ROLE OF CLINICAL PHARMACIST IN PREVENTION OF ADVERSE DRUG EVENTS FOR RHEUMATOID ARTHRITIS OUTPATIENTS AT RAMATHIBODI HOSPITAL

SUTHATIP SOMJARIT

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Thesis
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ROLE OF CLINICAL PHARMACIST IN PREVENTION OF ADVERSE DRUG EVENTS FOR RHEUMATOID ARTHRITIS OUTPATIENTS AT RAMATHIBODI HOSPITAL

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ABSTRACT

The objective of this prospective controlled study was to determine whether clinical pharmacist's interventions could reduce adverse drug events (ADEs) in outpatients with rheumatoid arthritis (RA) at the rheumatology clinic, Ramathibodi Hospital, Thailand. The study was performed from April 30th to August 30th, 2007. ADEs were detected and classified as either preventable or non-preventable before (the 1st visit) and after the intervention period (the 2nd visit) in the intervention and control groups. Pharmacist's interventions were performed in the intervention group while the control group received the usual standard care. The pharmacist's interventions consisted of the detection and management of potential ADEs, prescribing errors, and providing patient counseling. The rate of preventable ADEs and the acceptance of pharmacist's intervention from physicians were primary and secondary outcome measures, respectively. The differences in the rates of preventable ADEs at the 2nd visit and the 1st visit were compared between the intervention and control groups. P value $\leq$ 0.05 was defined as statistically significant using the Chi-squared test. 70 and 72 participants were enrolled in the control group and intervention group, respectively. The difference in rates between the intervention and control groups at the 2nd visit was 10.7% ($p = 0.08$) and at the 1st visit was 6.2% ($p = 0.29$). Forty two pharmacist's interventions were made in total on the study group. Of these, 73.7% were accepted, 16.7% were partially accepted, and 9.6% were rejected. Despite non-significant differences in the preventable ADEs rates between the intervention group and the control group, the pharmacist's intervention seemed to have some impact on ADE reduction in outpatients with RA. The acceptance of pharmacist's intervention by physicians suggests that clinical pharmacist should have a role in identifying, preventing, resolving, and/or reducing ADEs in outpatients with RA.

KEY WORDS: ADVERSE DRUG EVENTS / PHARMACIST / RHEUMATOID ARTHRITIS / OUTPATIENT / INTERVENTION / ACCEPTANCE

142 pages

บทบาทเภสัชกรคลินิกในการป้องกันการเกิดเหตุการณ์ไม่พึงประสงค์จากการใช้ยาชนิดที่ป้องกันได้ของผู้ป่วยนอกโรคข้ออักเสบรูมาตอยด์ ณ โรงพยาบาลรามาธิบดี

ROLE OF CLINICAL PHARMACIST IN PREVENTION OF ADVERSE DRUG EVENTS FOR RHEUMATOID ARTHRITIS OUTPATIENTS AT RAMATHIBODI HOSPITAL

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บทคัดย่อ

วัตถุประสงค์ของการศึกษาแบบไปข้างหน้าและมีกลุ่มเปรียบเทียบนี้ คือ ต้องการวัดประสิทธิผลของเภสัชกรคลินิกในการลดการเกิดเหตุการณ์ไม่พึงประสงค์จากการใช้ยา (ADEs) ในผู้ป่วยนอกโรคข้ออักเสบรูมาตอยด์ ณ โรงพยาบาลรามาธิบดี โดยทำการศึกษาเก็บข้อมูลระหว่างวันที่ 30 เมษายนถึงวันที่ 30 สิงหาคม พ.ศ. 2550 การประเมินความน่าจะเป็นและการป้องกันได้ ก่อน(การนัดหมายครั้งที่ 1) และหลังจากมีเภสัชกร (การนัดหมายครั้งที่ 2) เปรียบเทียบระหว่างกลุ่มควบคุมที่ได้รับการดูแลรักษาตามมาตรฐานและกลุ่มศึกษา ที่เภสัชกรทำการศึกษาโดยประเมินและเสนอแนะแนวทางแก้ไข potential ADEs, ความคลาดเคลื่อนทางยา ตลอดจนให้คำปรึกษาปัญหาจากการใช้ยา ผลลัพธ์หลักและผลลัพธ์รอง คือ อัตราของการเกิด ADEs และผลการยอมรับจากแพทย์ ความแตกต่างของอัตราการเกิดเหตุการณ์ไม่พึงประสงค์ชนิดที่ป้องกันได้ ที่การนัดหมายครั้งที่ 2 และการนัดหมายครั้งที่ 1 ถูกเปรียบเทียบระหว่างกลุ่มศึกษาและกลุ่มควบคุม โดยใช้สถิติไคสแควร์ ที่ระดับนัยสำคัญ 0.05 จำนวนผู้ป่วยเข้าร่วมการศึกษาแบ่งเป็นกลุ่มควบคุมจำนวน 70 รายและกลุ่มศึกษาจำนวน 72 ราย ความแตกต่างของอัตราการเกิดเหตุการณ์ไม่พึงประสงค์ชนิดที่ป้องกันได้ ที่การนัดหมายครั้งที่ 2 ระหว่าง 2 กลุ่ม คิดเป็นร้อยละ 10.7 ($p = 0.08$) ที่การนัดหมายครั้งที่ 1 คิดเป็นร้อยละ 6.2 ($p = 0.29$) เภสัชกรเสนอแนะแนวทางแก่แพทย์ในกลุ่มศึกษาจำนวน 42 ครั้ง ได้รับการยอมรับจากแพทย์ร้อยละ 73.7 ได้รับการยอมรับบางส่วน ร้อยละ 16.7 และได้รับการปฏิเสธร้อยละ 9.6 แม้ว่าความแตกต่างของอัตราการเกิดเหตุการณ์ไม่พึงประสงค์ชนิดที่ป้องกันได้ ระหว่างทั้ง 2 กลุ่ม ไม่มีนัยสำคัญทางคลินิก แต่ดูเหมือนว่าการเสนอแนะแนวทางแก้ไขปัญหาของเภสัชกรและผลการยอมรับจากแพทย์จะมีผลต่อการลดอัตราการเกิดเหตุการณ์ไม่พึงประสงค์ชนิดที่ป้องกันได้ และแสดงให้เห็นบทบาทของเภสัชกรในการดูแลผู้ป่วยนอกโรคข้ออักเสบรูมาตอยด์

142 หน้า

CONTENTS

CONTENTS (cont.)

LIST OF TABLES

LIST OF TABLES (cont.)

LIST OF FIGURES

LIST OF ABBREVIATIONS

95% CI	95% confidence interval
a.m.	ante meridiem (before midday)
ACR	The American College of Rheumatology
ACRSRA	The American College of Rheumatology Subcommittee on Rheumatoid Arthritis
ADE	adverse drug event
ADR	adverse drug reaction
AE	adverse event
AIR	Allergy Immunology and Rheumatology
Alk Phos	alkaine phosphate
Anti-TNF	antitumor necrosis factor
APPROVe	Adenomatous Polyps Prevention on VIOXX
ASHP	American Society of Health System Pharmacisits
b.i.d.	bis in die (twice a day)
Baso	basophils
BUN	blood urea nitrogen
CABG	coronary artery bypass graft
Chol	cholesterol
Cl	chloride
CNS	central nervous system
cont.	continued
COX	cyclooxygenase
CQ	chloroquine
CRP	C-reactive protein
CYP	cyclophosphamide
D. bili	direct bilirubin
DMARDs	disease modifying antirheumatic drugs
DRPs	drug related problems

LIST OF ABBREVIATIONS (cont.)

DTPs	drug therapy problems
e.g.	exempli gratia (for example)
Eos	eosinophils
Epi. Sq.	epithelial square
ESR	erythrocyte sedimentation rate
et al	et alii (and others)
GGT	gamma glutamyl transferase
GI	gastrointestinal
HAQ-DI	health assessment questionnaire – disease index
Hb	hemoglobin
HCQ	hydroxychloroquine
Hct	hematocrit
HDL	high density lipoprotein
HIV	human immunodeficiency virus
HN	hospital number
HPF	high-power field
hr	hour
i.e.	id est (that is)
ICU	intensive care unit
IM	intramuscular
IV	intravenous
K	potassium
kg	kilogram
LDL	low density lipoprotein
LEF	leflunomide
LFTs	liver function tests
LPF	low-power field
Lym	lymphocytes

LIST OF ABBREVIATIONS (cont.)

MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCP joint	metacarpophalangeal joint
MCV	mean corpuscular volume
MEs	medication errors
mg	milligram
min	minute
Mono	monocytes
MTP joint	metatarsophalangeal joint
Na	sodium
NCC MERP	The National Coordinating Council for Medication Error Reporting and Prevention
Neu	neutrophils
NSAIDs	non steroidal anti-inflammatory drugs
OMNIUM	Omerprazole versus Misoprostol for NSAIDs-induced Ulcer Management
OR	odds ratio
p.m.	post meridiem (after midday)
p.o.	per os (by mouth)
p.r.n.	pro re nata (as-needed)
pADEs	preventable adverse drug events
PG	prostaglandin
PIP joint	proximal interphalangeal joint
Plts	platelets
potADE	potential adverse drug events
PPI	proton pump inhibitor
pred	prednisolone
q	quaque (every)

LIST OF ABBREVIATIONS (cont.)

RA	rheumatoid arthritis
RBC	red blood cell
RCT	randomized controlled trial
RES	reticuloendothelial system
RUCAM	Roussel Uclaf Causality Assessment Method
SAEs	serious adverse events
sc	subcutaneous
SCr	serum creatinine
SD	standard deviation
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SPSS	Statistical Package for Social Science
SSZ	sulfasalazine
T. billi	total bilirubin
TB	tuberculosis
TG	triglyceride
tNSAIDs	traditional non steroidal anti-inflammatory drugs
vs.	versus
WHO	World Health Organization
wk	week

CHAPTER I
INTRODUCTION

Background and rationale

Treatment goals in rheumatoid arthritis (RA) include control of signs and symptoms, restoring physical function and preventing or slowing progression of joint damage. Main classes of drugs currently used for pharmacotherapy in RA consist of non-steroidal anti-inflammatory drugs (NSAIDs), disease modifying anti-rheumatic drugs (DMARDs) and corticosteroids (1). High incidence of adverse drug event (ADE) from these drug groups has been reported affecting various organ systems. Unwanted effects not only cause an increasing in morbidity rate, but also mortality rate.

