very high	7 (43.75)
Overall satisfaction with tool, n (%)	
▪ Very low	0 (0.00)
▪ Low	0 (0.00)
▪ Moderate	0 (0.00)
▪ High	11 (68.75)
▪ Very high	1 (31.25)

CHAPTER 5
Discussion and Conclusion

This study was divided into 3 phases including review information using SR-MA technic, development and modified TaWai tool in Lao version, and evaluation of modified TaWai tool in Lao version. The discussion and conclusion of the results for each phase were shown below.

5.1 Part 1: Discussion part of SR-MA

In this section, we found 8 RCTs evaluating the outcomes of education programs for HCPs using face to face, repeated telephone, and letter or email and effects of reward were examined in one RCT. Nevertheless, no RCT evaluated technology aids such internet-based ADR reporting programs or ADR reporting apps. Meta-analysis indicated that a face-to-face workshop-based education program has been shown to statistically significantly enhance the quantity and quality of ADR reporting in HCPs. Our findings are consistent with prior SR-MA (19) in that the educational intervention increase quality and quantity of ADR reporting by HCPs compared to the control group. Nonetheless, the amount of ADR reporting in our analysis is more than in prior studies (4.5 vs. 3.5 times), which may be because more trial and update data were included. In terms of interventions, the prior study discovered more interventions than our study did because all forms of interventional designs such as pre-post study design were considered.(19)

The post-marketing safety of drugs can be improved through spontaneous ADR reporting, although under-reporting is a major issue with this method. Thus, it is crucial to design tools and tactics that will increase spontaneous ADR reporting. Our findings suggested that educational programs using a variety of methods might enhance ADR reporting, but all of them lacked long-term evaluation. Because spontaneous ADR reporting requires persistent interventions and outcomes evaluation throughout time, models for continuing professional development must be implemented rather than one-time training sessions to ensure the sustainability of interventions.

Although technology has an essential influence on our present lives, there was no experimental study with a control group to assess this tool to improve ADR reporting. In addition, the most countries evaluated impact of interventions to improve ADR reporting were located in western or high income countries. As a result, further research should therefore concentrate on enhancing spontaneous ADR reporting in middle and low-and-middle-income countries (LMIC), considering their significant

contribution to the global burden of disease and rising rates of medication usage. However, LMICs may have particular obstacles, such as a lack of a blame-free culture, a professional hierarchy, or busy to report. So, in such environments, educational interventions may not be enough to change practice. In order to improve ADR reporting in LMIC, technological tools like web-based ADR reporting programs or ADR reporting apps may be incorporated.

This is the most recent systematic review incorporating a meta-analysis to determine the impact of tools for enhancing the ADRs report. In addition, we adhered to Cochrane guidelines (50) and Preferred Reporting Items for Systematic Review and Meta-Analysis reporting guidelines (PRISMA) (51) to conduct and report the review, respectively. A protocol was prepared using Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols. Thus, internal validity of this study is strong. However, this study has some limitations. Nearly all of the included trials' quality was graded as having all high risk of bias and heterogeneity was found in meta-analysis. Moreover, although most of included studies reported to have improved ADR reporting similar to meta-analysis results, there was a lack of a high quality large scale, multi-centre RCTs, and long-term follow up of the outcomes. As a result, the study's findings should be taken with care and further high quality RCTs with long term follow up were needed to confirm these finding. In addition, this study did not include pre-post trial or real world use of tool without controlled so technology tools or web-based programs which available only in pre-post design or real world use study were excluded study with-out control group. We excluded these types of studies because there is more confounder or bias and we aim to evaluate true effect of all available tools so intervention studies with controlled group were more appropriated design to fit study aim. In addition, effect of this type of studies had been published elsewhere (6).

According phase 1 study we can concluded that the scant evidence suggested that active intervention including education using face-to-face workshop and repeated phone calls to HCPs could enhance ADR reporting. Nonetheless, given the short term evaluation outcomes and the poor quality of the included studies, the results should be interpreted with caution. So we suggested that high quality studies with long term measurement is need to confirm this finding. Moreover, it is need to developed and tested tools for enhancing ADR reporting in other regions such as in countries low-and-middle income countries.

5.2 Part 2 and 3: Developing and evaluating of modified TaWai in Lao version

The modified TaWai mobile application (App) in Lao version was developed and modified from TaWai App in Lao version rate and quality of spontaneous ADR reporting by HCPs compared with control group which received only face to face in Thai version incorporated with information from phase 1 study, the context or basic problems of HCPs, and situation related ADR report system in Lao PDR. In summary, the domains in TaWai mobile App in Lao version were similar to TaWai in Thai version and covered all important issues for ADR report suggested by WHO. The content validity and usability test of this App were good validity, good feasibility and easy to use.

In phase 3, the cluster RCT was performed to determine the effect of face to face educational program plus modified TaWai mobile App in Lao version on rate and quality of spontaneous ADR reporting by HCPs compared with control group which received only face to face educational program. The result of this RCT showed that during the 4 months of the trial, the rate of spontaneous ADR reporting increased statistically significantly by 10 times more in the intervention group compared to the control group. Moreover, the intervention group's rate of high-quality ADR reporting was 14 times higher than that of the control group. By taking into account the rate of ADR reporting in each group, the rate was greater than their baseline.

The increasing of ADR reporting in control group, received education program, compared to baseline was consistent with the results of meta-analysis in phase 1 and consistent with several prior RCTs conducted to determine effect of educational program on increasing ADR reporting (43, 46, 47). However, rate of overall ADR reporting and high-quality reporting in the intervention group was greater than previous studies (43, 46, 47). The difference in the finding of this study with prior studies might be due to difference in intervention (educational program vs. ADR reporting Apps), study and healthcare environments, time and awareness about the importance of ADR report.

In general, rate of spontaneous ADR reporting in Lao is very low. Data from national PV center showed that only 25 reports from all hospitals in Lao PDR were submitted to the PV center during 4 years (2017-2020). Focus on setting of study, there were 6 and 5 ADR reports in hospital assigned as intervention and control group during 1 year (2021) and there was no ADR report during the first four months of year 2022. During 4 months of this study in year 2022, 28 and 3 ADR reports from intervention and control groups were submitted. Rate of ADR reporting in this study was significantly greater than general practice. This implied that intervention such as

education program or TaWai mobile App or both should be implemented to increase ADR reporting in Lao PDR.

Focus on characteristic of intervention, prior study indicated that rate of ADR reporting was decreased over time after the educational program was discontinued (48). This implied that if education program was used to increase rate of ADR reporting, continued intervention may be required to maintain the high number of reporting. In this study, although educational program was provided only 2 times in 1 weeks, the rate of ADR reporting in the intervention still high. This implied that adding ADR reporting application as modified TaWai app to educational program may enhance ADR reporting and also maintain the high rate of reporting. The high rate of ADR reporting in the intervention group may be due to characteristics of modified TaWai app that easily to use and shorten time to report ADR rather than usual practice in Lao PDR.

The result of satisfaction assessment showed that TaWai App in Lao version helps HCPs to reduce time, problems or obstacles in ADR report. This information supported the main finding that rate of ADR report is more increased in group using TaWai App. Moreover, the quality of the reports in the intervention group (group using Tawai App) was high quality. Based on policy viewpoint, if this system can be used or linked to the country's PV system in Lao PDR, it may reduce the workload of HCPs, reduce time of ADR reports and policy may have more ADR report than previous and get more quality information for decision maker. However, this is the first study to evaluate the effect of this system in tertiary hospital, more studies in other setting in Lao PDR are needed to confirm this effect before established in national level.

In terms of implementation, modified TaWai App in Lao version may suitable for use in Lao PDR due to several reasons. Firstly, this App was modified from TaWai App in use in Thai where people have nearly culture to Lao people and in development process we considered and included specific culture of Lao PDR such as meaning of language, law or situation related to ADR report in Lao PDR into the App. Secondly, the properties of App were user friendly, easily to use or access (can access every time and everywhere via mobile or smart phone), and reduce time to report. These good properties were confirmed by high rate satisfaction of modified TaWai App in Lao version from HCPs participated in this study. The last reason, cost of implementation was inexpensive when compared with web-based program. However, this study conducted only in tertiary hospitals and there were only 2 departments participated in this study because of the covid-19 pandemic. In addition, duration of study and follow up time was short due to limitation of grant support. These factors may affect the outcomes and the number of ADR reports. Therefore, to have more information for decision maker, the implementation in real situation and cost effectiveness of this tools should be conducted in the future.

Based on our knowledge, this is the first RCT evaluating effectiveness of TaWai mobile apps as technology-aids to report ADR. Although this application was original developed in Thailand, there was no RCT to determine its' effect in Thailand. There was only one trial designed as pre-post study conducted in the Southern of Thailand (55). The study in Thailand showed that 634 and 932 cases were reported via TaWai program in year 2019 and 2020, respectively (55) and 749 cases in year 2022 from TaWai database. Trend of ADR reporting in our study was similar to the study conducted in Thailand but the number of reports in Thailand were higher than the reports in Lao PDR. The difference of this finding may due to the difference of study design, study setting, scope of reporting case, time and duration of study, and baseline ADR reporting. In addition, this is the first RCT conducted to determine technology-aids to report ADR in Lao PDR. According to our systematic review, there was no RCT conducted to determine technology tool as aids for ADR reporting. The study design of available studies on technology-aids was pre-post design without paralleled control group (19) thus risk of bias may be produced. Evaluating effect of interventions by conducting RCT is a standard method for reducing selective bias, made people have more confidence on the study result rather than non-RCT design, and can implied that study result come from effect of intervention. However, several factors, including short duration of study, open-label designed, small number of participated HCPs, limited participated department, and pandemic of COVID-19- which limited a number of patients to go to the hospital, may have an impact on study findings and lead to a lower rate of ADR reporting than actual occurrence. In fact, duration of study on ADR report was vary from 3 months to 3 years, so we decided to follow the outcome at 4 months due to limitation of grant support. This may not affect real occurrence of ADR due to fluctuation between times of study. In addition, previous study (6) indicated that ADRs reports decreased after discontinuation of the intervention, so interventions should be repeated or reintroduced to raise awareness of the importance of reporting. However, having equipment or the program allows for the convenience of reporting. For example, in this study, it is likely to provide a higher reporting rate than education or a workshop alone. For non-blinding issue, it is common limitation due to characteristic of intervention. Non-blinding participants may produce performance bias because HCPs participated in intervention group may

eager to report more than control group. However, this limitation was found in studies such interventions were provided. According to these limitation, further RCTs conducted in a large number of hospitals and HCPs participated with long term assessment, and follow-up in normal situation should be required to confirm the finding of this study.

Besides increase rate and quality of ADR report for policy system, this study provided direct benefit to patients. Since in Lao PDR medicine allergy cards are not issued to patients, we provided medicine allergy card to patient when data were obtained from ADR report. This process aims to reduce recurrent of drug allergy. This issue may need to be further considered and implemented systematically.

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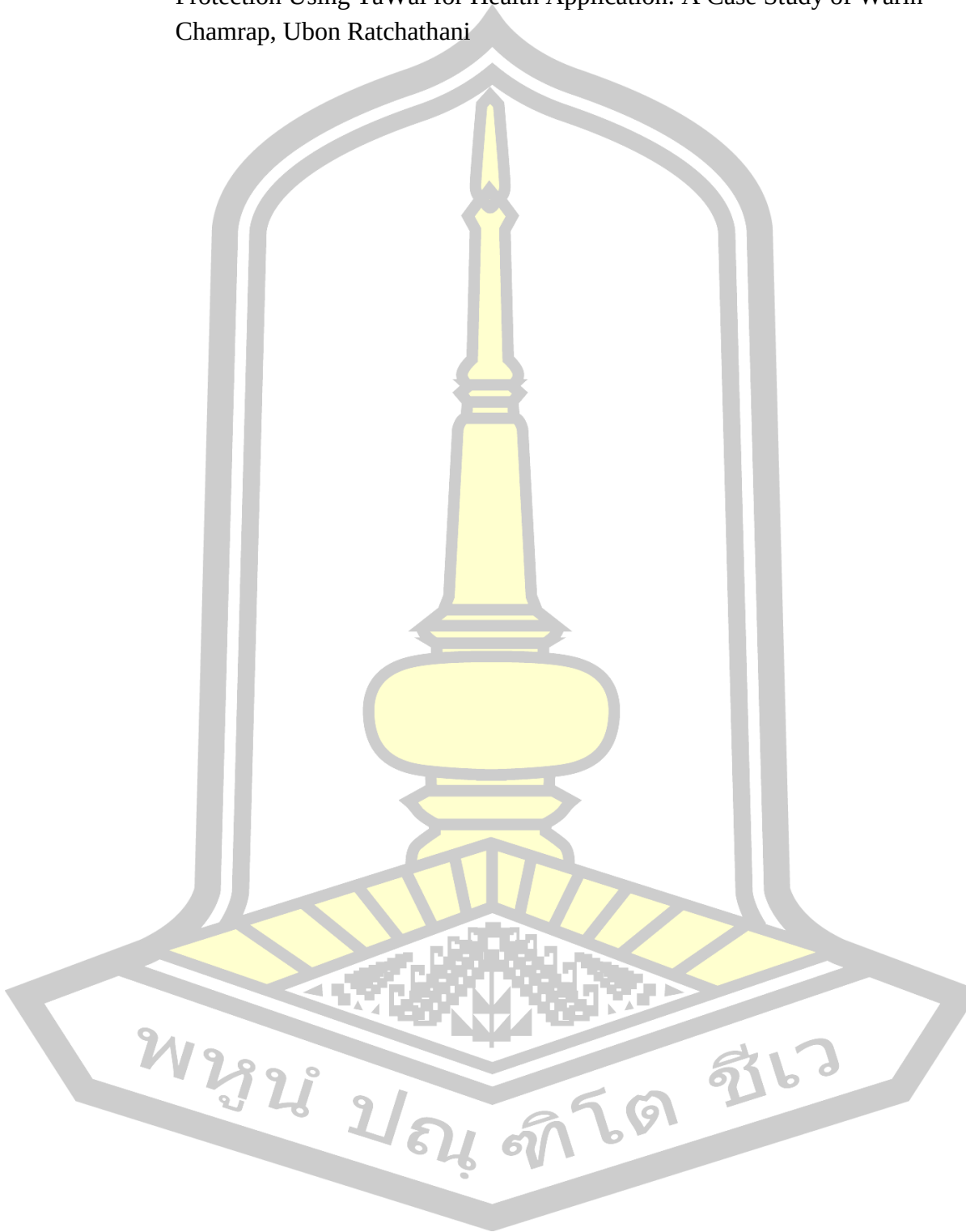
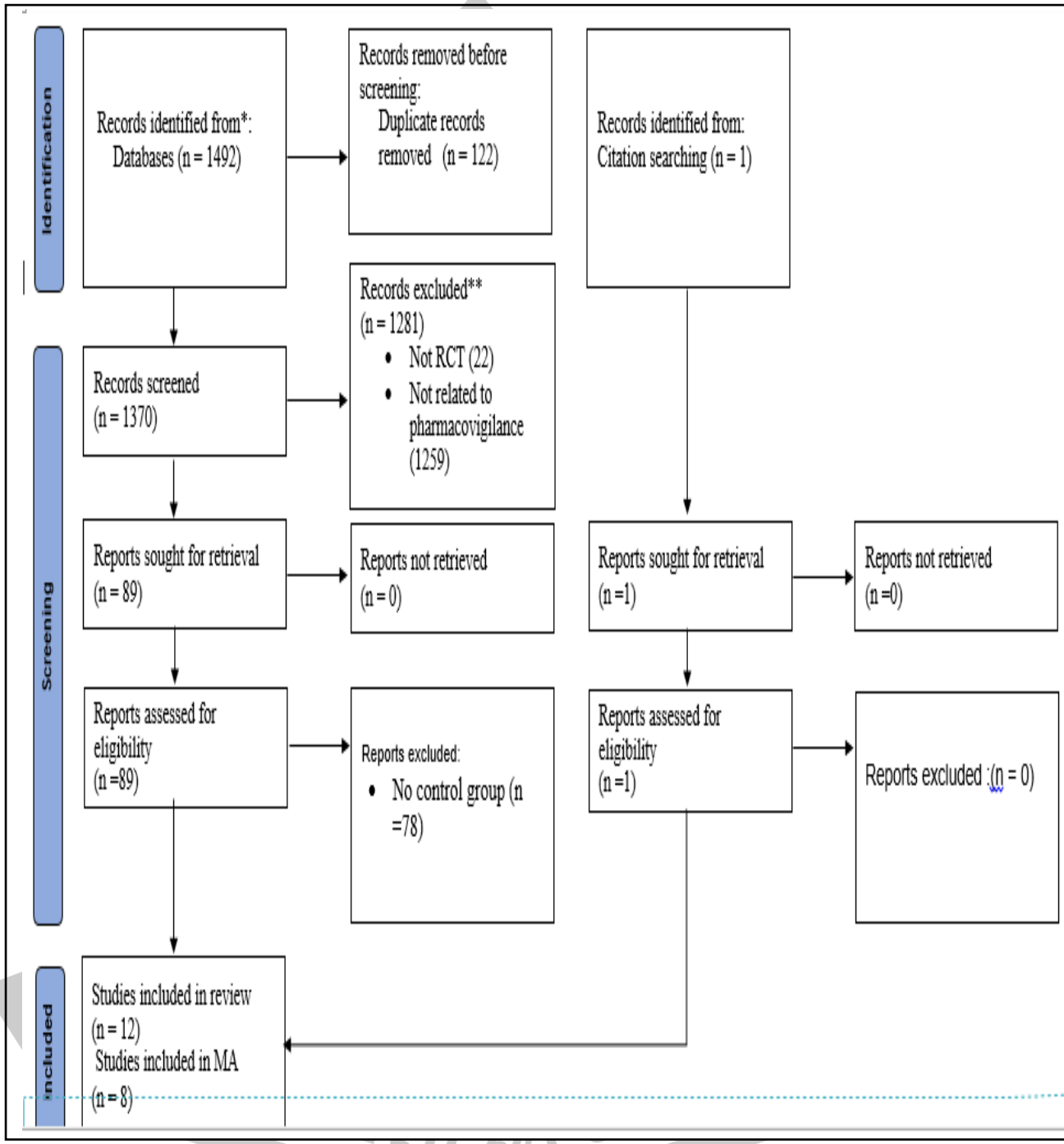


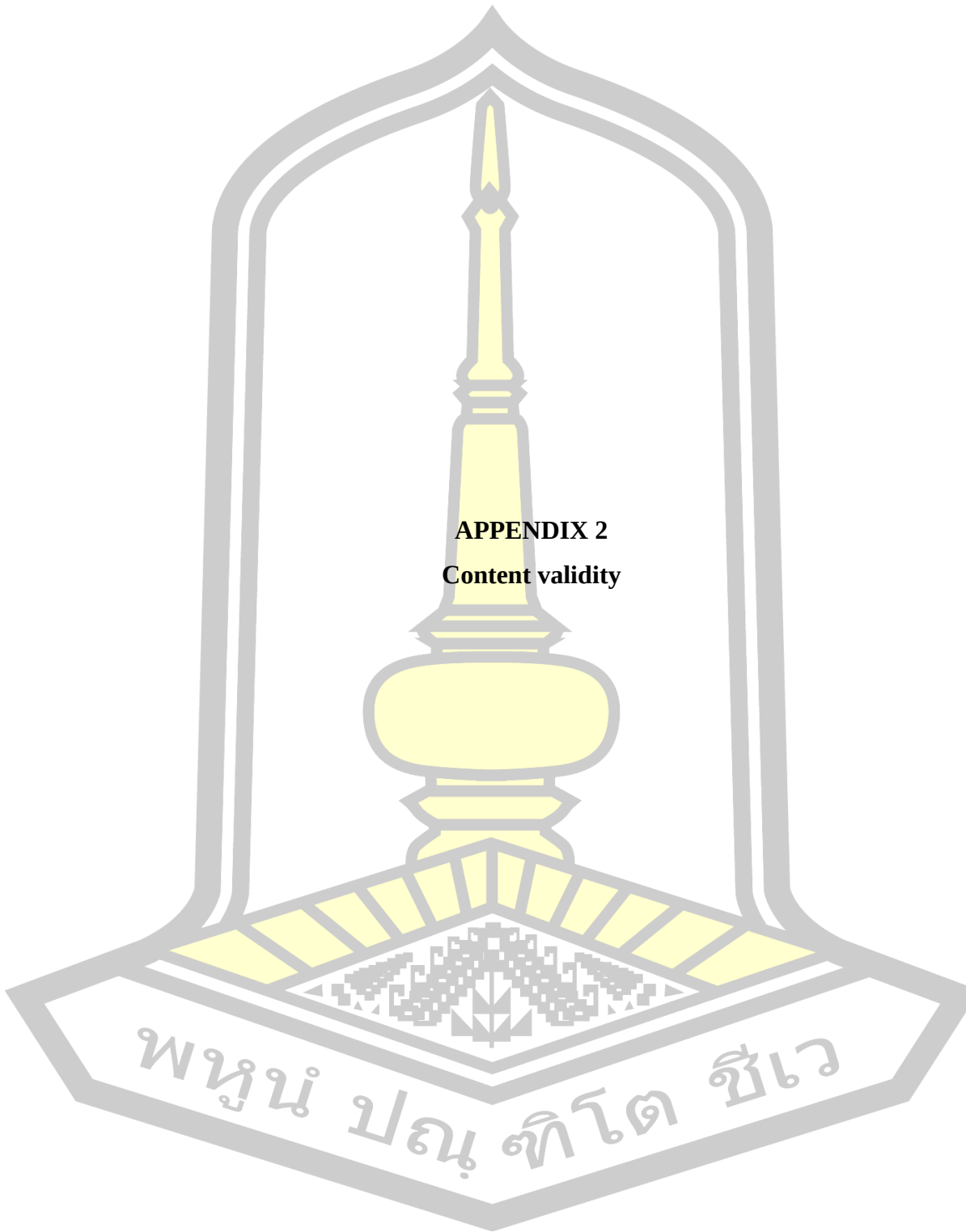
APPENDIX

APPENDIX 1

PRISMA Flowchart diagram

PRISMA Flowchart diagram





APPENDIX 2

Content validity

Content validity

แบบประเมินค่าดัชนีความสอดคล้อง (IOC) ของประเด็นความสอดคล้องของข้อคำถาม

ในเครื่องมือ TaWai for health

เรื่อง คำศัพท์และข้อคำถามในแครื่องมือ TaWai for health

คำชี้แจง โปรดพิจารณาความสอดคล้องของประเด็นข้อคำถามเพื่อใช้สอบถามในแครื่องมือ TaWai for health
ในการรายงานอาการไม่พึงประสงค์จากยาในโรงพยาบาลว่าแต่ละข้อว่ามีความสอดคล้อง และ มีความถูกต้องเหมาะสมหรือไม่ เมื่อพิจารณาแล้วให้ใส่เครื่องหมาย ✓ ลงในช่องความคิดเห็น โดยใช้เกณฑ์การพิจารณา ดังนี้

+ 1 หมายถึง เห็นด้วย หรือ สอดคล้อง
0 หมายถึง ไม่แน่ใจ
-1 หมายถึง ไม่เห็นด้วย หรือ ไม่สอดคล้อง

รหัส IOC	ประเด็นข้อคำถามภาษาไทย	ระดับความคิดเห็น			หมายเหตุ
		+1	0	-1	
A1	ชื่อ-สกุล ของผู้ป่วย				
A2	เพศ ของผู้ป่วย				
A3	สัญชาติ ของผู้ป่วย				
A4	อายุ โดยประมาณของผู้ป่วย				
A5	น้ำหนักโดยประมาณของผู้ป่วย				
A6	เบอร์ติดต่อผู้ป่วยหรือผู้ดูแล				
A7	ผู้ป่วยมีประวัติแพ้ยาหรือผลิตภัณฑ์สุขภาพ หรือไม่?				
A8	ผู้ป่วยมีโรคประจำตัวหรือไม่ ?				
A9	ผู้ป่วยมีภาวะอื่น เช่น การตั้งครรค์ หรือ ให้นมบุตร หรือไม่ ?				
A10	กรุณาพิมพ์บรรยายรายละเอียดอาการที่เกิดขึ้น				
A11	ท่านมีรูปภาพอาการหรือความผิดปกติของผู้ป่วย หรือไม่ ?				
A12	กรุณาระบุ “ช่วงเวลาที่เกิดอาการดังกล่าว” โดยประมาณ				
A13	กรุณาระบุสถานที่ที่พบอาการผิดปกติของผู้ป่วย				
A14	สำหรับอาการที่เกิดขึ้นในครั้งนี้ ผู้ป่วยได้เข้ารับการรักษา ณ โรงพยาบาลหรือไม่?				
B1	กรุณาระบุชื่อผลิตภัณฑ์				

รหัส IOC	ประเด็นข้อคำถามภาษาไทย	ระดับความคิดเห็น			หมายเหตุ
		+1	0	-1	
B2	เลือกประเภทผลิตภัณฑ์				
B3	มีฉลากภาษาไทยหรือไม่?				
C1	รูปแบบผลิตภัณฑ์				
C2	วิธีการใช้				
C3	ท่านมีรูปผลิตภัณฑ์ ดังกล่าวหรือไม่ ?				
C4	ท่านทราบเลขทะเบียนผลิตภัณฑ์ หรือ เลขทะเบียน อย. ของผลิตภัณฑ์ ดังกล่าวหรือไม่?				
C5	กรุณาระบุปริมาณการใช้ผลิตภัณฑ์ของผู้ป่วย (ต่อครั้ง/ต่อวัน)				
C6	กรุณาระบุวัตถุประสงค์ของผู้ป่วยที่ใช้ผลิตภัณฑ์				
C7	กรุณาระบุ ช่วงเวลาที่เริ่มใช้ผลิตภัณฑ์				
C8	กรุณาระบุข้อสงสัยเพิ่มเติมที่เกี่ยวข้องกับผลิตภัณฑ์ นี้				
D1	กรุณาเลือก หรือ ระบุแหล่งที่มาของผลิตภัณฑ์ นี้				
D2	กรุณาระบุรายระเอียดเพิ่มเติม เช่น ที่ตั้งของร้าน เป็นต้น				
D3	ท่านมีรูปภาพของแหล่งที่มาเพิ่มเติมหรือไม่				

ลงชื่อ.....ผู้ประเมิน

(.....)

ตำแหน่ง .....

...../...../.....

APPENDIX 3

TaWai for Health in Chatbot questionnaire in

Thai version and Lao version

TaWai for Health in Chatbot questionnaire in Thai version and Lao version

ตัวอย่างการพัฒนาคำถามเพื่อใส่ใน chatbot ส่วนหน้าบ้าน

คำถามใน Tawai chat bot Thai version	คำถามใน Tawai chat bot Lao version (ภาษาไทย)	คำถามใน Tawai chat bot Lao version (ภาษาลาว)	ที่มาของคำถาม/ ข้อมูล
I. ข้อมูลผู้ป่วย	I. ข้อมูลผู้ป่วย	I. ຂໍ້ມູນທົ່ວໄປຂອງຄົນເຈັບ	ข้อมูลผู้ป่วยทั้งหมดในฉบับภาษาลาว อ้างอิงตาม PV guideline in Lao และ อ้างตามเกณฑ์ของ WHO
1. ชื่อ-สกุล ของผู้ป่วย.....	1. ชื่อ และ นามสกุล ของคนเจ็บ	1. ຊື ແລະ ນາມສະກຸນຄົນເຈັບ:.....	
2. เพศ ของผู้ป่วย: - ชาย - หญิง - เพศเดิมชาย - เพศเดิมหญิง	2. เพศ ของผู้ป่วย: - ชาย - หญิง - เพศเดิมชาย - เพศเดิมหญิง	2. ເພດຂອງຄົນເຈັບ: - ຊາຍ - ຍິງ - ເພດເດີມຊາຍ - ເພດເດີມຍິງ	
3. สัญชาติ ของผู้ป่วย - ต่างชาติ - ไทย	3. สัญชาติ ของคนเจ็บ: - ต่างชาติ (ถ้าเลือกจะมีเชื้อชาติให้เลือกต่อ คือ เอเชีย อเมริกัน แอฟริกา ยุโรป ลาติน อื่นๆ..... - ลาว	3. ກະລຸນາລະບຸສັນຊາດ - ຕ່າງຊາດ (ຖ້າເລືອກຈະມີສັນຊາດໃຫ້ເລືອກຕໍ່ ຄື ເອເຊຍ, ອາເມກາ, ເອີຣົບ, ລາຕິນ , ອື່ນໆ .....) - ລາວ	
4. อายุ โดยประมาณของผู้ป่วย.....	4. กรุณาระบุอายุ ของคนเจ็บ:.....	4. ກະລຸນາລະບຸອາຍຸຄົນເຈັບ:	