NSAIDs-induced adverse events are frequently reported and affected many organ systems such as gastrointestinal tract, renal, liver. Severity ranges from more commonly mild reaction to rare, but severe undesirable effects. The burden of adverse drug reaction (ADR) has been demonstrated as a cause of admission in the 18,820 patients during six month period which showed that NSAIDs were the most common drugs causing hospital admission up to 30% of all admissions by ADRs (2). Major ADRs in that study were GI bleeding, peptic ulceration, and renal impairment. In addition, two retrospective studies also suggested that 5% and 16% of anaphylaxis resulting from NSAIDs (3, 4).

The treatment of RA is principally based on DMARDs which reduce inflammatory synovitis, improve function and prevent structural damage. Although progression of disease could be decreased by DMARD therapy, treatment using single DMARD often fails to control RA. Combination DMARDs therapy has been used increasingly, and their advantage has been demonstrated in various studies using different approach, for example, type of patient (early or established RA), study designs (step-up, parallel or step-down) and utilized range of outcome measures.

However, these studies were mostly controlled trials consisting of too small sample size, and short period of monitoring to provide the information on rare serious events. Therefore, the efficacy and undesirable effects of combination DMARD therapy need to be integrated. At least six systematic-reviews of the efficacy and toxicity of combining DMARDs in RA management have been reported. Two early systematic-reviews did not show the advantage of combination DMARDs therapy (5, 6). In contrast four recent systematic-reviews revealed that combination therapy was more effective than monotherapy but had resulted in many withdrawals from drug toxicity (7-10).

Although the exact patterns of medical usage in RA patients have not been elucidated, many surveys of alternative medical products in America, Europe and Australia showed that their usage was high and growing (11). Furthermore, patients' beliefs about safety of DMARDs and their emotional impact had an influence on the initiation or withdrawal from these medications (12). These findings demonstrated the importance of health care professionals' awareness to adverse effects and drug interaction of DMARDs to drug therapy failures (11, 12). Therefore patient's counseling and education about disease status, benefit of the treatment including its precaution might increase the appropriate medical usage and patients' benefit from slow progression of their diseases with a reduction of avoidable ADEs.

For this reason, the clinical pharmacist who might have a role in the care team to help improve patients' safety and reduce ADEs (13). Participation of clinical pharmacist should include counseling, identification, monitoring and resolving ADEs, which might prevent potential ADEs (14). The benefit of clinical pharmacist's participation has been well demonstrated in many chronic diseases, for example, diabetic mellitus, cardiovascular disease, HIV disease, and asthma, in terms of economic outcomes and quality of life, thus indicating that clinical pharmacist could reduce and prevent ADEs (15-18). The evaluation of the efficacy of multidisciplinary team care in RA patients was also reported (19-21). However, no study has been conducted to confirm the role of the clinical pharmacist in reduction of ADEs in RA patients. Moreover, in Thailand, there are even fewer studies demonstrating the role of

pharmacist in chronic disease outpatient (22-29). For this reason, we have performed the preliminary ADE detection by retrospectively review the medical record of RA patients at Ramathibodi Hospital during June to July, 2006 (30). It was found that 80.5 % out of 200 patients were historically suffered from at least one ADE and 70% of all ADEs were preventable. The most frequent medication groups were DMARDs and NSAIDs by 54.0% and 24.7%, respectively. The preliminary study showed that ADE occurrence was relatively high. However, these results were cumulative data since the beginning of the medical therapy at Ramathibodi Hospital.

Therefore, the present study aimed to determine whether clinical pharmacist could help in identification, resolving, and the reduction of preventable ADEs.

Objectives

1. To determine the incidence of preventable ADEs and potential ADEs in RA outpatients during the study period.
2. To characterize clinical pharmacist's intervention and physicians' acceptance.

Expected outcomes and benefits

1. Clinical pharmacist participation could reduce preventable ADEs and prevent potential ADEs in RA outpatients.
2. Improvement of patients' outcome after pharmacist's intervention.
3. This study may be strategy for development of collaboration in multidisciplinary care team of ambulatory RA patients in Ramathibodi Hospital.

CHAPTER II
LITERATURE REVIEW

Part I: Rheumatoid arthritis

1. Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by persistent synovial tissue inflammation of the joint. Over time, bone erosion, destruction of cartilage, and complete loss of joint integrity can occur. Eventually, multiple organ systems may be affected. Estimated prevalence is approximately 0.5-1.5% of the general population. The annual incidence of RA in the United States was thought to be approximately 30 per 100,000 (31). The incidence and prevalence of RA are 2-3 times higher among women than men. Although the onset of RA may occur at any age, it most commonly strikes people between 30 and 60 years of age, with the incidence continuing to increase until approximately age of 85 (32). It is responsible for an estimated 250,000 hospitalizations and 9 million physician visits each year (13). In the United States, a systematic review revealed that the average annual medical cost associated with RA is US$ 5,720 per patient of which in-patient cost is the largest component (33). Its economic impact is magnified by the high level of functional impairment that is if left untreated, 20-30% of RA patients would become permanently work-disabled within 3 years of diagnosis. In Thailand, the survey study found a 0.12% prevalence of rheumatoid arthritis (34). The average societal cost of RA is estimated to be US$2,682 per patient per year, of which is estimated to be 41.4 per cent of a patient’s average annual income. Direct and indirect costs are estimated to be US$2,135 and US$547 per patient per year, respectively (35).

Female sex, a positive family history, older age, silicate exposure, and smoking are associated with an increased risk for development of RA. Consumption of more than 3 cups of coffee daily particularly decaffeinated coffee also may be a contributing factor (36). Patient with RA appear to be at higher risk for subclinical atherosclerosis, cardiovascular events, lymphomas, preeclampsia and preterm delivery,

depression and anxiety. Increased inflammation, as measured by C-reactive protein (CRP), is associated with hypertension, increased triglycerides and homocysteine level, and decreased high-density lipoprotein cholesterol and insulin sensitivity. Co-morbidities associated with RA and its therapy included peptic ulcer disease, osteoporosis, and infection. Males with RA have a higher risk for hypogonadism, possibly secondary to a central mechanism that controls hormonal synthesis or secretion. However, patients with RA are less likely to have atopic diseases (e.g., hay fever, allergies) (37).

Genetic and environmental factors play role in pathogenesis of RA. Although laboratory testing and imaging studies can help confirm the diagnosis and evaluate disease progression, RA is primarily clinical diagnosed and no single laboratory test alone is sufficient for diagnosis. The American College of Rheumatology Association (ARA) revised its criteria for the classification of RA in 1988 (Table 1). In typical outpatient practice, a definitive diagnosis using these criteria may be difficult to obtain early in the disease process. During the initial visit, patients should be asked about degree of pain, duration of stiffness and fatigue and functional limitations. A careful joint examination looking for the characteristics described above is vital.

Table 1 Criteria for the classification of rheumatoid arthritis.

Criterion	**Definition**
The patient must meet 4 of the following 7 criteria to be classified as having RA	
Morning stiffness	Morning stiffness in and around the joints, lasting at least 1 hour before maximal improvement
Arthritis of $\geq$ 3 joint areas	At least 3 joint areas simultaneously have had soft tissue swelling or fluid (not bony overgrowth alone) observed by a physician. The 14 possible areas are right or left PIP, MCP, wrist, elbow, knee, ankle, and MTP joints.

Table 1 Criteria for the classification of rheumatoid arthritis (cont.) (38).

Criterion	Definition
Arthritis of hand joints	At least 1 area swollen (as defined above) in a wrist, MCP, or PIP joint
Symmetric arthritis	Simultaneous involvement of the same joint areas (as defined in criteria 2) on both sides of the body (bilateral involvement of PIPs, MCPs, or MTPs is acceptable without absolute symmetry) [a,b]
Rheumatoid nodules	Subcutaneous nodules, over bony prominences, or extensor surfaces, or in juxtaarticular regions, observed by a physician[b]
Serum rheumatoid factor	Demonstration of abnormal amounts of serum rheumatoid factor by any method for which the result has been positive in < 5% of normal control subjects
Radiographic changes	Radiographic changes typical of rheumatoid arthritis on posteroanterior hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localized in or most marked adjacent to the involved joints

[a] Present for at least 6 weeks.

[b] must be observed by physician.

No single diagnostic test definitively confirms the diagnosis of RA. However, several tests can provide objective data that increase diagnostic certainty and allow disease progression to be followed. The American College of Rheumatology Subcommittee on Rheumatoid Arthritis (ACRSRA) recommends that baseline laboratory evaluations include a complete blood cell count with differential, rheumatoid factor, and erythrocyte sedimentation rate (ESR) or CRP. Baseline evaluation of renal and hepatic function also is recommended because these findings

will guide medication choices. Table 2 summarizes the laboratory findings associated with RA.

Table 2 Laboratory and imaging findings associated with RA (36).

Laboratory test	Associated findings
C-reactive protein	Typically increased to > 0.7 picograms per mL; may be used to monitor disease course.
Erythrocyte sedimentation rate*	Often increased to > 30 mm per hour; may be used to monitor disease course.
Hemoglobin/ hematocrit*	Slightly decreased, hemoglobin averages around 10 g/ dL; normochromic anemia, also may be normocytic or microcytic.
Liver function*	Normal or slightly elevated alkaline phosphatase
Platelets*	Usually increased
Radiographic findings of involved joints*	May be normal or show osteopenia or erosions near joint spaces in early disease, wrist and ankle films are useful as baselines for comparison with future studies.
Rheumatoid factor*	Negative in 30% of patients early in illness; if initially negative, can repeat 6-12 months after disease onset; can be positive in numerous other processes (e.g. lupus; scleroderma; Sjogren's syndrome; neoplastic disease; sarcoidosis; various viral, parasitic, or bacterial infections); not an accurate measure of disease progression.
White blood count*	May be increased
Anticyclic citrullinated peptide antibody	Tends to correlate well with disease progression, increase sensitivity when used in combination with rheumatoid factor; more specific than rheumatoid factor (90% vs. 80%); not readily available in many laboratories.
Antinuclear antibody	Limited value as a screening study for RA

Table 2 Laboratory and imaging finding associated with RA (cont.) (36).

Laboratory test	Associated findings
Complement levels	Normal or elevated
Immunoglobulins	Elevated alpha-1 and alpha-2 globulins possible
Joint fluid evaluation	Consider if an affected joint can be tapped and diagnosis is uncertain; straw-colored fluid with fibrin flecks often seen; fluid may clot at room temperature; 5,000 to 25,000 white blood cells per mm^3 with 85% polymorphonuclear leukocytes a common finding; in RA, cultures are negative, there are no crystals, and fluid glucose level typically is low.
Urinalysis	Microscopic hematuria or proteinuria may be present in many connective tissue diseases.