5. น้ำหนักโดยประมาณของผู้ป่วย.....	5. กรุณาระบุน้ำหนักของคนเจ็บ	5. ກະລຸນາລະບຸນ້ຳໜັກຄົນເຈັບ:	
6. เบอร์ติดต่อผู้ป่วยหรือผู้ดูแล.....	6. กรุณาระบุเบอรโทรของคนเจ็บหรือผู้ดูแล.....	6. ກະລຸນາລະບຸເບີໂທຄົນເຈັບ ຫຼື ຜູ້ດູແລ:	
7. ผู้ป่วยมีประวัติแพ้ยาหรือผลิตภัณฑ์สุขภาพหรือไม่? - ไม่มี - มี (ถ้ามีระบุ ชื่อยาและรายละเอียดการแพ้..... ผู้ป่วยมีบัตแพ้ยาหรือไม่?.....)	7. คนเจ็บมีประวัติแพ้ยาบ่อ ? - บ่อมี - มี (ถ้ามีระบุ ชื่อยาและรายละเอียดการแพ้)	7. ຄົນເຈັບມີປະຫວັດແພ້ຢາບໍ່ - ບໍ່ມີ - ມີ : ຖ້າມີ ຊື່ຢາ:.....; ລາຍລະອຽດການແພ້.....	ตัดผู้ป่วยมีบัตรแพ้ยาหรือไม่ออก เพราะที่ลาวไม่ได้ทำบัตรแพ้ยาให้ผู้ป่วย
8. ผู้ป่วยมีโรคประจำตัวหรือไม่ ? - ไม่มี - มี (ถ้ามี ชื่อโรคประจำตัว)	8. คนเจ็บมีพะยาดประจำตัวบ่อ - บ่อมี - มี (ถ้ามีระบุ ชื่อพะยาด ประจำตัว)	8. ຄົນເຈັບມີພະຍາດປະຈຳຕົວບໍ່? - ບໍ່ມີ - ມີ : ຖ້າມີຊື່ພະຍາດປະຈຳຕົວ:	
9. ผู้ป่วยมีภาวะอื่น เช่น การตั้งครรภ์ ให้นมบุตร หรือ ไม่ ? - ไม่มี - มี	9. คนเจ็บมีพาวะอื่น เช่น การถือพา หรือให้นมลูกบ่อ? - บ่อมี - มี	9. ຄົນເຈັບມີພາວະອື່ນເຊັ່ນ ການຖືພາ ຫຼື ໃຫ້ນົມລູກ ບໍ່ ? - ບໍ່ມີ - ມີ	
10. กรุณาพิมพ์บรรยายรายละเอียดอาการที่เกิดขึ้น.....	10.กรุณาเขียนบรรยายรายละเอียดอาการที่เกิดขึ้น.....	10. ກະລຸນາຂຽນບັນຍາຍລາຍລະອຽດອາການທີ່ເກີດຂຶ້ນ:	
11. ท่านมีรูปอาการหรือความผิดปกติของผู้ป่วยหรือไม่ ? - ไม่มี	๑๑.ท่านมีรูปพาบหรืออาการผิดปกติของคนเจ็บบ่อ - บ่อมี	11. ທ່ານມີຮູບພາບ ຫຼື ອາການຜິດປົກະຕິຂອງຄົນເຈັບບໍ່ - ບໍ່ມີ	

- มี (ถ้ามีสามาดแนบรูปถ่ายลงได้)	- มี (ถ้ามีสามาดแนบรูปถ่ายลงได้)	-ມີ : ຖ້າມີສາມາດຖ່າຍຮູບລົງໄດ້ ຫຼື ອັບຮູບລົງໄດ້ -	
12. กรุณาระบุ "ช่วงเวลาที่เกิดอาการดังกล่าว" โดยประมาน.....	12.กรุณาระบุ ช่วงวันเวลาที่เกิดอาการ	12. ກະລຸນາລະບຸຊ່ວງອັນເວລາທີ່ເກີດອາການ:	
13. กรุณาระบุสถานที่พบอาการผิดปกติของผู้ป่วย (กรอกข้อมูล)	13.กรุณาระบุสถานที่พบอาการของคนเจ็บ.....	13. ກະລຸນາລະບຸສະຖານທີ່ພົບອາການຂອງຄົນເຈັບ:	
	สำหรับอาการที่เกิดขึ้นในครั้งนี้ เป็นอาการที่ร้ายแรงบ่อ? -บ่อร้ายแรง - ร้ายแรง	ສຳລັບອາການທີ່ເກີດຂຶ້ນໃນຄັ້ງນີ້ເປັນອາການີ້ຮ້າຍແຮງບໍ່? - ບໍ່ຮ້າຍແຮງ (ເຊັ່ນ ເສຍຊີວິດ, ເປັນອັນຕະລາຍຕໍ່ຊີວິດ, ພິການ - ຮ້າຍແຮງ (ເຊັ່ນ ເປັນຜື່ນ, ວິນຫົວ, ຮາກ, ໄອ ເປັນຕົ້ນ)	ເພີ່ມຄຳຖາມຈາກເດີມ ໂດຍອີງຕາມ PV guideline in Lao (ນິຍາມຄຳວ່າ ຮ້າຍແຮງ ຄືອ ຜູ້ປ່ວຍເສຍຊີວິດ ເປັນອັນຕະລາຍຕ່ອຊີວິດ ຫຼືອ ພິການຊົ່ວຄຣາວ/ຖາວອຣ ໄມ່ຮ້າຍແຮງຄືອ ເປັນຜື່ນ ເວຍນຫົວ ອາເຈັຽນ ໄອ ເປັນຕ້ນ)
14. สำหรับอาการที่เกิดขึ้นในครั้งนี้ ผู้ป่วยได้เข้ารับการรักษา ณ โรงพยาบาลหรือไม่? อย่างไร?..... - ไม่ได้รับ - ได้รับ	14.สำหรับอาการที่เกิดขึ้นในครั้งนี้ คนเจ็บได้เข้ารับการปิ่นปัวในโรงหมอบ่อ -บ่อได้รับ - ได้รับ	14. ສຳລັບອາການທີ່ເກີດຂຶ້ນໃນຄັ້ງນີ້ຄົນເຈັບໄດ້ເຂົ້າຮັບການປິ່ນປົວໃນໂຮງໝໍບໍ່ - ບໍ່ໄດ້ຮັບ - ໄດ້ຮັບ	
II. ข้อมูลผลิตภัณฑ์	ข้อมูลผลิตภัณฑ์	II.ຂໍ້ມູນຜະລິດຕະພັນ	ข้อมูลผลิตภัณฑ์ทั้งหมด อิงตาม WHO
15. กรุณาระบุชื่อผลิตภัณฑ์ (หากไม่	15.กรุณาระบุชื่อผลิตภัณฑ์ที่ก่อให้เกิด	15. ກະລຸນາລະບຸຊື່ຜະລິດຕະພັນທີ່ກໍ່ໃຫ້ເກີດອາການ	

ชาบ ระบุว่า ไม่ชาบ).....	อาการบ่อพึ่งปาดถะหนา:	บ่เพิ่งปาดຖะໜา:	
16. เลือกประเภทผลิตภัณฑ์ - ยาแผนปัจจุบัน - ยาแผนโบราณ/ยาที่พัฒนามาจากสมุนไพร - ยาสมุนไพร - ยาชุด - วัตถุออกฤทธิ์/ วัตถุเสพติด - เครื่องมือแพทย์ - อาหาร	16.กรุณาเลือกประเภทผลิตภัณฑ์ - ยาแผนปัจจุบัน - ยาแผนโบราณ - ยาสมุนไพร - ยาชุด - วัตถุออกฤทธิ์/ วัตถุเสพติด - เครื่องมือแพทย์ - อาหาร	16. ກະลุบาเลือกปะเพดผะลิดตะพัน - ยาแผนปะจุบัน - ยาแผนบุฮาม - ยาสะมุนไพ - ยาชุด - อาหานเสิม - อัดถุอกาลิด ຫຼື อัดถุเสบติด - เถื่องมิแผด - อาหาน	
17. มีฉลากภาษาไทยหรือไม่? - ไม่มี - มี	17.มีฉลากยาบ่อ? - บ่อมี - มี	17. มิสะຫຼากยาบ่? - บ่มิ - มิ	ที่ลาวมียาที่จำหน่ายและนำเข้ามาจากต่างประเทศหลายพอสมควร
III. กรุณาระบุรายระเอียดของการใช้ผลิตภัณฑ์ดังกล่าว (กรอกข้อมูล)	III.รายละเอียดข้อมูลผลิตภัณฑ์	III.ลายละอຽดข้มูนผะลิดตะพัน	
18. รูปแบบผลิตภัณฑ์ - ยาแคปซูล - ยาเม็ด - ยาน้ำ - ยาทา	18.รูปแบบของผลิตภัณฑ์ - ยาแคปซูล - ยาเม็ด - ยาน้ำ - ยาทา	18. ฮูบแบบะอຽงผะลิดตะพัน: - ยาแถับซูม - ยาเม็ด - ยาน้ำ - ยาทา	

- ยาฉีด - ยาเหน็บ - ยาหยอด - ยาพ่น	- ยาสัก - ยายัด - ยาหยอด - ยาพ่น	- ยาสัมา - ยายัด - ยายอด - ยาพิ่น	
19. วิธีการใช้ - กิน - ทา/พอก/ป้ายสิว - อม - ฉีด - สูด/พ่น - บ้วนปาก/ป้ายปาก - สระ/พอกศรีษะ	19.วิธีการใช้ - กิน - ทา/พอก/ทาสิว - อม - สัก - สูดดม/พ่น - บ้วนปาก/ทาปาก - สะหัว	19. อิทิทางใช้ - กิม - ทา/พอม/ทาสิอ - อิม - สัมา - สูดดิม/พิ่น - ข้อมปาม/ทาปาา - สะหิอ	
20. ท่านมีรูปผลิตภัณฑ์ ดังกล่าว หรือไม่? - ไม่มี - มี (ถ้ามีสามารถแนบรูปถ่ายได้)	20.ท่านมีรูปภาพผลิตภัณฑ์ยาบ่อ - บ่อมี - มี (ถ้ามีสามารถเอารูปถ่ายลงได้)	20. ข่านมิฮูบพาบผะลิดตะพันยาบ่ - บ่มิ - มิ : ถ้ามิสามาดอับฮูบใส	
21. ท่านหราบเลขทะเบียนผลิตภัณฑ์ หรือ เลขทะเบียน อย ของผลิตภัณ ดั่งกล่าวหรือไม - ไม่หราบ - หราบ	21.ท่านรู้เลขทะเบียนผลิตภัณฑ์ หรือ เลขทะเบียน อย บ่อ -บ่อรู้ - รู้	21. ข่านะฮู้ลายละองดของผะลิดตะพัน หื เลาทะบวม อย บ่ - บ่ฮู้ - ฮู้	
22. กรุณาระบุปริมาณการใช้ผลิตภัณฑ์ของผู้ป่วย (ต่อครั้ง/ต่อวัน)	22.กรุณาระบุปริมาณการใช้ผลิตภัณ ของคนเจ็บ (ต่อครั้ง/ต่อ	22. กะลุนาละบุปะลิมานกานใฮ้ผะลิดตะพัน ดองคันเจ็บ (ต่ถ้ง/ต่อัน):	

.....	วัน).....	.....	
23. กรุณาระบุวัตถุประสงค์ของผู้ป่วยที่ใช้ผลิตภัณฑ์	23.กรุณาระบุวัตถุประสงค์ของคนเจ็บที่ใช้ผลิตภัณฑ์	23. ກະລຸນາລະບຸວັດຖຸປະສົງຂອງຄົນເຈັບທີ່ໃຊ້ຜະລິດຕະພັນ:	
24. กรุณาระบุ ช่วงเวลาที่เริ่มใช้ผลิตภัณฑ์ ดังกล่าว โดยประมาณ	24.กรุณาระบุ ช่วงวันเวลาที่เริ่มใช้ผลิตภัณฑ์.....	24. ກະລຸນາລະບຸອັນເວລາໃນການໃຊ້ຜະລິດຕະພັນ:	
25. กรุณาระบุข้อสงสัยเพิ่มเติมที่เกี่ยวข้องกับผลิตภัณฑ์ นี้ (หากไม่มี ระบุว่า ไม่มี)	25.กรุณาระบุข้อสงสัยเพิ่มเติมที่เกี่ยวข้องกับผลิตภัณฑ์นี้ (หากบ่อมี ระบุว่า บ่อมี)	25. ກະລຸນາລະບຸຂໍ້ສົງໃສເພີ່ມເຕີມທີ່ກ່ຽວຂ້ອງກັບຜະລິດຕະພັນນີ້ (ຫາກບໍ່ມີໃຫ້ລະບຸວ່າບໍ່ມີ)	
IV. แหล่งที่มาของผลิตภัณฑ์	IV.แหล่งที่มาของผลิตภัณฑ์	IV.ແຫຼ່ງທີ່ມາຂອງຜະລິດຕະພັນ	
26. กรุณาเลือก หรือ ระบุแหล่งที่มาของผลิตภัณฑ์นี้ (หากไม่ทราบให้ระบุว่า ไม่ทราบ) - วิทยุ - โทรทัศน์ - โรงพยาบาลรัฐ - โทรศัพท์ - อินเทอร์เน็ต - บุคคลอื่น ๆ - ร้านขายผลิตภัณฑ์เสริมสุขภาพ - ร้านขำ - ร้านขายยา	26.กรุณาเลือก หรือ ระบุแหล่งที่มาของผลิตภัณฑ์ นี้ (หากไม่ทราบให้ระบุว่า ไม่ทราบ) - วิทยุ - โทรทัศน์ - โรงพยาบาลรัฐ - โทรศัพท์ - อินเทอร์เน็ต - บุคคลอื่น ๆ - ร้านขำ - ร้านขายยา	26. ກະລຸນາເລືອກ ຫຼື ລະບຸແຫຼ່ງທີ່ມາຂອງຜະລິດຕະພັນ (ຫາກບໍ່ຮູ້ໃຫ້ຂຽນວ່າບໍ່ຮູ້) - ວິທະຍຸ - ໂທລະທັດ - ໂຮງໝໍລັດ - ໂທລະສັບ - ອິນເຕີເນັດ - ບຸກຄົນອື່ນໆ - ຮ້ານຂາຍເຄື່ອງທົ່ວໄປ - ຮ້ານຂາຍຢາ	ลาวไม่มีร้านขายผลิตภัณฑ์เสริมสุขภาพ

27. กรุณาระบุรายระเอียดเพิ่มเติม เช่น ที่ตั้งของร้าน เป็นต้น หากไม่ทราบให้ระบุว่า ไม่ทราบ	27.กรุณาระบุรายระเอียดเพิ่มเติม เช่น ที่ตั้งของร้าน เป็นต้น หากบ่อรู้ให้ระบุว่า บ่อรู้	27. ทะลุมาฉะบุลายฉะองดเพิ่มเติมเช่น ชื่ธ้าม, ที่ตั้งธ้ามเป้นต็ม (ในทำฉะมิบ่ธู้ใช้ฉะบุอ่าบ่ธู้)	
28. ท่านมีรูปภาพของแหล่งที่มาเพิ่มเติมหรือไม่ - ไม่มี - มี (ถ้ามีสามารถเอารูปลงได้)	ท่28.านมีรูปภาพของแหล่งที่มาผลิตภัณฑ์เพิ่มเติมบ่อ - บ่อมี - มี (ถ้ามีสามารถเอารูปลงได้)	28 . ท่านมิธูบพายเพิ่มเติมฮองแห่งที่มาผะลิดตะพัน ซื่ บ่ - บ่มิ มิ : ถ้ามิสามาดอับธูบลิงได้ -	

APPENDIX 4

ตัวอย่างการพัฒนาคำถามเพื่อใส่ใน chat bot ส่วนหลังบ้าน

ตัวอย่างการพัฒนาคำถามเพื่อใส่ใน chat bot ส่วนหลังบ้าน

การสรุป Case อาการไม่พึงประสงค์ (Summary report)

1. ข้อมูลผู้รายงาน
   ชื่อ
2. ข้อมูลผู้ได้รับผลกระทบ
   ชื่อผู้ป่วย เพศ (ชาย หรือ หญิง) อายุ ..... ปี อายุ น้ำหนัก เบอร์โทร มีประวัติแพ้ยา ..... มีโรคประจำตัว .....ชื่อยาที่แพ้..... รายระเอียดของโรคประจำตัว..... วันที่พบเกิดอาการ..... สะถานที่พบผลิตภัณฑ์ ..... การรักษา.....