* Recommended for initial evaluation for RA.

Note: renal function, although not likely to change as a direct effect of disease, should be followed to assess renal effects from drug therapy.

The treatment of RA is a real challenge. The effective management of patients with RA involves a multidisciplinary approach which endeavors to deal with functional, psychosocial as well as physical problems. The aims of treatment include relief of pain, reduction of inflammation, functional improvement, control of disease activity and prevention of deformities.

Patient education

Patient education is important for long term management of RA, by providing information on the disease and its therapies which gives the patient a realistic outlook regarding the disease and allows them to be involved in the therapeutic decisions.

Non-pharmacologic treatment in RA

Non-pharmacologic treatment in RA involves a balance of rest and exercise, adequate nutrition, physical measures (39)**.**

Diet and exercise

Although no specific dietary modifications are found to be useful in the management of rheumatoid arthritis, addition of fish oil or fish supplements which are rich in omega-3 fatty acid are found to reduce the inflammation in the joints. The omega-3 fatty acids compete with arachidonic acid for the lipoxygenase enzyme resulting in decreased production of leukotrienes with pro-inflammatory properties. Studies show that fish oil supplementation has enabled reduction or even discontinuation of non-steroidal anti-inflammatory drugs in some patients with RA. It is also important to advice regular exercise program to improve and maintain general fitness and maintain muscle bulk around the joints to all patients with RA.

2. Pharmacologic treatment in RA

Pharmacologic therapy for RA often consists of combinations of NSAIDs, DMARDs, and/or corticosteroids. NSAIDs provide pain relief but have no effect on disease progression. DMARDs are more effective at reducing pain and swelling but have a slower onset of action. They can produce an improvement in the biochemical markers of disease activity but, in long-term studies, their ability to prevent joint destruction has been disappointing. Corticosteroids can also improve symptomatic relief but long-term use has gone out of favor owing to their undesirable side effect profile. DMARDs are now used much earlier in the management of RA and guidelines from the American College of Rheumatology (ACR) recommended that treatment with these drugs should be initiated within 3 months in patients with established diagnosis of RA and ongoing signs of active disease (40). The profile and adverse reactions of individual drug categories are summarized below.

NSAIDs: NSAIDs inhibit cyclooxygenase (COX) enzymes and thus decrease production of prostaglandins. Some prostaglandins under COX-1 control have important effects in many parts of the body (i.e., they protect gastric mucosa and inhibit platelet adhesiveness). Other prostaglandins are induced by inflammation and are produced by COX-2. The initial treatment of RA usually involves the use of salicylates, NSAIDs, or a selective COX inhibitor to reduce joint pain and swelling and to improve joint function. These agents have analgesic and anti-inflammatory

properties but do not alter the course of disease or prevent joint destruction. Thus, they should not be used as the single treatment for RA. Because DMARDs have the potential to reduce or prevent joint damage and preserve joint integrity and function, they have recently received more attention in RA treatment. However, the role of NSAIDs as the initial palliative drug therapy to reduce joint inflammation and pain is still clinically important. Choice of available agents is considered based on efficacy, safety, convenience, and cost. Because of the nature of long-term treatment of RA, sufficient attention must be paid not only to the efficacy of drugs but also to their safety. Common adverse reactions to NSAIDs, including gastrointestinal (GI) disorder, renal disorder, hepatic disorder, asthma, allergic rash, and disturbed hematopoiesis are attributed to the inhibition of prostaglandin (PG) production. Among them, GI disorder is of particular concern. Serious adverse reactions such as gastroduodenal ulcer, perforating ulcer, and GI hemorrhage resulting from damaged GI mucosa are clinically significant. In addition, other GI symptoms such as abdominal pain and dyspepsia should be closely observed because these subjective symptoms may disturb prescription compliance during long-term treatment with these drugs. Silverstein et al. (41) reported that approximately 20% of RA patients (not taking GI remedies) assigned to take NSAIDs for 6 months in a clinical study had intolerable GI symptoms and, because of these events, dropped out from the study. The recent meta-analysis intended to compare the incidence of upper GI symptoms (42) in a large-scale study for safety evaluation of NSAIDs (43) revealed that the most common GI adverse reactions in patients receiving NSAIDs were dyspepsia, abdominal pain, and nausea/vomiting. Although some investigators claim that these GI symptoms do not necessarily predict more serious adverse drug reactions such as ulcer and bleeding, but a relatively large number of patients complain of these symptoms, may need dosage reduction, discontinuation of treatment, and modifications of the prescribed drugs (44, 45).

GI adverse events are usually mild but are the most common adverse effects (in approximately 10% of patients on NSAIDs), followed by renal events and skin rashes. Other possible adverse effects of all NSAIDs include headache, confusion

and other CNS symptoms, increased blood pressure, worsening of hypertension, edema, and decreased platelet function. Recent clinical trials have also demonstrated an apparent increased risk of cardiovascular adverse events in patients taking COX-2 inhibitors (46), that is higher rate of thrombotic events (including myocardial infarctions) compared with traditional NSAIDs (tNSAIDs). However, the effect of tNSAIDs on cardiovascular risk is still unclear. Use of tNSAIDs and selective COX-2 inhibitors should be avoided in conditions associated with diminished intravascular volume or edema, such as congestive heart failure, nephritic syndrome, or cirrhosis, and in patients with serum creatinine levels $\geq$ 2.5 mg/dL.

Risk factors for the development of NSAIDs associated gastroduodenal ulcers include advanced age ($\geq$ 75 years), history of ulcer, concomitant use of corticosteroids or anticoagulants, higher dosage of NSAID, use of multiple NSAIDs, or a serious underlying disease. Three recent studies indicate that some tNSAIDs are associated with a higher gastrointestinal risk than others (47-49). The first is a meta-analysis of case-control studies, the second is a cohort study of 130,000 patients over 50 years in the United Kingdom, and the third is a case-control study of 780,000 patients from Italy. These three studies gave clear differences in gastrointestinal risks with the different tNSAIDs, and some compounds are clearly associated with higher risks of upper gastrointestinal bleeding than others. In general, ibuprofen has the lowest risk among tNSAIDs, while diclofenac and naproxen have intermediate risks, and piroxicam and ketorolac carry the greatest risk. It should be noted that the advantage of "low risk" drugs may be lost once their dose is increased. This information is vital when considering the types of tNSAIDs to prescribe for patients.

Several strategies may be used to decrease the risk of tNSAID-associated gastrointestinal events. First, gastrointestinal complications can be avoided by the use of non-traditional NSAID analgesics, when possible (e.g., acetaminophen). Second, use of the lowest effective dose of a tNSAID will decrease the incidence of complications. The analgesic property of tNSAIDs has a ceiling effect (notably, the ceiling dose may be different in acute and chronic pain), meaning that higher doses do not result in enhanced pain control but merely result in more adverse effects. Third,

anti-ulcer co-therapy can be used in high risk patients. Gastroprotective agents, which are effective in decreasing NSAIDs associated gastroduodenal ulceration, include high dose H_2 blockers, proton-pump inhibitors, and oral prostaglandin analogs (1). Finally, the COX-2 inhibitors can be used as an alternative analgesic to decrease the risk of gastrointestinal events. The evidence is summarized in Table 3.

Table 3 Evidence for reduced gastrointestinal risks with gastroprotective agents.

Use of Anti-Ulcer Treatments				
Proton Pump Inhibitor Co-therapy				
Authors (years)	**Method**	**Number of patients**	**Duration of follow up**	**Results**
Yeomans et al. (1998) (50)	double-blind placebo RCTs	541	4-8 weeks	The gastric ulcer recurrence rate at 6 months was 5.2% with omeprazole and 16.3% with ranitidine.
Hawkey et al. (1998) (51)	double-blind placebo RCTs	935	4-8 weeks	The percentage of patients with gastric ulcer recurrence in the OMNIUM study was 13% with omeprazole and 10% with misoprostol.
Use of COX-2 Inhibitors				
Bombardier et al. (2000) (52)	RCTs	8,076	9 months	The efficacy of rofecoxib and naproxen were equivalent. However, the incidence of confirmed upper gastrointestinal adverse events per 100 patient-years in the rofecoxib group was less

Table 3 Evidence for reduced gastrointestinal risks with gastroprotective agents (cont.).

Authors (years)	**Method**	**Number of patients**	**Duration of follow up**	**Results**
				than half that observed in the naproxen group.
Silverstein et al. (2000) (43)	RCTs	8,059	6 months	Among patients receiving celecoxib, the annualized incidence of upper gastrointestinal complications alone and in combination with symptomatic ulcers was half that observed in patients who received tNSAIDs.
Singh et al. (2006) (53)	RCTs	13,274	12 weeks	They were equally effective but celecoxib-treated patients had significantly lower rates of any adverse events, including withdrawal due to abdominal pain and serious upper-gastrointestinal events (producing an 8:1 advantage on safety endpoint.

Evidence from several large scale RCTs and epidemiologic studies of structurally distinct COX-2 inhibitors has indicated that such compounds elevate the risk of myocardial infarction and stroke (Table 4). This evidence led to the subsequent worldwide withdrawal of rofecoxib and valdecoxib. Notably, valdecoxib was also withdrawn because of an unexpectedly high number of serious dermatological side effects such as Stevens-Johnson syndrome. Although, COX-2 inhibitors may increase the risk for cardiovascular events, the risk differs to some degree between individual agents, is dose-related, and varies with the duration of therapy. For example, the APPROVE clinical trial showed that the risk was only apparent after 18 months of continuous intake of rofecoxib (54). Highest risk is found among patients receiving the 50 mg dose than 25 mg dose, and the risk is not detected among those receiving 12.5 mg. In some high risk patients (e.g., following coronary artery bypass graft [CABG]), valdecoxib increased the cardiovascular events by 3-fold even in short-term application of only 10 to 14 days (55). This increased cardiovascular risk from short-term use of valdecoxib was not observed in patients undergoing general or orthopedic surgeries (56). Some studies suggested that celecoxib and lumiracoxib may have a slightly better safety profile than other COX-2 inhibitors. Because the benefits seem to outweigh potential cardiovascular risks, these two drugs had remained on the market (57, 58). Unfortunately, lumiracoxib has recently been withdrawn from the market because of fatal hepatic toxicity. Currently, celecoxib and etoricoxib are the only available COX-2 inhibitors and fulfilled the requirements for drug registration based on internationally accepted guidelines.

Table 4 Evidence for the cardiovascular effects of COX-2 inhibitors.

Authors (years)	**Method**	**Number of patients**	**Duration of follow up**	**Results**
Bombardier et al. (2000) (52)	Multicenter RCTs	8,076	9 months	It was found that there was a 5-fold divergence in the incidence of myocardial infarction (20 vs 4 events). This study was not originally designed to assess the incidence of cardiovascular event.
Bresalier et al. (2005) (54)	multicenter, placebo RCTs	2,586	18 months	This study found that the long-term use of the rofecoxib at 25 mg/day in 2,586 patients with a history of colorectal adenomas was associated with an 1.92-fold increased risk for thrombotic events (myocardial infarction and strokes) first observed after 18 months of therapy. This led to the subsequent worldwide withdrawal of rofecoxib on September 30, 2004.

Table 4 Evidence for the cardiovascular effects of COX-2 inhibitors (cont.).

Authors (years)	Method	Number of patients	Duration of follow up	Results
Graham et al. (2005) (59)	nested case-control	1.3 million patients	2.3 person-years	It was found that rofecoxib at doses above 25 mg/day was associated with a 3-fold higher incidence of myocardial infarction and/or cardiac deaths than were recorded among nonusers or remote users of anti-inflammatory drugs.
Johnsen et al. (2005) (60)	population-based case-control study	123,077		It was found that current and new users of rofecoxib, celecoxib and all classes of non-aspirin NSAIDs had elevated relative risk estimates for myocardial infarction.
Juni et al. (2004) (61)	meta-analysis of 18 RCTs and 11 observational studies	20,742		Overall, patients who received rofecoxib in these studies were at a 2.3-fold increased risk for myocardial infarction compared with those receiving placebo or other tNSAIDs

The evidence for the gastrointestinal and cardiovascular adverse effects of NSAIDs has substantial implications for public health, patient education and

therapeutic decision making by physicians responsible for pain-related conditions. A few organizations have published guidelines on the use of tNSAIDs and COX-2 inhibitors (62, 63). Generally, any recommendations should offer effective pain control along with optimal gastroprotection, together with an assessment of cardiovascular and gastrointestinal risks before initiation of tNSAIDs or COX-2 inhibitors therapy.

The Food and Drug Administration expert advisory committee recommends that (64)

- When COX-2 inhibitors and tNSAIDs are to be used for the management of individual patients, they should be prescribed with the lowest effective dose and for the shortest duration.
- They should not be prescribed for high risk patients, e.g., patients with a history of ischemic heart disease, stroke or congestive heart failure, or in patients who have recently undergone CABG.
- All prescription-strength NSAIDs will now display "black box" label warnings for the potential risk of cardiovascular and gastrointestinal adverse effects.
- Treatment with tNSAIDs alone in patients aged less than 65 years who do not have gastrointestinal risk factors is considered appropriate. Co-therapy with a PPI or treatment with a COX-2 inhibitor was considered unnecessary in these patients.
- The use of a tNSAID alone was considered inappropriate in any patient with a previous gastrointestinal event and in those who concurrently receive aspirin, steroids or warfarin. These patients should receive tNSAID plus a PPI or a COX-2 inhibitor.
- Use of a COX-2 inhibitor with PPI co-therapy is appropriate only in patients at very high risk, such as those with a previous gastrointestinal event who are taking aspirin, and those who are taking aspirin plus steroids or warfarin.

DMARDs: This drugs class can effectively suppress the disease activity and will prevent the progression of cartilage and bone degradation and also cause functional improvement. These drugs have slow onset of action but their potential importance as the treatment of RA at the earliest stage is increasingly recognized. Early suppression of synovial inflammation can arrest or retard the progressive irreversible joint damage. Nowadays, these drugs are started along with NSAIDS if the

arthritis persists for more than three months and continued at the lowest dose for 2 to 5 years or even longer after disease remission. Periodic assessment of the disease activity and clinical examination and investigations to monitor the toxicity are highly essential when the patient is put on DMARDs. In 2008, ARA recommended two types of DMARDs; non-biologic and biologic DMARDs. The biologic DMARDs is recommended only after failure of non-biologic DMARDs (65). The DMARDs commonly used in RA are summarized in Table 5.

Table 5 Dosage and adverse effects of DMARDs used in the treatment of RA.

Drug	Dosage	Adverse effects
Hydroxychloroquine	Initially, 400 mg po once/day (eg, with breakfast or dinner) for 4–12 wk, then may reduce to 200 mg once/day If improvement occurs, 200–400 mg once/day as long as effective	Usually mild dermatitis Myopathy Generally reversible corneal opacity Occasionally, irreversible retinal degeneration
Sulfasalazine	500 mg po in the evening, increased to 500 mg in the morning and 1,000 mg in the evening, then increased to 1,000–1,500 mg bid	Bone marrow suppression Gastric symptoms Neutropenia Hemolysis Hepatitis
Methotrexate	Single oral dose once/wk, starting at 7.5 mg and gradually increased as needed to a maximum of 25 mg Doses > 20 mg/wk best given subcutaneous to ensure bioavailability	Liver fibrosis (dose-related, often reversible) Nausea Possibly bone marrow suppression Stomatitis Rarely, pneumonitis (potentially fatal)

Table 5 Dosage and adverse effects of DMARDs used in the treatment of RA (cont.).

Drug	Dosage	Adverse effects
Leflunomide	20 mg once/day or, if adverse effects occur, reduced to 10 mg once/day	Skin reactions Hepatic dysfunction
Azathioprine	1 mg/kg (50–100 mg) po once/day or bid, increased by 0.5 mg/kg/day after 6–8 wk then q 4 wk to a maximum of 2.5 mg/kg/day	Liver toxicity Bone marrow suppression Possibly increased risk of cancer
Cyclophosphamide	2–3 mg/kg po once/day or IV pulse therapy (may not be as effective): 0.75 g/m^2 once/mo (increased to 1 g/m^2 for 6 month once/month if WBC > 3,000/µL), given over 30–60 min with oral or IV fluids and with mesna	With cyclosporine, impaired renal function
Cyclosporine	50 mg po bid not to exceed 1.75 mg/kg po bid	Renal insufficiency Anemia Hypertension
Gold injection	Start with a 10 mg test dose , followed by a loading dose of 50 mg intramuscularly every week until a cumulative dose of 1,000 mg is reached; the maintenance dose is 25-50 mg intramuscularly every 2-4 weeks	Myelosupression Proteinuria

Table 5 Dosage and adverse effects of DMARDs used in the treatment of RA (cont.).

Drug	Dosage	Adverse effects
Adalimumab	40 mg subcutaneous once every 1–2 wk	Potential risk of infection (particularly TB) or cancer
Etanercept	25 mg subcutaneous twice/wk or 50 mg sc once/wk	Lymphoma Liver toxicity Bone marrow
Infliximab	3-mg/kg IV infusion in saline at baseline, at 2 wk, and at 6 wk with subsequent injections q 8 wk (dosage may be increased to 10 mg/kg)	Abnormal liver function tests Antinuclear antibodies with or without SLE Demyelinating neurologic disorders

Donahue and colleagues (66) systemically reviewed 101 studies to compare effectiveness and harms of DMARDs for RA. Head-to-head trials (n=23), mostly examining synthetic DMARDs, showed no clinically important differences in efficacy among synthetic DMARDs (limited to methotrexate, leflunomide, and sulfasalazine) or among anti–tumor necrosis factor (TNF) drugs (adalimumab, eternacept, and infliximab). Monotherapy with anti–TNF drugs resulted in better radiographic outcomes than did methotrexate but no important differences in clinical outcomes (that is 20%, 50%, and 70% improvement according to American College of Rheumatology response criteria).Various combinations of biological DMARDs plus methotrexate improved clinical response rates and functional outcomes more than monotherapy with either methotrexate or biological DMARDs. In patients whose monotherapy failed, combination therapy with synthetic DMARDs improved response rates. Numbers and types of short-term adverse events were similar for biological and synthetic DMARDs. The evidence was insufficient to draw conclusions about

differences for rare but serious adverse events for biological DMARDs. Table 6 summarized the results of comparative studies of different DMARDs.

Table 6 Summary of comparative findings between different DMARDs on efficacy and harms of RA.

Key Comparisons	Key Comparisons Efficacy (Strength of Evidence)	Harms (Strength of Evidence)
Monotherapy vs. monotherapy Synthetic DMARDs		
Leflunomide vs. methotrexate	- Similar ACR 20 or radiographic responses (moderate) - Greater improvement in functional status (HAQ-DI) and health-related quality of life (SF-36 physical component) for lefunomide (moderate) - Similar work productivity outcomes (moderate)	No obvious major differences in adverse events and discontinuation rates (moderate)
Leflunomide vs. sulfasalazine	- Higher ACR 20 and ACR 50 response rates and greater improvement in functional capacity for leflunomide (low) - Similar radiographic responses (low)	No obvious major differences in adverse events and discontinuation rates (moderate)
Sulfasalazine vs. methotrexate	Similar ACR 20 response rates, disease activity scores, functional capacity, and radiographic responses (moderate)	No obvious major differences in adverse events; more patients receiving methotrexate than sulfasalazine (moderate)

Table 6 Summary of comparative findings between different DMARDs on efficacy and harms of RA (cont.).

Key Comparisons	Key Comparisons Efficacy (Strength of Evidence)	Harms (Strength of Evidence)
Biological DMARDs Biological DMARDs vs. biological DMARDs		
Anti-TNF drugs (adalimumab, etanercept, infliximab) vs. anti-TNF drugs	Similar ACR 20 and ACR 50 response rates among anti-TNF drugs (moderate)	Insufficient evidence (low)
Biological DMARDs vs. biological DMARDs	3 indirect comparisons based on fair- and good-quality meta-analyses consistently showed anakinra to have lower ACR 20 and ACR 50 response rates than anti-TNF drugs as a class (moderate)	Risk for injection site reactions higher for anakinra than for adalimumab and etanercept (moderate)
Biological DMARDs vs. synthetic DMARDs		
Anti-TNF drugs vs. methotrexate	- In patients with early RA, similar clinical response, functional capacity, and quality of life between adalimumab or etanercept and methotrexate; in patients receiving biological DMARDs, better radiographic outcomes than synthetic DMARDs (moderate) - In patients whose initial RA treatment failed, greater functional independence and remission for anti-TNF drugs as a class than	- No obvious major differences in adverse events in efficacy studies (low) - Insufficient evidence on differences in the risk for rare but severe adverse events (low)

Table 6 Summary of comparative findings between different DMARDs on efficacy and harms of RA (cont.).