✓ เกิดภาวะ (อาการตาม Medra, Vigifro) .....

✓ ข้อมูลผลิตภัณฑ์

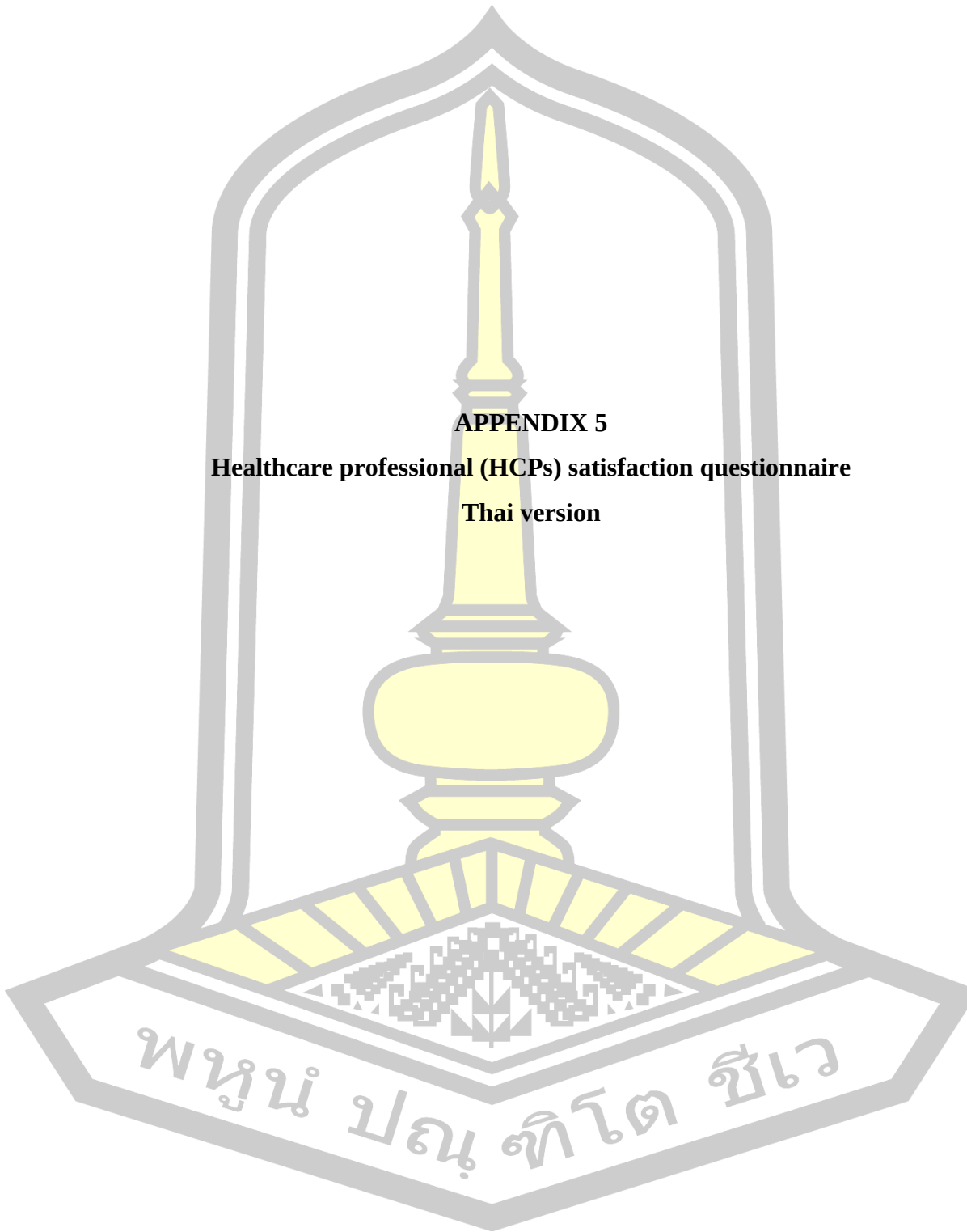
จากผลิตภัณฑ์ .....x..... ชนิด ประกอบด้วย

ผลิตภัณฑ์ที่ 1

ชื่อผลิตภัณฑ์..... ประเภทผลิตภัณฑ์ ..... มีสลากยาหรือไม่ ..... ข้อมูลการใช้ผลิตภัณฑ์..... รูปพาบ ..... ทะเบียน..... ผลิตภัณฑ์ (อย)..... วัตถุประสงค์การใช้ผลิตภัณฑ์..... ปริมาณการใช้ผลิตภัณฑ์ ..... แหล่งที่มาของผลิตภัณฑ์..... รูปภาพหรือไฟล์..... แหล่งที่มาของผลิตภัณฑ์ .....

✓ มีระดับความสัมพันธ์ (ระดับความน่าจะเป็น) แบบ ..... (ใช่แน่นอน (Certain), น่าจะใช่ (Probable), อาจจะใช่ (Possible))..... ผลิตภัณฑ์นี้มาจาก (ระบุตามที่มา)

3. อาการไม่พึงประสงค์มีสาเหตุมาจาก (ดึงข้อมูลมาจากการประเมินสาเหตุ ซึ่งอาจมีมากกว่า 1 สาเหตุ)
4. ผลที่เกิดขึ้นจากการรักษาอาการไม่พึงประสงค์พบว่า (ดึงข้อมูลมาจาก ผลที่เกิดขึ้นจากการรักษาอาการไม่พึงประสงค์)



APPENDIX 5

Healthcare professional (HCPs) satisfaction questionnaire

Thai version

แบบสอบถามความพึงพอใจของบุคลากรสาธารณสุขต่อการใช้เครื่องมือ TaWai for health ฉบับภาษาลาว ในรายงานอาการไม่พึงประสงค์จากยาในโรงพยาบาล

แบบสอบถามนี้พัฒนาขึ้นโดยมีวัตถุประสงค์เพื่อประเมินความพึงพอใจ และความคิดเห็นต่อการใช้เครื่องมือ TaWai for health ฉบับภาษาลาว ในรายงานอาการไม่พึงประสงค์จากยาในโรงพยาบาล โดยแบบสอบถามแบ่งเป็น 3 ส่วน ได้แก่ ส่วนที่ 1 ข้อมูลทั่วไป จำนวน 11 ข้อ ส่วนที่ 2 ข้อมูลความคิดเห็นของบุคลากรทางการแพทย์ จำนวน 4 ข้อ และส่วนที่ 3 ข้อมูลความพึงพอใจ จำนวน 30 ข้อ

คำแนะนำในการตอบแบบสอบถาม ขอให้ท่านทำเครื่องหมายกากบาท (X) หรือเติมข้อมูลลงในช่องว่างข้างหน้าในส่วนต่าง ๆ ที่ตรงกับข้อมูลของท่านหรือตรงกับระดับความคิดเห็นและความพึงพอใจของท่านมากที่สุด

ส่วนที่ 1 ข้อมูลทั่วไปของบุคลากรสาธารณสุข (HCPs Characteristics)

1. เพศ ( ) 1.ชาย ( ) 2.หญิง
2. วัน เดือน ปี เกิด.....
3. อาชีพ ( ) 1. แพทย์ ( ) 2. เภสัชกร
4.ระดับการศึกษาที่จบมา
( ) 1. อนุปริญญา ( ) 2. ปริญญาตรี ( ) 3. ปริญญาโท
( ) 4. สูงกว่าปริญญาโท ( ) 5. อื่นๆ โปรดระบุ.....

5. รายได้เฉลี่ยต่อเดือนของท่าน (รวมรายได้พิเศษอื่นๆแล้ว)
( ) 1. น้อยกว่าหรือเท่ากับ 5,000 บาท ( ) 2. 5,001-10,000 บาท ( ) 3. 10,001-15,000 บาท
( ) 4. 15,001-20,000 บาท ( ) 5. มากกว่าหรือเท่ากับ 20,001 บาท

6. สถานะภาพสมรส
( ) 1. โสด ( ) 2. แต่งงาน ( ) 3. หม้าย ( ) 4. หย่า ( ) 5. แยกกันอยู่
7. ระยะเวลาของการทำงานในโรงพยาบาล .....เดือน... ..... ปี
8. ท่านมีประสบการณ์ในการทำงานมาแล้วกี่ปี.....ปี

9. ท่านเคยพบอาการไม่พึงประสงค์ในระหว่างการทำงานหรือไม่ ?
( ) 1. ไม่พบ ( ) 2. พบ
10. ปกติท่านดำเนินการอย่างไรในกรณีพบอาการไม่พึงประสงค์ระหว่างการทำงาน
.....

11. แหล่งข้อมูลข่าวสารเกี่ยวกับการรายงานอาการไม่พึงประสงค์จากยาที่ท่านเคยได้รับที่ผ่านมา (สามารถเลือกได้ มากกว่า 1 ข้อ)

( ) 1. ผู้ให้บริการ (หมอ/พยาบาล/เภสัชกร) ( ) 2. สื่อวิทยุโทรทัศน์

( ) 3. สื่อสังคมออนไลน์ (Facebook, Line, Twitter...) ( ) 4. เพื่อน/ญาติพี่น้อง

( ) 5.บุคลากรของศูนย์ PV ( ) 6. อื่นๆ โปรดระบุ.....

<u>ส่วนที่ 2 ความคิดเห็นของบุคลากรสาธารณสุข</u>

1. ท่านคิดว่าตนเองมีองค์ความรู้ในระดับใดเพื่อใช้ในการรายงาน หรือ การประเมินอาการไม่พึงประสงค์จากยาของท่าน เพื่อประเมินว่า อาการรุนแรง หรืออไม่รุนแรง เป็นต้น

( ) 1. น้อยที่สุด ( ) 2. น้อย ( ) 3. ปานกลาง ( ) 4. มาก ( ) 5. มากที่สุด

2. ท่านมีความสามารถรับมือในการเกิดอาการไม่พึงประสงค์จากยาของท่านได้ในระดับใด ตัวอย่างเช่น ปรับเปรี่ยนยาเพื่อรักษา หลือ ยุดใช้ยา เป็นต้น

( ) 1. น้อยที่สุด ( ) 2. น้อย ( ) 3. ปานกลาง ( ) 4. มาก ( ) 5. มากที่สุด

3. ท่านมีความสามารถในระดับใดในการจะควบคุมไม่ให้เกิดอาการไม่พึงประสงค์จากยาในการรักษาโรค เป็นต้น

( ) 1. น้อยที่สุด ( ) 2. น้อย ( ) 3. ปานกลาง ( ) 4. มาก ( ) 5. มากที่สุด

4. ท่านมีความภูมิใจต่อความสามารถของท่านในการดูแลสุขภาพผู้ป่วยไม่ให้เกิดอาการไม่พึงประสงค์จากยา ในระดับใด

( ) 1. น้อยที่สุด ( ) 2. น้อย ( ) 3. ปานกลาง ( ) 4. มาก ( ) 5. มากที่สุด

<u>ส่วนที่ 3</u> <u>ความพึงพอใจ (Domains of Satisfaction) และความคิดเห็นต่อการใช้เครื่องมือ TaWai for health ในการรายงานเหตุการณ์ไม่พึงประสงค์จาการใช้ยาในโรงพยาบาล</u>

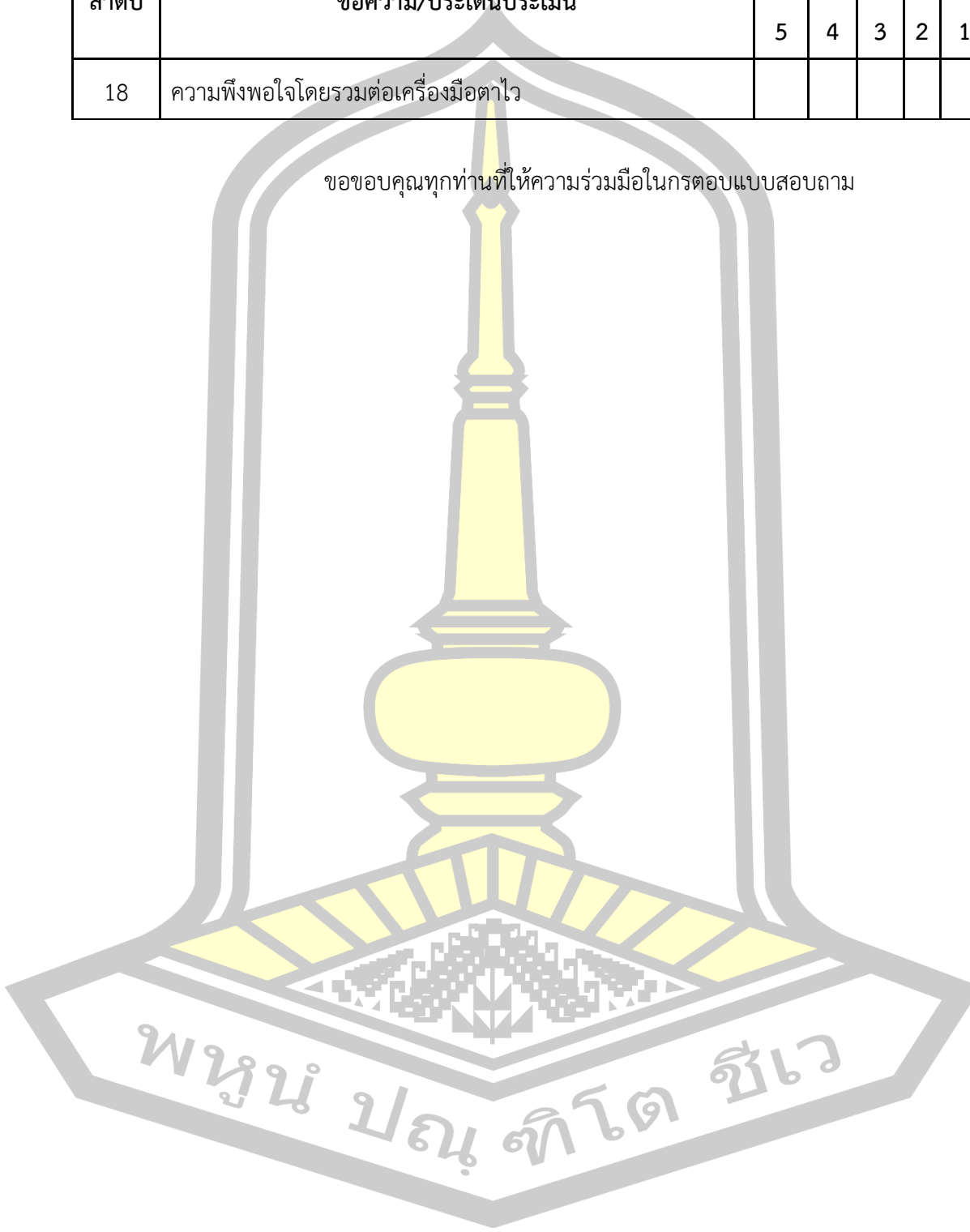
คำชี้แจง ขอให้ท่านอ่านข้อความหรือประเด็นต่อไปนี้แล้วทำเครื่องหมาย กากบาท (X) ลงในช่องว่างที่ตรงกับระดับความพึงพอใจของท่านมากที่สุด โดยมีระดับความพึงพอใจ ดังต่อไปนี้

1 = พึงพอใจมากที่สุด หรือเห็นด้วยมากที่สุด
4 = พึงพอใจมาก หรือเห็นด้วยมาก
3 = พึงพอใจปานกลาง หรือเห็นด้วยปานกลาง
2 = ไม่พึงพอใจ หรือ ไม่เห็นด้วย
1 = ไม่พึงพอใจมากที่สุด หรือไม่เห็นด้วยมากที่สุด
n/a = ไม่สามารถประเมินได้

ลำดับ	ข้อความ/ประเด็นประเมิน	ระดับความคิดเห็น					
		5	4	3	2	1	n/a
1	เครื่องมือตาไวสามารถเข้าใช้งานง่าย						
2	เครื่องมือตาไวสามารถเข้าถึงได้ง่าย						
3	เครื่องมือตาไวสามารถเข้าถึงได้ทุกที่ ทุกเวลา						
4	ลักษณะและขนาดตัวหนังสือของเครื่องมือตาไวมีความสวยงาม						
5	ลักษณะและขนาดตัวหนังสือของเครื่องมือตาไวมีความเหมาะสม						
6	เครื่องมือตาไวใช้เวลาในการเข้าถึงนาน						
7	เครื่องมือตาไวใช้งานง่าย						
8	เครื่องมือตาไวมีความสะดวกในการใช้งาน						
9	เครื่องมือตาไวมีความซับซ้อน ใช้งานยาก						
10	เครื่องมือตาไวช่วยลดระยะเวลาการรายงานเหตุการณ์ไม่พึงประสงค์ได้						
11	เครื่องมือตาไวช่วยลดความยุ่งยากในการรายงานเหตุการณ์ไม่พึงประสงค์ได้						
12	ข้อคำถามของเครื่องมือตาไวมีความสอดคล้องกับการปฏิบัติงานจริง						
<u>ความพึงพอใจต่อประโยชน์ที่ได้รับของผู้ใช้งานเครื่องมือตาไว</u>							
13	เครื่องมือตาไวมีประโยชน์กับผู้ป่วยมาก						
14	เครื่องมือตาไวมีประโยชน์กับบุคลากรทางการแพทย์มาก						
15	เครื่องมือตาไวมีความเหมาะสมกับบริบทของโรงพยาบาล						
16	เครื่องมือตาไวมีความเหมาะสมกับบริบทของประเทศลาว						
17	เครื่องมือตาไวมีความเหมาะสมมากที่ตะใช้ในโรงพยาบาล						

ลำดับ	ข้อความ/ประเด็นประเมิน	ระดับความคิดเห็น					
		5	4	3	2	1	n/a
18	ความพึงพอใจโดยรวมต่อเครื่องมือตาไว						

ขอขอบคุณทุกท่านที่ให้ความร่วมมือในกรตอบแบบสอบถาม



APPENDIX 6

Healthcare professional (HCPs) satisfaction questionnaire

Lao version

ແບບສອບຖາມຄວາມເພິ່ງພໍໃຈຂອງພະນັກງານສາທາລະນະສຸກໃນການໃຊ້ເຄື່ອງມືຕາໄວເຂົ້າໃນການລາຍງານອາການບໍ່ເພິ່ງປາດຖະໜາຂອງຄົນເຈັບ

ສ່ວນທີ 1: ຂໍ້ມູນທົ່ວໄປຂອງພະນັກງານສາທາລະນະສຸກ (HCPs Characteristics)

1. ເພດ ( ) 1.ຊາຍ ( ) 2.ຍິງ
2. ອັນເດືອນປີເກີດ.....
3. ອາຊີບ ( ) 1. ແພດໝໍ ( ) 2. ເພສັຊກອນ
4. ລະດັບການສຶກສາທີ່ຈົບມາ

( ) 1. ອານຸປະລິນຍາ ( ) 2. ປະລິນຍາຕີ ( ) 3. ປະລິນຍາໂທ

( ) 4. ສູງກ່ວາປະລິນຍາໂທ ( ) 5. ອື່ນໆ (ກະລຸນາບອກລະອຽດ).....

5. ລາຍໄດ້ສະເລ່ຍຕໍ່ເດືອນຂອງທ່ານ (ລວມລາຍໄດ້ພິເສດອື່ນໆແລ້ວ)

( ) 1. ໜ້ອຍກ່ວາ ຫຼື ເທົ່າກັບ 1.300.000 ກີບ ( ) 2. 1,300.000-2.500.000 ກີບ ( ) 3. 2.500.001-3.900.000 ກີບ ( ) 4. ຫລາຍກ່ວາ 3.900.000 ກີບ

6. ສະຖານະພາບສົມລົດ

( ) 1. ໂສດ ( ) 2. ແຕ່ງງານ ( ) 3. ໝ້າຍ

( ) 4. ຢ່າຮ້າງ ( ) 5. ແຍກກັນຢູ່

7. ໄລຍະເວລາຂອງການເຮັດວຽກໃນໂຮງໝໍ.....ເດືອນ.....ປີ

8. ທ່ານມີປະສົບການໃນການເຮັດວຽກມາແລ້ວຈັກປີ.....

9. ທ່ານເຄີຍພົບອາການບໍ່ເພິ່ງປາດຖະໜາຈາກຢາໃນລະຫວ່າງການເຮັດວຽກບໍ?

( ) 1. ບໍ່ເຄີຍ ( ) 2. ເຄີຍ

10. ຖ້າເຄີຍປົກກະຕິທ່ານດຳເນີນການແນວໃດໃນກໍລະນີພົບອາການບໍ່ເພິ່ງປາດຖະໜາລະຫວ່າງການເຮັດວຽກ

.....

11. ແຫຼ່ງຂໍ້ມູນຂ່າວສານກ່ຽວກັບການລາຍງານອາການບໍ່ເພິ່ງປາດຖະໜາຈາກຢາທີ່ທ່ານເຄີຍຮັບຜ່ານມາ (ສາມາດຕອບໄດ້ຫຼາຍກ່ວາ 1 ຂໍ້)

( ) 1. ຜູ້ໃຫ້ບໍລິການ (ໝໍ/ເພສັຊກອນ/ພະຍາບານ) ( ) 2. ສື່ໂທລະທັດ

( ) 3. ສື່ສັງຄົມອອນໄລ (Facebook, Line, Twitter…) ( ) 4. ໝູ່ເພື່ອນ/ຍາດພີ່ນ້ອງ

( ) 5.ບຸກຄະລາກອນຂອງສູນ Pharmacovigilance ( ) 6. ອື່ນໆ (ກະລຸນາບອກລະອຽດ).....

ສ່ວນທີ 2: ຄວາມຄິດເຫັນຂອງພະນັກງານສາທາລະນະສຸກ

5. ທ່ານຄິດວ່າຕົນເອງມີອົງຄວາມຮູ້ໃນລະດັບໃດເພື່ອໃຊ້ໃນການລາຍງານ ຫຼື ການປະເມີນອາການບໍ່ເພິ່ງປາດຖະໜາຈາກຢາຂອງທ່ານເພື່ອປະເມີນວ່າອາການຮຸນແຮງ ຫຼື ບໍ່ຮຸນແຮງເປັນຕົ້ນ

( ) 1. ໜ້ອຍທີ່ສຸດ ( ) 2. ໜ້ອຍ ( ) 3. ປານກາງ
( ) 4. ຫຼາຍ ( ) 5. ຫຼາຍທີ່ສຸດ

2. ທ່ານສາມາດຮັບມືໃນການເກີດອາການບໍ່ເພິ່ງປາດຖະໜາຈາກຢາຂອງທ່ານໄດ້ລະດັບໃດ ຕົວຢ່າງເຊັ່ນ ປັບຢາເພື່ອຮັກສາ ຫຼື ຢຸດຢາ ເປັນຕົ້ນ

( ) 1. ໜ້ອຍທີ່ສຸດ ( ) 2. ໜ້ອຍ ( ) 3. ປານກາງ
( ) 4. ຫຼາຍ ( ) 5. ຫຼາຍທີ່ສຸດ

3. ທ່ານມີຄວາມສາມາດໃນລະດັບໃດເພື່ອທີ່ຈະຄວບຄຸມບໍ່ໃຫ້ເກີດອາການບໍ່ເພິ່ງປາດຖະໜາຈາກຢາໃນການຮັກສາພະຍາດເປັນຕົ້ນ

( ) 1. ໜ້ອຍທີ່ສຸດ ( ) 2. ໜ້ອຍ ( ) 3. ປານກາງ
( ) 4. ຫຼາຍ ( ) 5. ຫຼາຍທີ່ສຸດ

4. ທ່ານມີຄວາມພູມໃຈຕໍ່ຄວາມສາມາດໃນການດູແລະສຸຂະພາບຜູ້ປ່ວຍບໍ່ໃຫ້ເກີດອາການບໍ່ເພິ່ງປາດຖະໜາຈາກຢາຂອງທ່ານໃນລະດັບໃດ

( ) 1. ໜ້ອຍທີ່ສຸດ ( ) 2. ໜ້ອຍ ( ) 3. ປານກາງ
( ) 4. ຫຼາຍ ( ) 5. ຫຼາຍທີ່ສຸດ

ສ່ວນທີ 3:ຄວາມເພິ່ງພໍໃຈ (Domains of Satisfaction) ແລະ ຄວາມຄິດເຫັນຕໍ່ການໃຊ້ເຄື່ອງມື TaWai for health ໃນການລາຍງານເຫດການບໍ່ເພິ່ງປາດຖະໜາຈາກການຢາໃນໂຮງໝໍ

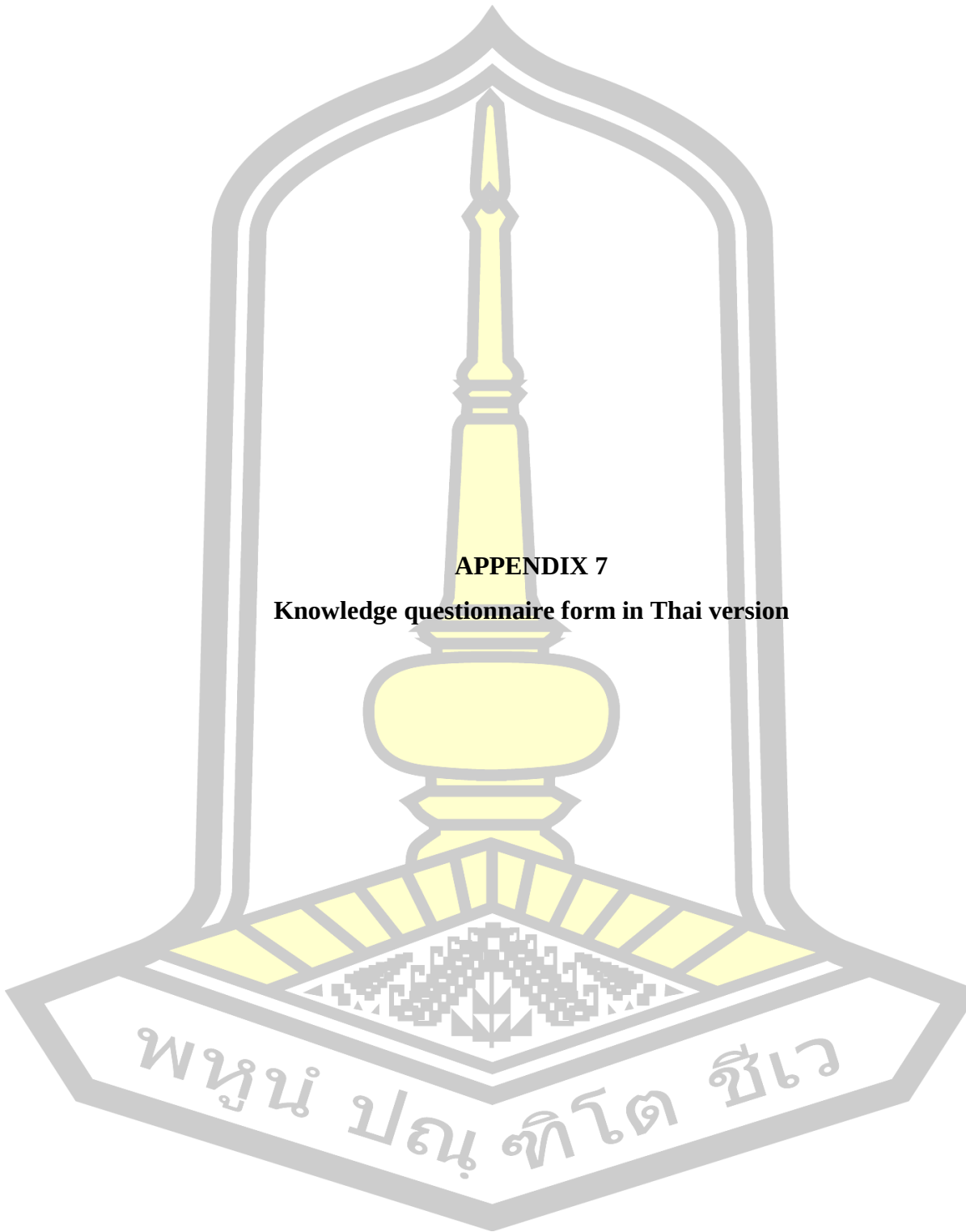
ຄຳຊີ້ແຈງ: ຂໍໃຫ້ທ່ານອ່ານຂໍ້ຄວາມ ຫຼື ປະເດັນຕໍ່ໄປນີ້ແລ້ວເຮັດເຄື່ອງໝາຍ ການກະບາດ (X) ລົງໃນຊ່ອງວ່າງທີ່ກົງກັບລະດັບຄວາມເພິ່ງພໍໃຈຂອງທ່ານຫຼາຍທີ່ສຸດ ໂດຍມີລະດັບຄວາມເພິ່ງພໍໃຈດັ່ງຕໍ່ໄປນີ້