Key Comparisons	Key Comparisons Efficacy (Strength of Evidence)	Harms (Strength of Evidence)
	synthetic DMARDs as a class (moderate)	
Combination therapy vs. monotherapy Synthetic DMARDs vs. synthetic DMARDs		
Sulfasalazine plus methotrexate vs. monotherapy	- In patients with early RA, similar ACR 20 response rates or radiographic changes (moderate) - In all patients, similar functional capacity (moderate) - In patients with early RA, significantly better disease activity scores with combination therapy (low)	No obvious major differences in withdrawal rates attributable to adverse events (moderate)
1, 2, or 3 synthetic DMARDs (methotrexate, sulfasalazine, hydroxychloroquine) plus prednisone vs. 1 synthetic DMARD	- In patients receiving 1, 2, or 3 synthetic DMARDs plus prednisone, improved ACR 50 response rates, disease activity scores, and less radiographicprogression (moderate) - In patients with early RA, significantly lower radiographic progression and fewer eroded joints (low) - Better outcomes with the combination strategies for functional capacity (low for each	No obvious major differences in discontinuation rates (moderate)

Table 6 Summary of comparative findings between different DMARDs on efficacy and harms of RA (cont.).

Key Comparisons	Key Comparisons Efficacy (Strength of Evidence)	Harms (Strength of Evidence)
	individual comparison; moderate for combination therapy vs. monotherapy)	
Biological DMARD combinations		
Biological DMARDs vs. biological DMARDs	No additional treatment effects from combination of etanercept plus anakinra compared with etanercept monotherapy (low)	Substantially higher rates of serious adverse events from combination of 2 biological DMARDs than from monotherapy (moderate)
Biological DMARDs plus methotrexate vs. biological DMARDs	- Better clinical response rates, functional capacity, and quality of life from combination therapy with biological DMARDs plus methotrexate than from monotherapy with biological DMARDs (moderate) - In methotrexate-naive patients with early aggressive RA, better ACR 50 response, greater clinical remission, and less radiographic progression in the combination therapy group (low)	- No obvious, major differences in adverse events in efficacy studies (low) - Insufficient evidence on differences in the risk for rare but severe adverse events (low)

Table 6 Summary of comparative findings between different DMARDs on efficacy and harms of RA (cont.).

Key Comparisons	**Key Comparisons Efficacy (Strength of Evidence)**	**Harms (Strength of Evidence)**
Biological DMARDs plus synthetic DMARD other than methotrexate vs. biological DMARDs	Similar clinical response rates, functional capacity,and quality of life between etanercept plus sulfasalazine and etanercept monotherapy (low)	- No obvious, major differences in adverse events in efficacy studies (low) - Insufficient evidence on differences in the risk for rare but severe adverse events (low)
Biological DMARD plus methotrexate vs. methotrexate	Better clinical response rates, functional capacity, and quality of life from combination therapy of biological DMARDs and methotrexate than from methotrexate monotherapy (moderate)	- No obvious, major differences in adverse events in efficacy studies (low) - Insufficient evidence to make conclusions ondifferences in the risk for rare but severe adverse events (low)

Table 6 Summary of comparative findings between different DMARDs on efficacy and harms of RA (cont.).

Key Comparisons	Key Comparisons Efficacy (Strength of Evidence)	Harms (Strength of Evidence)
Combination therapy vs. combination therapy or other treatment strategy		
Sulfasalazine plus methotrexate plus hydroxychloroquine vs. 2 drugs	- In patients previously receiving monotherapy, higher ACR 20 and ACR 50 response rates for triple therapy than for 2-drug combinations (moderate) - In patients with no previous use of study drugs, higher ACR 20 and ACR 50 response rates in the triple combination therapy group than in the methotrexate plus sulfasalazine group or methotrexate plus hydroxychloroquine group (low)	No obvious, major differences in withdrawal rates attributable to adverse events (moderate)
Sequential monotherapy starting with methotrexate vs. step-up combination therapy vs. combination with tapered high-dose prednisone vs. combination with infliximab	Less radiographic progression, lower disease activity scores, and better functional ability from initial combination therapy with methotrexate, sulfasalazine, and tapered high-dose prednisone or initial combination therapy with infliximab plus methotrexate than from sequential DMARD monotherapy or step-up combination therapy (low)	No obvious, major differences in serious adverse events between groups (low)

Corticosteroids: Corticosteroids are the most controversial drugs used in the treatment of RA. These drugs are highly potent anti-inflammatory agents with a wide range of actions. Steroids inhibit the recruitment of leukocytes at inflammatory sites by blocking the adhesion of these cells to endothelial cell wall. They also inhibit cellular activation and secretion of inflammatory mediators. Finally they block the tissue effects of many pro-inflammatory cytokines. In spite of all these actions steroids lost their popularity due to the plethora of side effects, but are very useful drugs in chronic inflammatory arthritis like RA if judiciously used. The major indications of steroid the RA are given below.

1. Bridge therapy

Steroids are well known to rapidly suppress synovitis, and the recent data have shown their disease modifying actions as well as the ability to reduce radiological progression in the initial phase of disease. Thus steroids at lower doses can be used along with DMARDs in the first 2-3 months of the treatment. Once the DMARDs begin its action, steroid should be taped off and stopped. The usual dose is 5 - 7.5 mg prednisolone per day or 80 – 120 mg methyl prednisolone once in every 2-3 weeks. Long term use of even small dose steroids in RA should be strongly discouraged due to the side effects especially osteoporosis.

2. Extra-articular disease

In cases of severe life threatening visceral organ or sight-threatening eye involvement, such as rheumatoid vasculitis, scleritis, intestitial lung disease, neuropathy or other extra-articular disease, high dose systemic steroids are strongly recommended. Prednisolone 40-60 mg/day orally or intravenous methyl prednisolone 1gm/day for 3 days followed by oral prednisolone is recommended in these cases which can be tapered off more slowly.

3. Pregnancy

In pregnancy almost all NSAIDS and many of the DMARDS (except sulfasalazine and hydroxychloroquine which are relatively safe) are contra-indicated, low dose prednisolone at a dose of 5-15 mg/day can be tried as prednisolone at this dose will not cross the placenta.

4. Intraarticular / intralesional steroids

Local steroid injections are useful in relieving synovitis if one or two joints are out of proportionately inflammed compared to generalized disease activity. Intralesional steroids are also useful in tenosynovitis, bursitis and carpal tunnel syndrome.

5. Refractory RA

Low dose oral steroids may be the only choice when arthritis is refractory to all other mode of therapy (NSAIDs, combination of DMARDS and biological agents). But as far as possible oral steroids should be taped off once the disease activity has been controlled.

Table 7 summarized dosage and adverse effects of corticosteroids use in the treatment of RA.

Table 7 Dosage and adverse effects of corticosteroids use in the treatment of RA.

Drug	**Dosage**	**Adverse effects**
Methyl prednisolone acetate	Depends on the joint	With long-term use: inflammation and rarely infection at injection site
Triamcinolone acetonide	Depends on the joint	
Triamcinolone hexacetonide	10–40 mg, depending on the joint	
Prednisone	Not to exceed 7.5 mg p.o. once/day (except in patients with severe systemic manifestations)	With long-term use: - Weight gain - Diabetes - Hypertension - Osteoporosis

A meta-analysis of safety of medium to long-term corticosteroid therapy in RA showed that medium- to long-term glucocorticoid therapy in RA is associated with limited toxicity compared to placebo (67). Six RCTs with total of 689 patients met the inclusion criteria. However, the longest duration of the study was only 2.5 year with prednisolone dosage ranged from 5-10 mg/day. All studies allowed concomitant use of

NSAIDs and DMARDs. Toxicity of glucocorticoid therapy based on number of patients withdrawn from the study was borderline (OR=1.09; 95% CI 0.52, 2.25). Number of AEs per patient-year (OR=1.19; 95% CI 0.91, 1.57) and SAEs (OR =1.06; 95% CI 0.67, 1.67) were similar. Efficacy/toxicity ratio was good for glucocorticoid therapy (number needed to harm/number needed to treat = 0.25). Characteristics of RCTs and results were shown in Table 8 and Table 9, respectively.

Table 8 Characteristics of RCTs included in the meta-analysis.

Authors	**Trial duration (years)**	**Numbers of patient**	**Treatment**	**Prednisolone dose, mg/day**
Chamberlain and Keenan	3.5	30	Pred + IM gold vs placebo + IM gold	5
Kirwan et al.	2	128	DMARD + Pred vs DMARD + placebo	7.5
Van Everdingen et al.	2	81	Pred + SSZa vs placebo + SSZa	10
Capell et al.	2	167	SSZ + Pred vs SSZ + placebo	7
Choy et al.	2	91	IM depomedrone + DMARD vs placebo + DMARD	5
Wassenberg et al.	2	192	DMARD + Pred vs DMARD + placebo	5

Table 9 Meta-analysis of overall adverse event (AEs) and serious adverse events (SAEs) based on patient-year.

Authors	OR of overall AEs (95% Cl)	OR of overall SAEs (95% Cl)
Chamberlain and Keenan	2.43 (0.64, 9.18)	1.00 (0.08, 12.56)
Kirwan et al.	0.65 (0.15, 2.78)	Not estimated
van Everdingen et al.	0.56 (0.26, 1.22)	0.97 (0.36, 2.57)
Capell et al.	1.69 (0.60, 4.75)	2.00 (0.18, 22.49)
Choy et al.	1.41 (0.78, 2.52)	1.86 (0.32, 10.72)
Wassenberg et al.	1.25 (0.84, 1.87)	0.99 (0.56, 1.75)

3. Role of pharmacist in rheumatology

RA is inadequately managed by one specialist, thus a multidisciplinary care team is required. Multidisciplinary team care aimed to improve disease activity, functional and vocational status, and psychosocial health, with the ultimate goal of assisting patients to achieve and maintain personal independence. Theodora and colleagues (19) reviewed 35 clinical trials of multidisciplinary team care. In 12 trials, 6 inpatient and 6 outpatient multidisciplinary programs were compared with regular outpatient care. It found that in most of the trials comparing short-term inpatient multidisciplinary team care program with regular outpatient care, favorable effects on disease activity were seen. However, the benefit of prolonged outpatient multidisciplinary team care is scanty. Results of trials comparing inpatient with outpatient team care remain inconclusive. When long-term effectiveness of care was established, it appear to underscore that clinical nurse specialist interventions is an effective innovation in the care for patients with RA (20).