5 = ເພິ່ງພໍໃຈຫຼາຍທີ່ສຸດ ຫຼື ເຫັນດີນຳຫຼາຍທີ່ສຸດ 4 = ເພິ່ງພໍໃຈຫຼາຍ ຫຼື ເຫັນດີນຳຫຼາຍ 3 = ເພິ່ງພໍໃຈປານກາງ ຫຼື ເຫັນດີນຳປານກາງ 2 = ບໍ່ເພິ່ງພໍໃຈ ຫຼື ບໍ່ເຫັນດີນຳ 1 = ບໍ່ເພິ່ງພໍໃຈຫຼາຍທີ່ສຸດ ຫຼື ບໍ່ເຫັນດີນຳຫຼາຍທີ່ສຸດ n/a = ບໍ່ສາມາດປະເມີນໄດ້

ລຳດັບ	ຂໍ້ຄວາມ/ປະເດັ່ນປະເມີນ	ລະດັບຄວາມເພິ່ງພໍໃຈ					
		5	4	3	2	1	n/a
1	ເຄື່ອງມືຕາໄວສາມາດເຂົ້າໃຊ້ງານງ່າຍ						
2	ເຄື່ອງມືຕາໄວສາມາດເຂົ້າຖຶງໄດ້ງ່າຍ						
3	ເຄື່ອງມືຕາໄວສາມາດເຂົ້າຖຶງໄດ້ທຸກທີ ທຸກເວລາ						
4	ລັກສະນະ ແລະ ຂະໜາດຕົວໜັງສືຂອງເຄື່ອງມືຕາໄວມີຄວາມສວຍງາມ						
5	ລັກສະນະ ແລະ ຂະໜາດຕົວໜັງສືຂອງເຄື່ອງມືຕາໄວມີຄວາມ ເໝາະສົມ						
6	ເຄື່ອງມືຕາໄວໃຊ້ເວລາໃນການເຂົ້າເຖິງດົນ						
7	ເຄື່ອງມືຕາໄວໃຊ້ງານງ່າຍ						
8	ເຄື່ອງມືຕາໄວສະດວກໃນການໃຊ້ງານ						
9	ເຄື່ອງມືຕາໄວມີຄວາມຊັບຊ້ອນ ໃຊ້ງານຍາກ						
10	ເຄື່ອງມືຕາໄວຊ່ວຍຫຼຸດເລບະເວລາໃນການລາຍງານເຫດການອາການບໍ່ເພິ່ງປາດຖະໜາໄດ້						
11	ເຄື່ອງມືຕາໄວຊ່ວບຫຼຸດຄວາມຫຍຸ້ງຍາກໃນການລາຍງານເຫດການອາການບໍ່ເພິ່ງປາດຖະໜາໄດ້						
12	ຂໍ້ຄຳຖາມຂອງເຄື່ງມືຕາໄວມີຄວາມສອດຄ່ອງກັບການປະຕິບັດງານຕົວຈິງ						
<u>ຄວາມເພິ່ງພໍໃຈຕໍ່ປະໂຫຍດທີ່ໄດ້ຮັບຂອງຜູ້ໃຊ້ງານເຄື່ອງມືຕາໄວ</u>							
13	ເຄື່ອງມືຕາໄວມີປະໂຫຍດກັບຄົນເຈັບຫຼາຍ						
14	ເຄື່ອງມືຕາໄວມີປະໂຫຍດກັບພະນັກງານການແພດຫຼາຍ						

ລຳດັບ	ຂໍ້ຄວາມ/ປະເດັ່ນປະເມີນ	ລະດັບຄວາມເພິ່ງພໍໃຈ					
		5	4	3	2	1	n/a
15	ເຄື່ອງມືຕາໄວມີຄວາມເໝາະສົມກັບບໍລິບົດຂອງໂຮງໝໍ						
16	ເຄື່ອງມືຕາໄວມີຄວາມເໝາະສົມກັບບໍລິບົດຂອງປະເທດລາວ						
17	ເຄື່ອງມືຕາໄວມີຄວາມເໝາະສົມຫຼາຍທີ່ຈະໃຊ້ໃນໂຮງໝໍ						
18	ຄວາມພຶ່ງພໍໃຈໂດຍລວມຕໍ່ເຄື່ອງມືຕາໄວ						

ຂອບໃຈທຸກທ່ານທີ່ໃຫ້ຄວາມຮ່ວມມືໃນການຕອບແບບສອບຖາມ



APPENDIX 7

Knowledge questionnaire form in Thai version

แบบประเมินความรู้ของบุคลากรต่ออาการไม่พึงประสงค์จากการใช้ยา

แบบสอบถามนี้พัฒนาขึ้นโดยมีวัตถุประสงค์เพื่อประเมินความรู้ต่ออาการไม่พึงประสงค์จากการใช้ยา โดยแบบสอบถามมีข้อมูลความความรู้เกี่ยวกับ ต่ออาการไม่พึงประสงค์จากการใช้ยา จำนวน 23 ข้อ

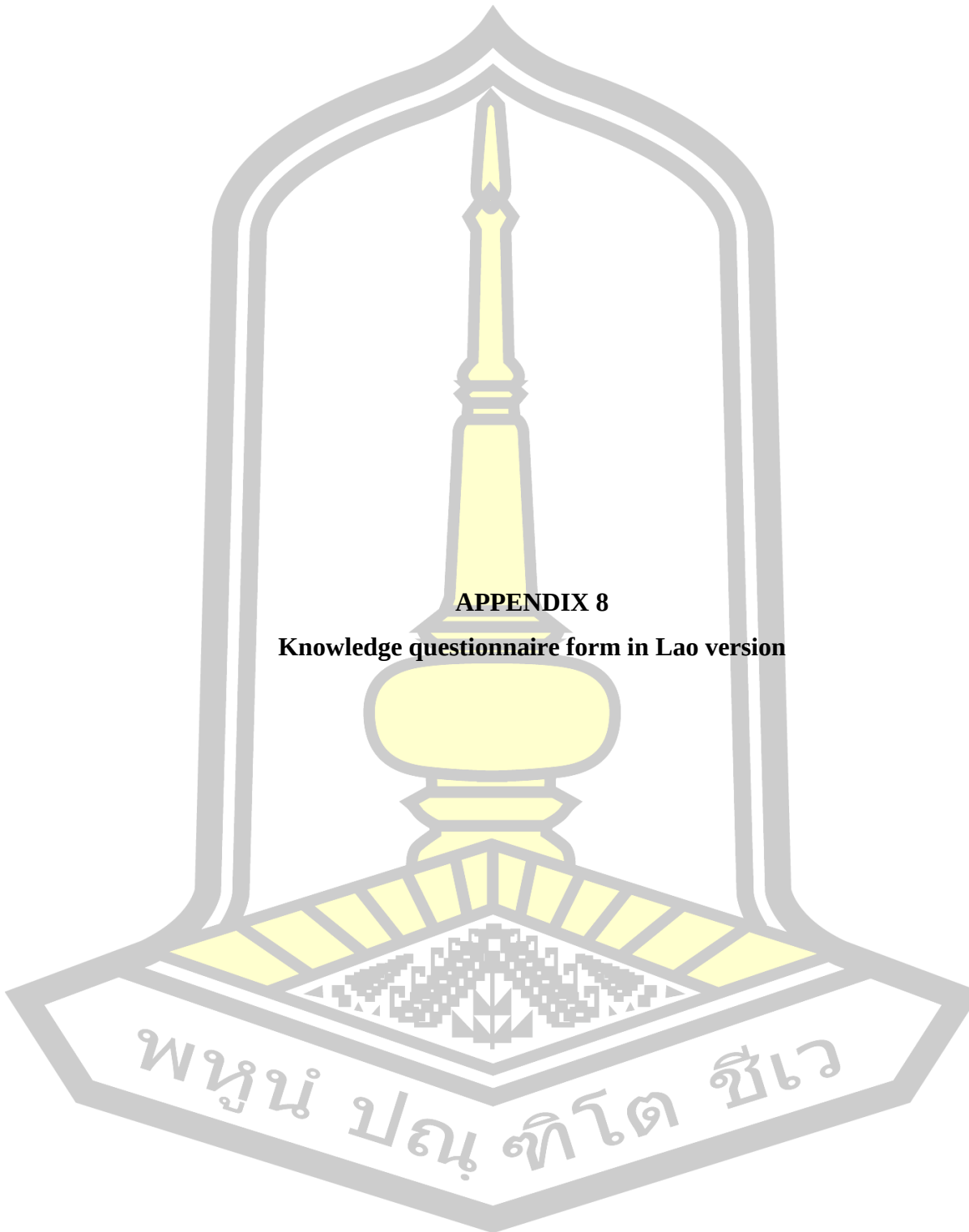
คำชี้แจง ขอให้ท่านอ่านข้อความหรือประเด็นต่อไปนี้แล้วทำเครื่องหมาย กากบาท (X) ลงในช่องว่างที่ท่านคิดว่าถูกต้องกับความคิดของท่านมากที่สุด ดังต่อไปนี้

ลำดับ	ข้อความ/ประเด็นประเมิน	ความคิดเห็น		
		ไม่ใช่	ใช่	ไม่รู้
ความหมายของอาการไม่พึงประสงค์จากการใช้ยา (ADR) และ นิยามของ Pharmacovigilance (PV)				
1	ADR คือ การตอบสนองต่อยาที่เป็นอันตรายและไม่ได้จงใจให้เกิดขึ้น ซึ่งเกิดขึ้นในขนาดการใช้ยาตามปกติในมนุษย์			
2	ADR สามารถเกิดขึ้นได้เมื่อใช้ยาในขนาดปกติเพื่อป้องกัน วินิจฉัย บรรเทา รักษาโรค หรือ เปลี่ยนแปลงแก้ไขการทำงานของร่างกาย			
3	อาการไม่พึงประสงค์ของยา คือ อาการใด ๆ ที่เกิดขึ้นจากการใช้ยาในขณะการรักษาแล้วเกิดผลหรืออาการที่ไม่ต้องการให้เกิดขึ้น โดยไม่รวมถึงการใช้ยาเกินขนาด หรือการจงใจใช้ยาในทางที่ผิด จนเกิดอันตราย			
4	อาการไม่พึงประสงค์สามารถแบ่งออกเป็นสองประเภทได้ตามกลไกของการเกิดอาการไม่พึงประสงค์จากการใช้ยา คือ type A และ type B			
5	อาการไม่พึงประสงค์ type A หมายถึง อาการไม่พึงประสงค์ที่เกิดจากฤทธิ์ทางเภสัชวิทยาของยา ระดับความรุนแรงของอาการ แปรผันตามขนาดยาและการตอบสนองของแต่ละบุคคล			
6	อาการไม่พึงประสงค์ type B หมายถึง อาการไม่พึงประสงค์ที่ไม่สามารถทำนายได้ล่วงหน้าจากฤทธิ์ทางเภสัชวิทยาของยา อาจเกี่ยวข้องกับปฏิกิริยาภูมิคุ้มกันหรือไม่ก็ได้			
7	PV หมายถึง กระบวนการที่เกี่ยวข้องกับการค้นหา ประเมินและป้องกันเหตุการณ์ไม่พึงประสงค์ (adverse event) หรือปัญหาอื่นๆ ที่เกี่ยวข้องกับยา			
8	PV มีวัตถุประสงค์หลัก คือ เพื่อให้มีการดูแลผู้ป่วยเพิ่มขึ้น และ			

ลำดับ	ข้อความ/ประเด็นประเมิน	ความคิดเห็น		
		ไม่ใช่	ใช่	ไม่รู้
	เกิดความปลอดภัยในการใช้ยาในผู้ป่วยมากขึ้น			
ผลกระทบต่อสุขภาพ				
9	อาการไม่พึงประสงค์จากยาสามารถส่งผลกระทบที่สำคัญต่อผู้ป่วยและระบบสุขภาพ			
10	อาการไม่พึงประสงค์จากยาเป็นสาเหตุสำคัญของการเข้ารับการรักษาในโรงพยาบาล และ เป็นสาเหตุสำคัญของการเสียชีวิต			
11	อาการไม่พึงประสงค์จากยามีอัตราที่สูงขึ้นตามอายุที่มากขึ้น จำนวนยาที่รับประทาน และ ระยะเวลาการพักรักษาตัว			
ข้อมูลเกี่ยวกับความสัมพันธ์ระหว่าง ADR กับความเจ็บป่วย อัตราการตายและต้นทุนของ ADR				
12	ADRs เป็นภาระสำคัญด้านการดูแลสุขภาพทั่วโลกและถือเป็นหนึ่งในสาเหตุสำคัญของการเจ็บป่วยและการเสียชีวิต			
13	อาการไม่พึงประสงค์จากยามีผลต่ออัตราการเข้ารับการรักษาในโรงพยาบาลอย่างมีนัยสำคัญ			
14	การรักษาโรคที่เกิดจาก ADR ต้องใช้ทรัพยากรทางการเงินจำนวนมากและหลายประเทศใช้งบประมาณโรงพยาบาล 15% ถึง 20% เพื่อรักษาภาวะแทรกซ้อนจากยา			
ความสำคัญของการรายงาน ADR ที่เกิดขึ้น (an spontaneous report of ADR or SRS)				
15	การรายงานอาการที่เกิดขึ้นเอง (SRS) เป็นวิธีการหนึ่งในการควบคุมอาการไม่พึงประสงค์จากยา			
16	การรายงานอาการต้องอาศัยแรงจูงใจของบุคคลในการรายงานอาการไม่พึงประสงค์จากยาที่น่าสงสัยไปยังศูนย์เภสัชกรรมในพื้นที่หรือระดับชาติ			
17	**SRS** สามารถระบุผลข้างเคียงหรือประโยชน์ของยาที่ไม่ทราบมาก่อนได้			
18	SRS มีคุณลักษณะที่สำคัญ คือ เป็นหัวใจสำคัญของการรายงาน ADR และครอบคลุมการใช้ยาในประชากรทั้งหมดในช่วงเวลาที่ไม่จำกัด และผลิตภัณฑ์ทั้งหมดของยาแต่ละชนิด			
ADR ที่เกิดขึ้นบ่อยกับยา TB และ HIV				

ลำดับ	ข้อความ/ประเด็นประเมิน	ความคิดเห็น		
		ไม่ใช่	ใช่	ไม่รู้
19	ADR ที่เกิดขึ้นบ่อยกับยา TB ในระดับรุนแรงน้อย คือ มีอาการเป็นผื่นร่วมกับอาการคันโดยไม่มีไข้ และอาการตามระบบอื่น			
20	ADR ที่เกิดขึ้น ในระดับรุนแรงปานกลาง คือ มีรอยโรคที่ผิวหนังร่วมกับอาการตามระบบอื่น เช่น ไข้ ออ่นเพลีย ปวดข้อ แขนชา ตับ ม้ามโต			
21	ADR ที่เกิดขึ้น ในระดับรุนแรงมาก ได้แก่ Steven Johnson's syndrome, toxic epidermal necrolysis, exfoliative dermatitis			
22	ADR ที่พบบ่อยกับยา HIV ได้แก่ นอนหลับยาก (insomnia) และปวดศีรษะ			
23	ผลข้างเคียงที่รุนแรง ได้แก่ การแพ้ยาและการทำงานของตับผิดปกติในคนไข้ที่มีการติดเชื้อไวรัสตับอักเสบบีและซีร่วมด้วย, Steven Johnson's syndrome			

ขอขอบคุณทุกท่านที่ให้ความร่วมมือในกรตอบแบบสอบถาม



APPENDIX 8

Knowledge questionnaire form in Lao version

ແບບປະເມີນຄວາມຮູ້ຂອງບຸກຄະລາກອນຕໍ່ອາການບໍ່ເພິ່ງປະສົງ ຈາກການນຳໃຊ້ຢາ

ແບບສອບຖາມນີ້ພັດທະນາຂຶ້ນໂດຍມີວັດຖຸປະສົງ ເພື່ອປະເມີນຄວາມຮູ້ຕໍ່ອາການບໍ່ເພິ່ງປະສົງຈາກການໃຊ້ຢາ ໂດຍແບບສອບຖາມຈະມີຂໍ້ມູນຄວາມຮູ້ກ່ຽວກັບອາການບໍ່ເພິ່ງປະສົງຈາກການໃຊ້ຢາ 23 ຂໍ້

ຄຳຊີ້ແຈງ: ຂໍໃຫ້ທ່ານອ່ານຂໍ້ຄວາມ ຫຼື ປະເດັນຕໍ່ໄປນີ້ແລ້ວກາເຄື່ອງໝາຍການກະບົດ (X) ລົງໃນຊ່ອງວ່າງທີ່ທ່ານຄິດວ່າຖືກກັບຄວາມຄິດຂອງທ່ານຫຼາຍທີ່ສຸດ ດັ່ງຕໍ່ໄປນີ້.

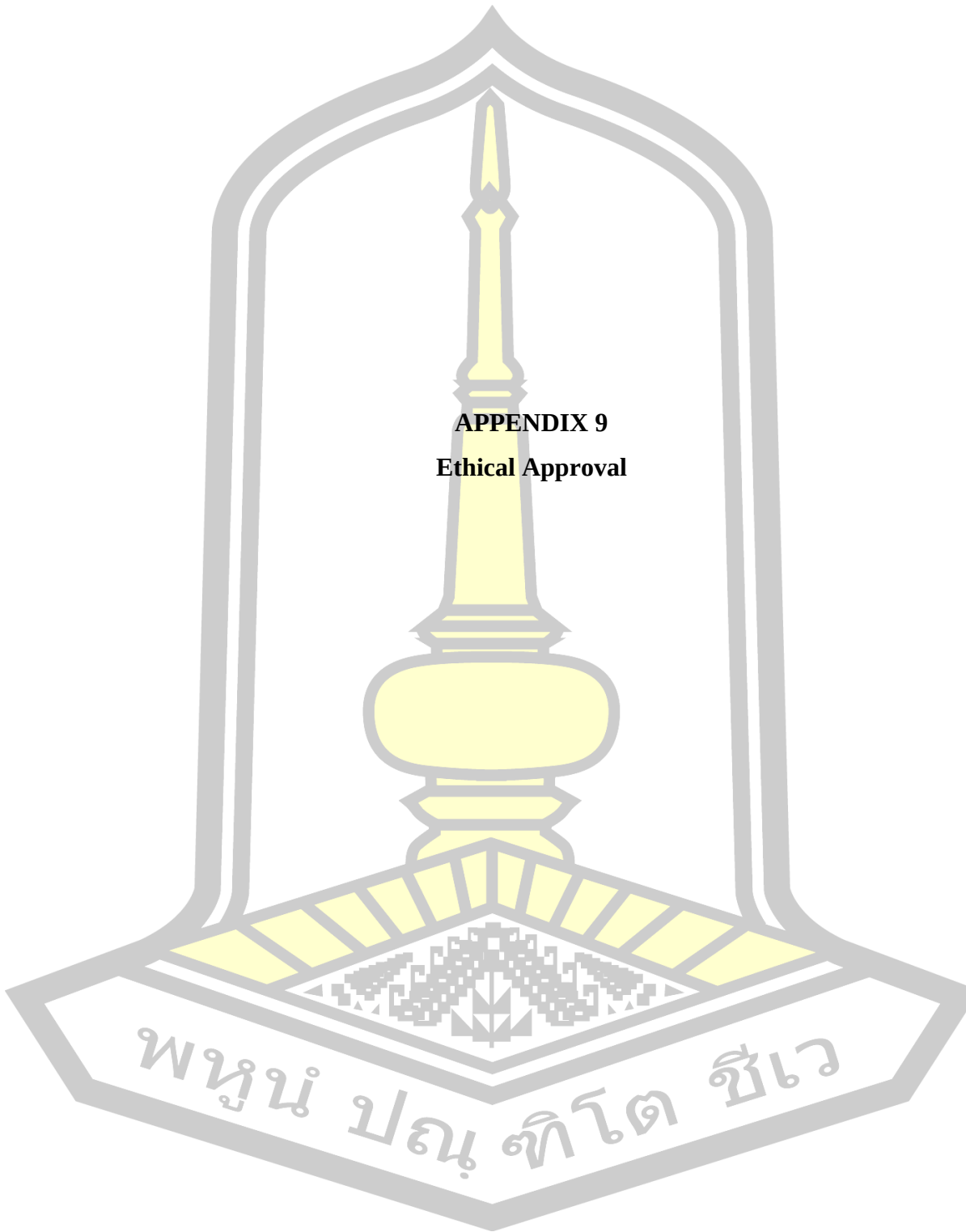
ລຳດັບ	ຂໍ້ຄວາມ/ປະເດັນປະເມີນ	ຄວາມຄິດເຫັນ		
		ແມ່ນ	ບໍ່ແມ່ນ	ບໍ່ຮູ້
ຄວາມໝາຍຂອງອາການບໍ່ເພິ່ງປະສົງຈາກການໃຊ້ຢາ (ADR) ແລະ ນິຍາມຂອງການເຝົ້າລະວັງການນຳໃຊ້ຢາ ຫຼື Pharmacovigilance (PV)				
1	ADRs ແມ່ນ ການຕອບສະໜອງຕໍ່ຢາທີ່ເປັນອັນຕະລາຍ ແລະ ບໍ່ໄດ້ຈົງໃຈໃຫ້ເກີດຂຶ້ນ ຊຶ່ງເກີດຂຶ້ນໄດ້ໃນຂະໜາດການໃຊ້ຢາຕາມປົກກະຕິໃນຄົນ			
2	ADRs ສາມາດເກີດຂຶ້ນໄດ້ເມື່ອໃຊ້ຢາໃນຂະໜາດປົກກະຕິເພື່ອປ້ອງກັນ,ບົ່ງມະຕິພະຍາດ, ບັນເທົາ, ປິ່ນປົວພະຍາດ ຫຼື ປ່ຽນແປງ ແກ້ໄຂການຮັດວຽກຂອງຮ່າງກາຍ			
3	ADRs ແມ່ນ ອຸການໃດໆທີ່ເກີດຂຶ້ນຈາກການໃຊ້ຢາໃນຄະນະປິ່ນປົວແລ້ວເກີດຜົນ ຫຼື ອາການທີ່ບໍ່ຕ້ອງການໃຫ້ເກີດຂຶ້ນ ໂດຍບໍ່ລວມເຖິງການໃຊ້ຢາເກີນຂະໜາດ ຫຼື ການຈົງໃຈໃຊ້ຢາໃນທາງທີ່ຜິດຈົນເກີດອັນຕະລາຍ			
4	ADRs ສາມາດແບ່ງອອກເປັນ 2 ປະເພດໄດ້ຕາມກົນໄກຂອງການເກີດອາການບໍ່ເພິ່ງປະສົງຈາກການໃຊ້ຢາຄື type A ແລະ type B			
5	ADRs ຂອງ type A ໝາຍເຖິງອາການບໍ່ເພິ່ງປະສົງທີ່ເກີດຈາກລິດທາງເພສັລວິທະຍາ ແລະ ລະດັບຄວາມຮ້າຍແຮງຂອງອາການແມ່ນແປຜັນຕາມຂະໜາດຢາ ແລະ ການຕອບສະໜອງຂອງແຕ່ລະບຸກຄົນ			
6	ADRs ຂອງ type B ໝາຍເຖິງອາການບໍ່ເພິ່ງ			

ລຳດັບ	ຂໍ້ຄວາມ/ປະເດັນປະເມີນ	ຄວາມຄິດເຫັນ		
		ແມ່ນ	ບໍ່ແມ່ນ	ບໍ່ຮູ້
	ປະສົງທີ່ບໍ່ສາມາດທຳນາຍໄຊ້ລ່ວງໜ້າຈາກລິດທາງເພສັຊວິທະຍາຂອງຢາທີ່ກ່ຽວຂ້ອງກັບປະຕິກິລິຍາພູມຄຸ້ມກັນຂອງແຕ່ລະບຸກຄົນ			
7	PV ໝາຍເຖິງ ຂະບວນການທີ່ກ່ຽວຂ້ອງກັບການສືບຄົ້ນ ຄົ້ນຫາ ປະເມີນ ແລະ ປ້ອງກັນເຫດການບໍ່ເພິ່ງປະສົງ (adverse event) ຫຼື ບັນຫາອື່ນໆທີ່ກ່ຽວຂ້ອງກັບຢາ			
8	PV ມີວັດຖຸປະສົງຫຼັກຄື ເພື່ອໃຫ້ມີການປົນປ່ວດຸແລເບິ່ງແຍງຄົນເຈັບເພີ່ມຂຶ້ນ ແລະ ເກີດຄວາມປອດໄພໃນການໃຊ້ຢາໃນຄົນເຈັບຫຼາຍຂຶ້ນ			
ຜົນກະທົບຕໍ່ສຸຂະພາບ				
9	ADRs ສາມາດສົ່ງຜົນກະທົບຫຼາຍຢ່າງຕໍ່ຄົນເຈັບ ແລະ ລະບົບສຸຂະພາບ			
10	ADRs ເປັນສາເຫດສຳຄັນຂອງການເຂົ້າຮັບການປົນປ່ວໃນໂຮງໝໍ ແລະ ເປັນສາເຫດສຳຄັນຂອງການເສຍຊີວິດ			
11	ADRs ມີອັດຕາການຜຸ້ດທີ່ສູງຂຶ້ນ ຕາມອາຍຸທີ່ຫຼາຍຂຶ້ນ,ຈຳນວນຢາທີ່ກິນ ແລະ ໄລຍະເວລາການປົນປ່ວ			
ຂໍ້ມູນກ່ຽວກັບຄວາມສຳພັນລະຫວ່າງ ADRs ກັບ ຄວາມເຈັບປ່ວຍ, ອັດຕາການຕາຍ ແລະ ຕົ້ນທຶນຂອງ ADRs				
12	ADRs ເປັນພາລະສຳຄັນດ້ານການດູແລສຸຂະພາບທົ່ວໂລກ ແລະ ຖືເປັນໜຶ່ງໃນສາເຫດສຳຄັນຂອງການເຈັບປ່ວຍ ແລະ ການເສຍຊີວິດ			
13	ADRs ມີຜົນຕໍ່ອັດຕາການເຂົ້າປົນປ່ວໃນໂຮງໝໍຢ່າງມີໄນຍະສຳຄັນ			
14	ການປົນປ່ວພະຍາດທີ່ເກີດຈາກ ADR ຕ້ອງໃຊ້ຄ່າໃຊ້ຈ່າຍຫຼາຍ ເພື່ອຮັກປົນປ່ວອາການ ຫຼື ຜົນຂ້າງຄຽງທີ່ເກີດຈາກຢາ			

ລຳດັບ	ຂໍ້ຄວາມ/ປະເດັນປະເມີນ	ຄວາມຄິດເຫັນ		
		ແມ່ນ	ບໍ່ແມ່ນ	ບໍ່ຮູ້
ລາຍງານ ADR ທີ່ເກີດຂຶ້ນ (spontaneous report of ADR or SRS)				
15	ການລາຍງານອາການທີ່ເກີດຂຶ້ນ(SRS)ເປັນ ວິທີການໜຶ່ງໃນການຄວບຄຸມອາການບໍ່ເຜິ່ງ ປະສົງຈາກຢາ			
16	ການລາຍງານອາການຕ້ອງອາໃສແຮງຈູງໃຈ ຂອງບຸກຄົນໃນການລາຍງານ ADRs ທີ່ໜ້າສົງ ໃສໄປຫາສູນເຝົ້າລະວັງຄວາມປອດໄພຂອງຢາ ຫຼື ລະດັບຊາດ			
17	SRS ສາມາດລະບຸຜົນຂ້າງຄຽງ ຫຼື ປະໂຫຍດ ຂອງຢາທີ່ບໍ່ຮູ້ມາກ່ອນໄດ້			
18	SRS ມີຄຸນລັກສະນະທີ່ສຳຄັນຄື ເປັນຫົວໃຈສຳ ຄັນໃນການລາຍງານ ADRs ແລະ ສາມາດ ຄວບຄຸມການໃຊ້ຢາໃນປະຊາກອນທັງໝົດໃນ ຊ່ວງເວລາທີ່ບໍ່ຈຳກັດ ແລະ ຜະລິດຕະພັນທັງ ໝົດຂອງຢາແຕ່ລະຊະນິດ			
ADRs ທີ່ເກີດຂຶ້ນເລື້ອຍໆກັບຢາ TB ແລະ HIV				
19	ADRs ທີ່ເກີດຂຶ້ນເລື້ອຍໆກັບຢາ TB ລະດັບບໍ ຮ້າຍແຮງເຊັ່ນມີອາການເປັນຜື່ນຮ່ວມກັບ ອາການໄຂ້, ວິນຫົວ ແລະ ມີອາການຕາມ ລະບົບອື່ນທີ່ບໍ່ຮ້າຍແຮງ			
20	ADRs ທີ່ເກີດຂຶ້ນໃນລະດັບຮ້າຍແຮງເຖິງປານ ກາງໂດຍມີພະຍາດຜິວໜັງຮ່ວມກັບອາການ ຕາມລະບົບອື່ນເຊັ່ນ ໄຂ້, ອ່ອນເພຍ, ປວດຕາມ ຂໍ້, ແຂນຂາຊາ, ຕັບ, ມ້າມຜິດປົກກະຕິ			
21	ADRs ທີ່ເກີດຂຶ້ນໃນລະດັບຮ້າຍແຮງຫຼາຍ ໄດ້ແກ່ Steven Johnson's syndrome, toxic epidermal necrolysis, exfoliative dermatitis			
22	ADRs ທີ່ພົບເລື້ອຍກັບຢາ HIV ໄດ້ແກ່ ນອນ ລັບຍາກ(insomnia),ເຈັບຫົວ,ວິນຫົວ,ແລະ ປວກຮາກ			