Before the early 1990s, there were relatively few agents available for treatment of RA as well as professional education for pharmacists and pharmacy students with regard to the pathogenesis and treatment of RA and other musculoskeletal conditions. Combination of pharmacologic agents tends to be standard treatment of RA at the present. Because of their potential toxicity, careful monitoring is required. Although, specialist rheumatology nurse have become well

established in many hospitals and have enhanced patient satisfaction. Only a small number of nurse practitioners in rheumatology departments provide a link between hospital and community and co-ordinate an effective extended team. As a result, a practice pharmacist could readily fill this gap, by providing the knowledge of drugs used in RA, together with the adverse effects, drug-drug interactions and drug-disease interactions. Pharmacists are also skilled in pain management and are able to respond to drug information requests. Knowledge of interface issues, patient counseling and clinical audit are also useful skills provided by pharmacists. Copeland (68) and Wilson (69) suggested scope for role of specialist pharmacist in rheumatology. These were summarized as the followings:

1. Good communication with other members of the multidisciplinary team: an integral part of rheumatology practice is the identification of problems which may benefit from referral to other members of the team.

2. Patient identification: it was important that patients are reviewed the information relating to the purpose and nature of the clinic and are given the opportunity to select for the standard method of care in the practice. These detail should include

- Date of diagnosis of RA
- Full drug history, including dose and duration of current and past treatments, response to the treatment and use of alternative/homoeopathic remedies
- Compliance/frequency of prescription requests (available from computerized repeat prescription records)
- Ability to administer medicines and any required compliance aids
- Allergies and/or intolerance to drugs and adverse drug reactions
- Pain control
- Investigations and results
- Concurrent disease history

- Activities of daily living
- How the patient was previously reviewed (i.e., by practice nurse or hospital outpatient) and frequency of review
- Information obtained from the patient, including knowledge and perception of therapy

3. Monitoring: during each clinic appointment the pharmacists should review the following information of each patient:
   - Previous blood results
   - Changes of drug therapy
   - Side effects of therapy
   - Compliance and ability to administer medicines
   - Pain control and analgesic use
   - Changes in diet and exercise
   - Use of over-the-counter medicines and alternative remedies
   - Activities of daily living
4. Follow up work and therapeutic meetings

Part II: Adverse drug events (ADEs)

1. Introduction

Drug related problems (DRPs) are undesirable patient's experience involving drug therapy and that actually or potentially interferes with desired patient outcome. There are 8 major categories of DRPs relating to the patients as described below (70):

1. Untreated indications
2. The wrong drug is being taken
3. Subtherapeutic dosage
4. Overdosage
5. Adverse drug reactions (ADRs)
6. Drug interactions
7. Failure to receive the prescribed drugs

8. No valid medical indication

In 1998, pharmacists in the US increasingly took responsibility for patient's drug-related needs. It included any concern, expectation or lack of understanding identified by the patient/ practitioner and become DTPs. It is necessary to translate the patient's drug-related needs into DTPs. The DTP term has similar meaning to that of drug-related problems (DRPs) (17). They categorized into 7 items covering all pharmacological class, area of practice specialty, medical service, and level of pharmacist evaluation and training. They are not specific to a unique patient group based on age, state of disease, or healthcare plan. These are (71):

1. Need for additional therapy
2. Unnecessary drug therapy
3. Wrong drug
4. Dosage too low
5. Adverse drug reactions (ADRs)
6. Dosage too high
7. Noncompliance

Adverse drug reaction (ADR) which is one category of DTPs are noxious and unintended response to a drug which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for the modification of physiologic function (72). In summary, an ADR is harm directly caused by the drug at normal doses during normal use. General terms used in describing ADR and related terms are shown in Table 10.

Table 10 Definition of adverse drug event (ADE) and related terms.

Terms	Definition
To describe harm already occurred to the patients.	
Adverse event (AE)	Harm occurred in a patient administered a drug but not necessarily caused by a drug (73) .
Adverse drug event (ADE)	Harm caused by a drug or the inappropriate use of a drug (73).

Table 10 Definition of adverse drug event (ADE) and related terms (cont.).

Terms	Definition
Adverse drug reaction (ADR)	Any response to a drug which is noxious and unintended, and which occurs at doses normally used in humans for prophylaxis, diagnosis or therapy of disease, or for modification of physiological function. Whether or not considered drug related, including the following drug withdrawal, drug-abuse, accidental poisoning and drug overdose complications (72).
Preventable ADE	ADE is considered as preventable according to Schumock and Thornton's set of questions (74). Answering "yes" to one or more of the following seven questions suggests that ADE is considered as preventable. 1. Was the drug involved in the ADE not considered appropriate for the patient's clinical condition? 2. Was the dose, route, and frequency of administration not appropriate for the patient's age, weight and disease state? 3. Was required therapeutics drug monitoring or other necessary laboratory test not performed? 4. Was there a history of allergy or previous reactions to the drug? 5. Was a drug interaction involved in the reaction? 6. Was a toxic serum drug level documented? 7. Was a poor compliance involved in the reaction?
To describe harm which may occur	
Medication error	Inappropriate use of a drug that may or may not result in harm (73).
To describe possible harm not yet occur to the patients.	
Potential ADE	Circumstances that could result in harm by continuation use of a drug but did not yet harm the patient (73).

According to ADE and ADR definition, it clearly shows that ADE is broader than ADR. ADEs include ADRs, drug withdrawal adverse effects, therapeutic failures, and intentional overdoses. In addition, some medication errors result in ADR and ADE.

Figure 1 illustrates the relationship between medication error, ADR and ADE but the sizes of each parts of the diagram are imprecise. Section A in the Figure is medication errors which lead to no injuries. In section C, these medication errors cause ADRs whereas medication errors in section B cause ADEs. However, there are some ADRs which are not caused by medication error. i.e., in section D and thus some ADRs are the subset of ADEs. Injuries in section E are classified as ADEs which are not the results of medication errors. Thus, occurrence of some ADRs and ADEs, i.e., in section B and C are preventable according to the preventable ADEs criteria.

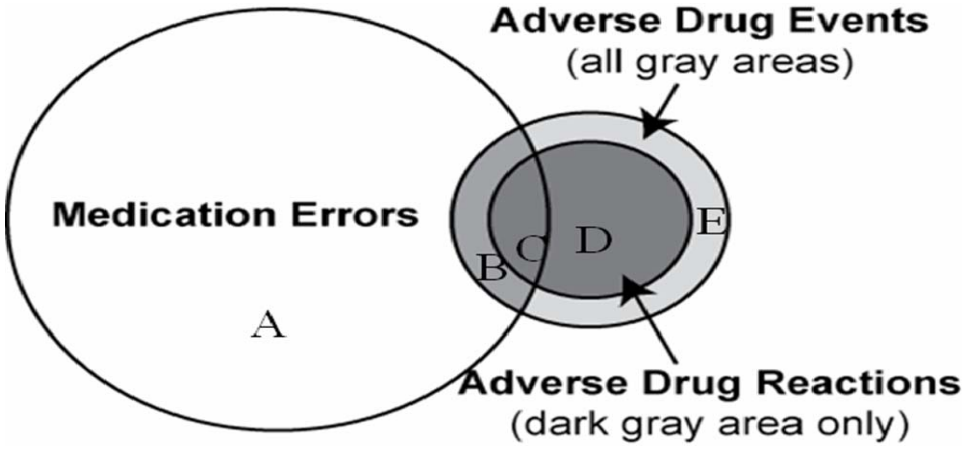

Figure 1 Relationship between medication error, ADR and ADE (75).

The severity of ADEs was adapted by Hartwig's definition (76) as shown in Table 11. These ADEs severity levels were categorized as Level 1, Level 2-4, Level 5-6 and Level 7 according to mild, moderate, severe and lethal, respectively.

Table 11 ADEs severity level adapted from Hartwig's definition (76).

Level	Descriptions
1	An ADE occurred but requires no change in treatment with the suspected drug.
2	The ADE required that treatment with the suspected drug be withheld, discontinued or otherwise changed. No antidote or other treatment is required, and there is no increase in length of stay.
2a	The ADE required that treatment with the suspected drug be changed dose.
2b	The ADE required that treatment with the suspected drug be changed to other drugs.
2c	The ADE required that treatment with the suspected drug be held, or discontinued.
3	The ADE required that treatment with the suspected drug be held, discontinued, or otherwise changed and/or an antidote or other treatment required. No caused to admission hospital.
4	The ADE was the reason for admission to hospital or emergency visit.
5	Any level 4 ADE which requires intensive medical care.
6	The adverse reaction caused permanent harm to the patient.
7	The adverse reaction either directly or indirectly led to the death of the patient.

Medication errors (MEs) are a frequent cause of ADEs. Published type of MEs related to ambulatory care preventable ADEs are as the followings (77):

- Omission
    - Inadequate drug monitoring
    - Inadequate patients' education
    - Ignoring clinical/ laboratory result
    - No prescribing of indicated drug

- Commission
    - Patient non-adherence
    - Prescribing inappropriate drug
    - Inappropriate dose/ frequency
    - Administration error

The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) has proposed a medication error index that serves to categorize errors based on the severity or outcome of the error. This index is divided into 4 main categories and 9 subcategories as shown in Table 12.

Table 12 Medication error levels based on the severity or outcome of the error (78).

Level/ Category	**Descriptions**
No error	
A	Circumstances or events that have the capacity to cause error.
Error, but no harm	
B	An error occurred but the error did not reach the patient.
C	An error occurred that reached the patient, but did not cause patient's harm. - Medication reaches the patient and is administered. - Medication reaches the patient but not administered.
D	An error occurred that reached the patient and required monitoring to confirm that it resulted in no harm to the patient and/or required intervention to preclude harm
Error and harm	
E	An error occurred that may have contributed to or resulted in temporary harm to the patient and required intervention.
F	An error occurred that may have contributed to or resulted in temporary harm to the patient and required initial or prolonged hospitalization.
G	An error occurred that may have contributed to or resulted in permanent patient's harm.

Table 12 Medication error levels based on the severity or outcome of the error (cont.).

Level/ Category	Descriptions
H	An error occurred that required intervention necessary to sustain life.
I	An error occurred that may have contributed to or resulted in the patient's death.

2. Role of clinical pharmacist in preventing ADEs

It is estimated that over 770,000 people are injured or die in hospitals from adverse drug events (ADEs) annually (79-81). Few studies have revealed incidence rates of ADEs ranging from 2 to 7 per 100 admissions (79, 82-84). A precise national estimate is difficult to calculate due to the variety of criteria and definitions used by each study. One study of preventable inpatient ADEs in adults demonstrated that 56% occurred at the step of ordering, 34% at administration, 6% at transcribing, and 4% at dispensing (83). In this study, the drug class most commonly associated with preventable ADEs were analgesics, sedatives and antibiotics. Even fewer studies have been conducted in the outpatient setting. One recent cross-sectional chart review and patient care survey found an ADE rate of 3% in adult primary care outpatients (85).

Clinical pharmacists may participate in all stages of the medication use process, including drug ordering, transcribing, dispensing, administering, and monitoring. The specific activities of clinical pharmacists vary substantially in the studies reviewed in this chapter. In the hospital setting, one study evaluated the role of a senior pharmacist fully participating in intensive care unit rounds and available throughout the day in person or by page for questions (86). Another study evaluated a ward pharmacy service to examine order sheets for new therapies and carry out checks that were formerly performed in the pharmacy department (87).

Pharmacists may also play a role at the time of discharge. One study reported the impact of clinical pharmacists' consultation for geriatric patients at the time of discharge (88), with pharmacists serving as consultants to physicians and reinforcing patients' knowledge of their medication regimen. The roles of clinical

pharmacists are similarly diverse in studies of ambulatory settings. Here they include the provision of consultative services (89-91), patient education (89-91), therapeutic drug monitoring (92), and even follow-up telephone calls to the patients (89-92). Many literatures have documented multiple roles of clinical pharmacists in variety of healthcare settings (92-99). Most of these studies focused on measures of impact not directly relevant to this Compendium—e.g., economic benefits (95, 99), patient compliance (97), and drug monitoring (92, 94). More recently, systems-based analyses of medication errors and ADEs have drawn attention to the impact of clinical pharmacists on the quality and safety of medication use (75, 100-102).

Table 13 showed evidence supporting the premise that direct participations of pharmacists' in clinical care reduces medication errors and ADEs in hospitalized and ambulatory patients.

Table 13 Studies of clinical pharmacists' impact on ADEs and medication error.

Study (year)	Study Design	Study Outcomes	Results
Leach, et al (1981) (87)	retrospective study before-after analysis 315 patients at Queen Elizabeth Hospital in Birmingham, England	various types of medication errors	40-50% overall reduction in medication errors. All of the 8 targeted error types decreased (results achieved statistical significance in 5 error types)
Ried, et al (1989) (92)	meta-analysis Pooled patient population not reported, but review of articles indicate the predominance of hospitalized patients (mostly adult)	measures of peak, trough and toxic serum drug concentrations for a variety of medications	More likely to have therapeutic peak and trough and less likely to have toxic peak and trough, but modest effect sizes (results achieved statistical significance

Table 13 Studies of clinical pharmacists' impact on ADEs and medication error (cont.).

Study (year)	Study Design	Study Outcomes	Results
			in only 2 measures)
Lipton, et al (1992) (88)	retrospective study before-after analysis 236 geriatric patients discharged from the hospital on three or more medications	prescribing problems	Less likely to have a "prescribing problem" (p=0.05)
Leape, et al (1999) (86)	prospective study before-after analysis with concurrent control Medical and cardiac intensive care unit patients at Massachusetts General Hospital, a tertiary care hospital in Boston	ADEs	66% decrease in the rate of preventable ADEs (p<0.001)
Gattis, et al (1999) (89)	RCT 181 patients left ventricular dysfunction heart failure followed in a general cardiology clinic	mortality and other clinical outcomes related to heart failure	16 versus 4 deaths or other heart failure events (p<0.005)

Table 13 Studies of clinical pharmacists' impact on ADEs and medication error (cont.).

Study (year)	Study Design	Study Outcomes	Results
Beney (2000) (91)	Systematic review Systematic review of the roles and impacts of pharmacists in ambulatory settings; reviewed studies have included 16,000 outpatients and 40 pharmacists	variety of patient outcomes, surrogate outcomes, impacts on physician prescribing practices and measures of resource use	Improvement in outcomes for patients with hypertension, hypercholesterolemia, chronic heart failure, and diabetes
Kucukarslan, et al (2003) (103)	Single-blind, standard care control study 165 patients in general medicine unit To compare patient receiving care team including pharmacist with those receiving standard care	pADEs	78% reduction from 26.5 per 1000 hospital days to 5.7 per 1000 hospital days
Gurwitz, et al (2005) (104)	Cohort study 9 months study to assess incidence and risk factor of ADE	Rate of pADEs	Rate of preventable ADEs were 4.1 preventable events per 100 resident-months and most often at the stage of ordering and monitoring

Table 13 Studies of clinical pharmacists' impact on ADEs and medication error (cont.).

Study (year)	Study Design	Study Outcomes	Results
Schnipper, et al (2006) (105)	RCT 178 patients in a large teaching hospital; the study group received pharmacist counseling at discharge.	Rate of pADEs	1% was detected in the study group versus 11% in control group after 30 day discharged.
Kane-Gill, et al (2006) (106)	Retrospective analysis 9 months study in 647 bed academic medical center with over 120 ICU beds	Rates of pADEs associated with high-cost and high-use drugs in ICU	The frequency, severity, and preventability of ADEs in the ICU were not associated with a drug's cost or frequency of use.
Murray, et al (2009) (107)	RCTs 800 outpatients with hypertension stratified into complicated and uncomplicated were followed by 12 months	Risk ratio of ADEs, pADEs, potADEs, and MEs	Risk of any events was 34% lower in the intervention group (risk ratio = 0.66), including lower risk of ADEs, pADEs, potADEs and ME were 0.65, 0.52, 0.70 and 0.63, respectively.

CHAPTER III
MATERIALS AND METHODS

Materials

The materials used in this study included

1. Patient's profile form (Appendix A): the profile comprised of 3 parts/forms, i.e.
   - Form I: Demographic data
   - Form II: Medication profile data
   - Form III: Laboratory data
2. Informed consent (Appendix B)
   - 2.1 Patient/participant information sheet
   - 2.2 Patient informed consent form
   - 2.3 Caregiver informed consent form
3. Check list of ADE form (Appendix C)
4. Roussel Uclaf Causality Assessment Method (RUCAM) algorithm (Appendix D)
5. Physician's opinion form (Appendix E)
6. Pharmacist's note (Appendix F)
7. Adverse drug events record form (Appendix G)
8. The list of system-organ classes according to WHO Collaborating Centre for international drug monitoring form (Appendix H)
9. Multi-compartment plastic boxes which contain the oral dosage forms of NSAIDs, DMARDs, and corticosteroids

Methods

1. Definition of terms

The terms that used throughout the study were defined as shown in Table 10 (page 32), including adverse drug event (ADE), adverse drug reaction (ADR), preventable ADE (pADE) and potential ADE (potADE)

Incidence, percentage and rate of ADEs or pADEs were calculated as the followings:

Incidence of ADEs

$$= \frac{\text{Number of patients experiencing ADE during the study period}}{\text{Number of all patients}} \times 100$$

$$\textbf{The percentage of pADEs} = \frac{\text{Number of pADEs}}{\text{Number of all ADEs}} \times 100$$

$$\textbf{pADE rate per 100 patients} = \frac{\text{Number of pADEs}}{\text{Number of all patients}} \times 100$$

Physicians: Rheumatologists and fellows working at Allergy Immunology and Rheumatology (AIR) unit, Department of Medicine, Ramathibodi Hospital between the study period. They provided patient care at four clinics per week (see Table 14).

Concurrent disease: the disease that occurs or exists with RA at the same time of previous visit.

2. Study design

This study was designed as a prospective controlled study to evaluate the benefit and outcome of research pharmacist's participation in RA outpatients. Patients were recruited and assigned into intervention group or control group. Intervention group received the education and counseling from research pharmacist, including detection and management of ADE, detection and early management to prevent potADE, and checking prescribing error, while control group received only standard detection and management of ADE. This process was conducted for at least 2 visits at the clinic. The overall of the study process was summarized in Figure 2.

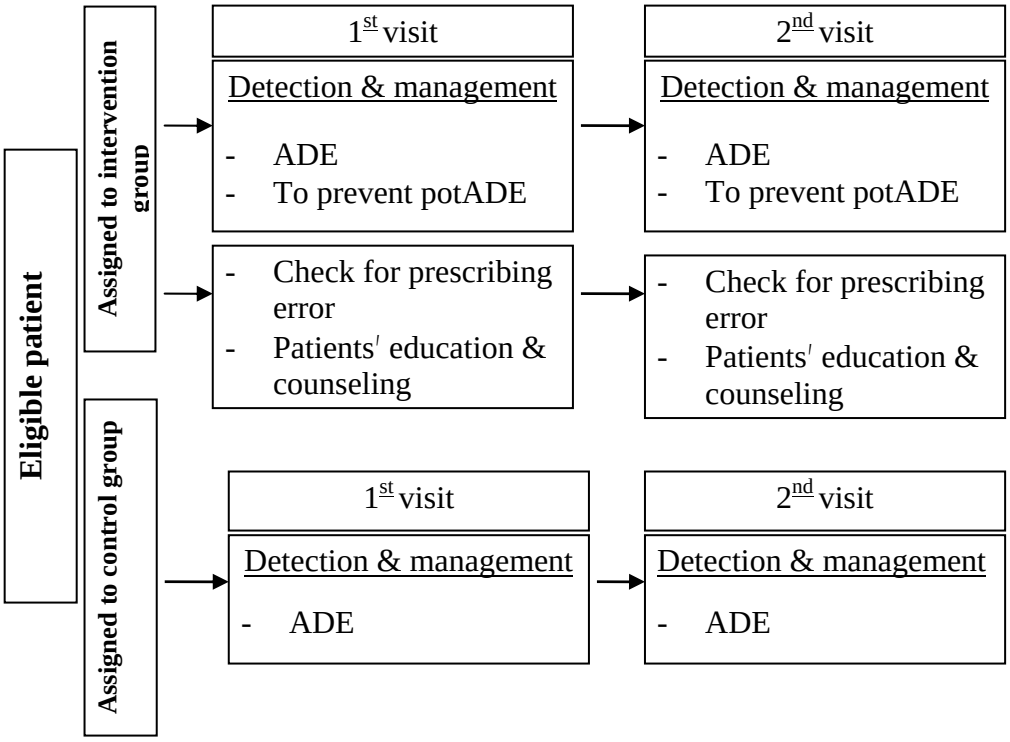

Figure 2 Summary of the study process.