ລຳດັບ	ຂໍ້ຄວາມ/ປະເດັນປະເມີນ	ຄວາມຄິດເຫັນ		
		ແມ່ນ	ບໍ່ແມ່ນ	ບໍ່ຮູ້
23	ຜົນຂ້າງຄຽງທີ່ຮ້າຍແຮງໄດ້ແກ່ ການແພ້ຢາ ແລະ ການເຮັດວຽກຂອງຕັບຜິດປົກກະຕິ ໃນຄົນເຈັບທີ່ມີການຕິດເຊື້ອໄວລັດຕັບອັກເສບບີ ແລະ ຊີ ຮ່ວມນຳ ແລະ Steven Johnson's syndrome			

ຂໍຂອບໃຈທຸກທ່ານທີ່ໃຫ້ຄວາມຮ່ວມມືໃນການຕອບແບບສອບຖາມ



APPENDIX 9

Ethical Approval

MAHASARAKHAM UNIVERSITY ETHICS COMMITTEE FOR
RESEARCH INVOLVING HUMAN SUBJECTS

Certificate of Approval

Approval number: 115-074/2022

Title : Effect of modify TaWai mobile system on adverse drug reaction report in Lao PDR.

Principal Investigator : Miss. Niphonh Mongkhonmath
Responsible Department : Faculty of Pharmacy
Research site : Tuberculosis and HIV department at Settathilad hospital (Lao PDR)

Review Method : Expedited Review

Date of Manufacture : 4 April 2022 **expire :** 3 April 2023

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.

Ratree S.
.....

(Asst. Prof. Ratree Sawangjit)
Chairman

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

Lao People's Democratic Republic
Peace Independence Democracy Unity Prosperity
000

Ministry of Health
National Ethics Committee for Health Research (NECHR)

No 065 /NECHR
Vientiane Capital 03 /12/2021

Approval Notice

Mrs. Niphonh Mongkhonmath
Email: niphonh.mkm@gmail.com
Tel: +856 20 59 757 373

RE: Ethical Approval for Health Research

Title: "Effect of modified TaWai mobile system on adverse drug reaction reports in Lao PDR" (Submission ID: 2021.35)

Dear Mrs. Niphonh Mongkhonmath,

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

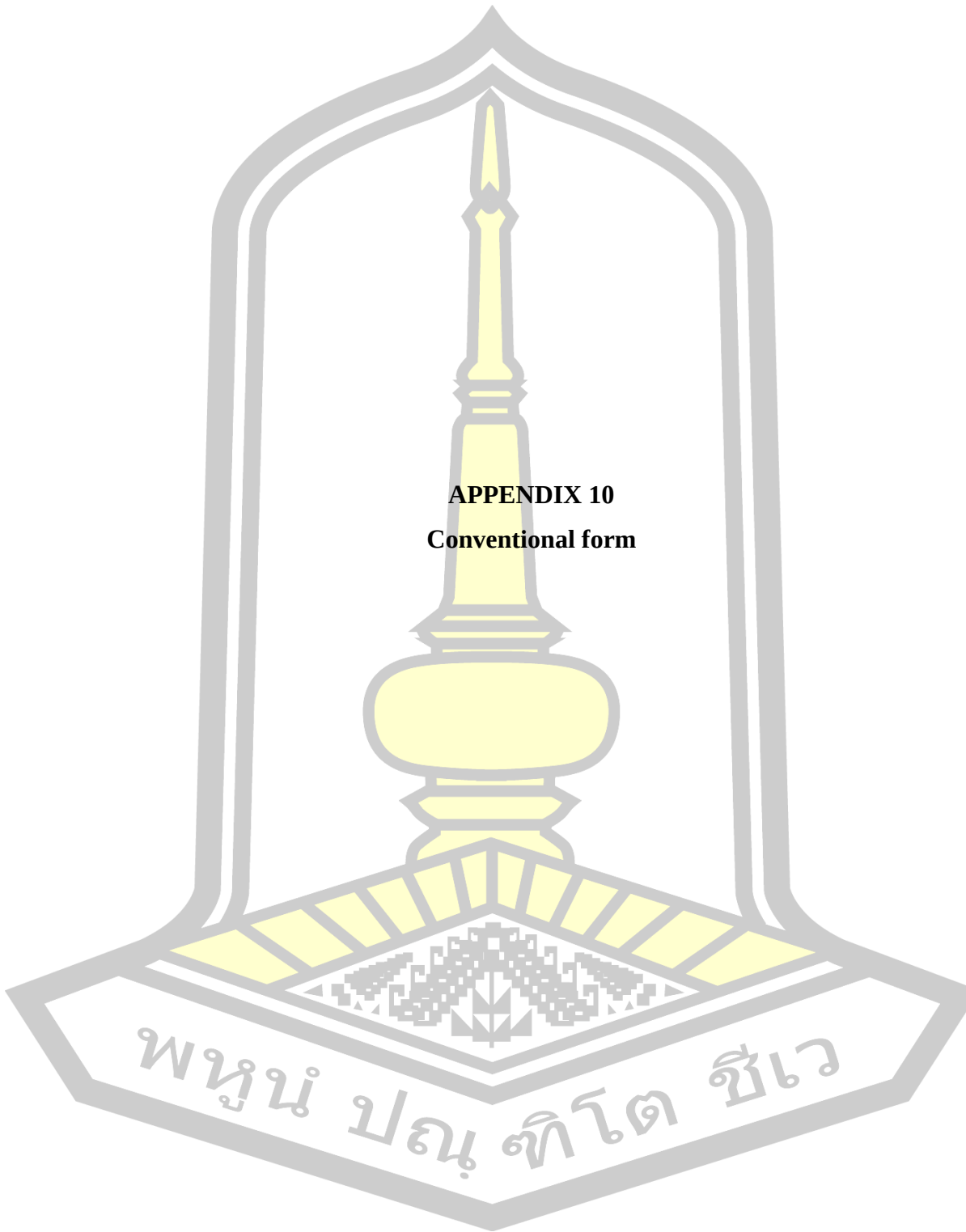
Please note the following information about your approved research protocol:

Approval period		November 2021 – November 2022	
Approved Subject Enrollment		65	
Study Site		Vientiane Capital	
Sponsor	Pierre Fabre Foundation	**Budget**	30.000.000 LAK
Implementing Panel/Project Investigator		Mrs. Niphonh Mongkhonmath	
Please note that the Ethics Committee reserves the right to ask for further questions, seek additional 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 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 NECHR

Dr. Sengchanh KOUNNAVONG



APPENDIX 10

Conventional form

Adverse Drug Reaction Reporting Form

ADR FORM

I Patient Information

Patient's initials: _____ Patient ID: _____

Date of Birth: __/__/____ Age: _____ Body height (cm): _____ Weight: _____ Sex: ☐ Male ☐ Female

II Details of Adverse Drug Reaction (ADR)

Date of onest: __/__/____ Outcome: ☐ Recovered *(Date)*: __/__/____ Not yet recovered: ☐

☐ Fatal *(Date of death)*: __/__/____ Unknown: ☐

Description of ADR(s):

Suspected drug(s) *Please specify brand name if known. For vaccines, please indicate batch no.*	Dosage	Frequency	Route	Date started	Date stopped	Indication(s) for using drug
1.						
2.						
3.						
4.						
5.						
Other drugs *(including complementary medicines, consumed at the same time and/or 3 months before*						
1.						
2.						
3.						

Other relevant information: e.g. medical history, allergies, pregnancy, smoking, alcohol use, challenge (if performed). Please enclose any relevant laboratory results.

III Management of Adverse Reaction

Hospitalisation *(following the ADR)*: ☐ Yes ☐ No ☐ Already hospitalized before ADR occurred

Do you consider the reaction to be serious? ☐ Yes ☐ No

If yes, please indicate why the reaction is considered to be serious (please tick ✓ all that apply)

☐ Patient died due to reaction

☐ Life threatening

☐ Congenital anomaly

☐ Involved or prolonged in-patient hospitalization

☐ Involved persistent or significant disability or incapacity

☐ Medically significant, please give details: .....

IV Particulars of reporter

Name and surname: _____

Position: _____ Date: __/__/____

Tel: _____ E-mail: _____

Signature:

Hospital: _____ Date: __/__/____

Ref No: ☐☐☐☐☐☐/_____

Certified by authority:

APPENDIX 11

consent form Lao version

ໜັງສືຍິນຍອມເຂົ້າຮ່ວມການສຶກສາ

ຊື່ໂຄງຄົ້ນຄວ້າ: "ຜົນຂອງການປັບປຸງລະບົບເຄື່ອງມື ຕາໄວ ໃນການລາຍງານອາການບໍ່ເພິ່ງປາດຖະໜາຈາກຢາ ທີ່ ສປປ ລາວ (Effect of modified TaWai mobile system on adverse drug reaction reports in Lao PDR).

ວັນທີໃຫ້ການຍິນຍອມ: _____ ລະຫັດຂອງຜູ້ຊ່ຽວຊານດ້ານສາທາລະນະສຸກ: _____

ຂ້າພະເຈົ້າມີຄວາມເຕັມໃຈທີ່ຈະມີສ່ວນຮ່ວມໃນການຄົ້ນຄວ້າ: "ຜົນຂອງການປັບປຸງລະບົບເຄື່ອງມື ຕາໄວ ໃນການລາຍງານອາການບໍ່ເພິ່ງປາດຖະໜາຈາກຢາ ທີ່ ສປປ ລາວ.

ຂ້າພະເຈົ້າໄດ້ຮັບການອະທິບາຍຈາກນັກຄົ້ນຄ້ວາ ກ່ຽວກັບແຫຼ່ງທີ່ມາ ແລະ ຈຸດປະສົງຂອງການຄົ້ນຄວ້າ, ຂັ້ນຕອນລາຍລະອຽດກ່ຽວກັບວິທີຄົ້ນຄ້ວາວິທີວິທະຍາ, ຜົນປະໂຫຍດທີ່ຄາດວ່າຈະໄດ້ຮັບຈາກການຄົ້ນຄວ້າ, ແລະ ຄວາມສ່ຽງທີ່ອາດຈະເກີດຂຶ້ນໃນລະຫວ່າງການຄົ້ນຄວ້ານີ້ຢ່າງລະອຽດ.

ຂ້າພະເຈົ້າເຂົ້າໃຈຂໍ້ຄວາມທັງໝົດຢູ່ໃນເອກະສານຂອງຜູ້ເຂົ້າຮ່ວມ. ອີກຢ່າງໜຶ່ງ, ຂ້າພະເຈົ້າມີເວລາຢ່າງພຽງພໍທີ່ຈະຖາມຂໍ້ສົງໃສຕ່າງໆກັບນັກຄົ້ນຄ້ວາ ແລະ ນັກຄົ້ນຄ້ວາໄດ້ອະທິບາຍ ແລະ ໄດ້ຕອບຄຳຖາມຈົນຫາຍຂ້ອງໃຈຈາກນັກຄົ້ນຄວ້າ. ຂ້າພະເຈົ້າມີສິດທີ່ຈະຍົກເລີກການເຂົ້າຮ່ວມການສຶກສາເມື່ອໃດກໍ່ໄດ້ໂດຍບໍ່ຈຳເປັນຕ້ອງແຈ້ງເຫດຜົນ.

ຂ້າພະເຈົ້າຈະສາມາດຕິດຕໍ່ຫາຄະນະກຳມະການດ້ານຈັນຍາບັນຂອງການຄົ້ນຄວ້າມະນຸດຢູ່ທີ່ຄະນະກຳມະການດ້ານຈັນຍາບັນແຫ່ງຊາດເພື່ອການຄົ້ນຄວ້າສຸຂະພາບຂອງ ສປປລາວ, ໂທຫາ +856-21-250670-207 ຫຼື 208. ຖ້າຂ້າພະເຈົ້າມີຄຳຖາມກ່ຽວກັບຂັ້ນຕອນການຄົ້ນຄວ້າໃນລະຫວ່າງໂຄງການ, ຂ້າພະເຈົ້າຈະສາມາດຕິດຕໍ່ກັບນັກຄົ້ນຄວ້າ ບາງ ນິພົນ ມົງຄົນມາດ ໄດ້ໂທຫາ: +856-20-59757373.

ຂ້າພະເຈົ້າມີການເພີ່ມມາດຕະການ ການປ້ອງກັນ Covid-19 ດັ່ງນີ້: ຂ້າພະເຈົ້າໄດ້ຮັບການສັກວັກຊີນຄົບ 2 ເຂັມແລ້ວ, ມີການໃຊ້ເຈວ Alcohol, ໃສ່ mask ແລະ ມີການເວັ້ນໄລຍະຫ່າງເຊິ່ງກັນ ແລະ ກັນ ໃນລະຫວ່າງການຄົ້ນຄວ້າ.

ຂ້າພະເຈົ້າໄດ້ອ່ານຂໍ້ມູນທີ່ກ່າວມາຂ້າງເທິງຢ່າງລະອຽດຖີ່ຖ້ວນແລ້ວ ແລະ ມີຄວາມເຂົ້າໃຈດີ, ຂ້າພະເຈົ້າຍິນດີທີ່ຈະເຂົ້າຮ່ວມການຄົ້ນຄ້ວາໃນຄັ້ງນີ້ພ້ອມທັງເຊັນໃບຍິນຍອມເຂົ້າຮ່ວມການຄົ້ນຄ້ວາດ້ວຍຄວາມສະໝັກໃຈ.

.... ລາຍເຊັນຜູ້ເຂົ້າຮ່ວມຄົ້ນຄ້ວາ

(..... .....) ວັນທີ ....

.... ລາຍເຊັນນັກຄົ້ນຄວ້າ

(Niphonh MONGKHONMATH) ວັນທີ .....

BIOGRAPHY

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