3. Ethical approval

The study was reviewed and approved by Committee on Human Rights Related to Researches Involving Human Subjects, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, based on the Declaration of Helsinki, protocol number 02-50-23.

4. Study population

RA adult patients at outpatient clinic of AIR unit, Department of Medicine, Ramathibodi Hospital were included.

Table 14 Day and time of outpatient service of AIR unit.

Clinic	Day	Time
General medicine	Monday	9.00-12.00 a.m.
Allergy & arthritis	Tuesday	1.00 - 4.00 p.m.
General medicine	Wednesday	9.00-12.00 a.m.
Arthritis	Thursday	1.00 - 4.00 p.m.

RA patients whom were followed up at these clinics during April 30, 2007 to August 30, 2007 were screened by two research pharmacists to detect ADEs and potADEs between zero visit and the 1st visit, then one research pharmacist was responsible for an intervention group, while another was responsible for control group. Patients were included in the study if they met the following criteria.

4.1 Inclusion criteria

1. Patients who had been diagnosed as RA by rheumatologists.
2. Patients were 15 years old or older.
3. Patients and/or their caregivers agreed to participate in the study.
4. Patients were able to take care of themselves or had caregivers to participate.
5. Patients received at least one item of medication.
6. Patients were able to join throughout the study, including at least two visits during the study period.

4.2 Exclusion criteria

1. Patients with poor compliance, i.e., they stopped their medications by themselves or not taken any medications during the zero visit and the 1st visit.
2. Patients had hearing loss or abnormal memory and had no caregivers.
3. Patients were not able to read or understand Thai language.
4. Patients had joined other research in which the detail of drug therapy was not disclosed.

4.3 Dropout condition

Patients were not able to meet the research pharmacists after the zero visit for any reasons until the end of study period, such as patients were lost to the follow up at 1st visit for longer than the study period or they were admitted to inpatient ward for longer than the time scheduled for the study.

4.4 Sample size

The sample size was estimated using pADE rate per 100 patients (14.5 events per 100 patients) as reported from preliminary ADE detection. The expected reduction of the percentage of pADE by 80% (i.e. 2.9 events per 100 patients) was used to calculate in the following formula (108).

$$2N = \frac{2\left[Z_{\alpha} (2\,\text{Þ}(1-\text{Þ})^{1/2} + Z_{\beta}\{p_c(1-p_c) + p_I(1-p_I)\}^{1/2} \right]^2}{(p_c-p_I)^2}$$

2N = total sample size (N = the number of patients per each group)

Z_{α} = 1.96 [Z score at probability of $\alpha = 0.05$ (95% confidence interval)]

Z_{β} = 0.84 (Z score at power of test $(1-\beta) = 80$ %)

p_c = 0.145 (the proportion of preventable ADE which is calculated from 14.5 events per 100 patients)

p_I = 0.029 (the proportion of preventable ADE which should be expected by 80% reduction)

Þ = 0.087 [mean of p_c and p_I]

$$2N = \frac{2[1.96\{2(0.528)(1-0.528)\}^{1/2} + 0.84\{0.704(1-0.704) + (0.352)(1-0.352)\}^{1/2}]^2}{(0.704-0.352)^2}$$

= 189

The addition by 10% was calculated to cover the patients who might drop out from the study giving the sample size of at least 208 patients, allocated into two groups (104 patients each group).

5. Period of the study

The data collection period was 4 months from 30th April to 30th August, 2007.

6. Investigation process

6.1 Literature review

Articles were reviewed by research pharmacists in the following topics:

- Pharmacotherapy and their ADEs in the treatment of RA
- Clinical pharmacist' s participation on management of ADE

6.2 *Document and material preparation*

6.2.1 The sample size was calculated as shown in topic 4.4 (page 47).

6.2.2 The forms for data collection were developed.

6.3 *Protocol submission*

6.3.1 The study protocol was submitted to ethical committee before commencing the study.

6.3.2 The research pharmacists and physicians in AIR unit were discussed and agreed on the objectives and the process of the study, and for the physicians to be familiar with the data collecting forms and work process.

6.4 *Steps of investigation*

At visit zero

6.4.1 Nine physicians in AIR unit were able to join this study, and were divided into two groups by lotting, comprising of four physicians for first group (intervention group) and five physicians for the latter (control group).

6.4.2 The research pharmacists searched for hospital number (HN) and name of RA patients followed up with selected physicians from hospital database related to patient appointment registration during 1 week before patients' appointment date designed as 1st visit.

6.4.3 All medical records from step 6.4.2 were reviewed in order to find eligible patients according to inclusion and exclusion criteria**.** Then they were assigned into intervention group or control group based on their physicians as previously selected in step 6.4.1.

6.4.4 Medical charts of the eligible patients were labeled as **"ADE monitoring**

I" for the intervention group and **"ADE monitoring C"** for the control group, using sticker.

6.4.5 The patients' demographic data, history of ADEs, current drug regimen, and laboratory data were reviewed and recorded in the "Patient's profile form" (Appendix A) before the 1st visit.

6.4.6 The research pharmacists made a telephone contact to selected patients to confirm their appointment (1st visit).

At the first visit

In the intervention group

6.4.7 The selected patients and their caregivers met research pharmacist at the manifold purposes court located nearby outpatient clinics to be informed about the objectives and detail of the study, according to the information in the "Patient/participant information sheet" (Appendix B).

6.4.8 The patients signed patient informed consent form or caregiver informed consent form (Appendix B) if they agreed to participate in the study. Those who could not join were excluded.

6.4.9 Research pharmacist reviewed the medical records again and interviewed the patients and/or their caregivers to look for adverse event (AE) occurring between the zero visit and the 1st visit using "Check list of ADE form" (Appendix C). The multi-compartment plastic boxes containing NSAIDs, DMARDs or corticosteroids were applied to remind drug's name to the patients and/or their caregivers.

6.4.10 Research pharmacist assessed causality of ADE using Roussel Uclaf Causality Assessment Method (RUCAM) (Appendix D). The causality assessment results of highly probable, probable or possible was categorized to **"May be ADE"**, then was further assessed whether it was preventable ADE according to Shumock & Thronton's criteria. On the other hand, AE with RUCAM results of unlikely or exclude was categorized to "**May not be ADE**", and was not further evaluated. All of the assessments were recorded in the "Physician's opinion form"

(Appendix E) and then it was attached in the medical records.

6.4.11 If any potential ADEs (potADEs) or drug therapy problems (DTPs) were detected, the research pharmacist gave patient counseling in order to resolve and prevent it, and then recorded their suggestions in the "Pharmacist's note" (Appendix F). This form was attached together with the "Physician's opinion form" (Appendix E) in the medical records.

6.4.12 The patients were sent to meet physicians.

6.4.13 Physicians assessed causality of ADE using clinical judgment. The causality assessment results of highly probable, probable or possible were categorized to **"May be ADE"**, and then were further assessed whether they were preventable ADEs according to Shumock & Thronton's criteria or other reasons. On the other hand, either unlikely or exclude results of causality assessment was categorized as "**May <u>not</u> be ADE**". Their assessments were also recorded in the "Physician's opinion form" (Appendix E).

6.4.14 If there was any ADE not detected by research pharmacist, but it was detected by physicians. Its causality and preventability assessment were recorded in the "Physician's opinion form" (Appendix E). Research pharmacists then later assessed and recorded (using step 6.4.10) when patients returned to meet her again.

6.4.15 ADEs were managed according to physicians' clinical decision.

6.4.16 Potential ADEs were managed according to physicians' clinical decision.

6.4.17 The patients returned to see research pharmacist.

6.4.18 All ADE assessment by physicians and research pharmacist were compared. The results were concluded as follows:

6.4.18.1 If both of them assessed "**May <u>not</u> be ADE**". The AE was not further assessed.

6.4.18.2 If both of them assessed "**May be ADE**". Their preventability assessments were compared.

- If both results were the same, i.e., either **"Yes"** or **"No"**. The preventability was concluded accordingly.
- If their results were different, i.e., one was **"Yes"** and another was **"No"**. Physicians and research pharmacist would be further discussed and final decision would be concluded primarily according to physicians' opinions.

6.4.18.3 If their results were different, i.e., one result was "**May be ADE**" and another result was **"May <u>not</u> be ADE"**. Both physicians and research pharmacist would further discussed and final decision would be concluded primarily according to physicians' opinions.

6.4.19 Research pharmacist recorded conclusion of ADE in "Physician's opinion form" (Appendix E).

6.4.20 The patients with no detected ADEs, potADE or other DTPs were provided with usual care service.

6.4.21 When any ADEs and/or potADEs were detected, research pharmacist gave counseling on how to resolve or prevent these ADES/potADEs and recorded their suggestions or counseling in "Pharmacist's note" (Appendix F).

6.4.22 Comparison of prescribing drugs between prescriptions order and medical records were made in order to detect any "prescribing errors". If there were, research pharmacist then directly asked consulting physicians and recorded in Appendix F.

6.4.23 Patients' education and counseling on drug use was performed by research pharmacist covering its indication, dosage, and precaution, and demonstrated drug samples were used to remind drugs' name. These included old drug and new drug prescription.

6.4.24 After the 1st visit, the missing data on physicians' ADEs assessment and their preventability assessment were completed by either the

consulting physicians or Prof. Suchela Janwityanujit, M.D. and/or Ticha Limsuwan, M.D., co-advisors of the study.

6.4.25 The acceptance of pharmacist's intervention was evaluated and was concluded in the "Pharmacist's note form" (Appendix F). The results were divided into accepted, partially accepted or rejected (see 7.3.2 page 58).

Before the 2nd visit

6.4.26 The medical records between the 1st and 2nd collection visit period were reviewed.

At the 2nd visit

6.4.27 Similar procedure was conducted as the 1st visit.

6.4.28 The patients were interviewed to determine their outcomes after pharmacist's interventions.

After the 2nd visit

6.4.29 Research pharmacist summarized the occurrence of ADEs and their severity assessment, management and outcome in "Adverse drug events record form (Appendix G).

After the end of the study

6.4.30 The occurrence rate of preventable ADEs between intervention group and control group among RA outpatients was compared.

6.4.31 Characteristics of pharmacist's intervention and the rate of physician acceptance of the interventions were evaluated.

In the control group

The patients in the control group were followed the same step as the intervention group by another research pharmacist except for evaluation and management of potADEs (step 6.4.11, 6.4.16, 6.4.21 to 6.4.23, 6.4.25 and 6.4.28).

The protocol flow chart, process of detection & management of ADE and process of detection & management of potential ADE are summarized in Figure 3, Figure 4 and Figure 5, respectively.

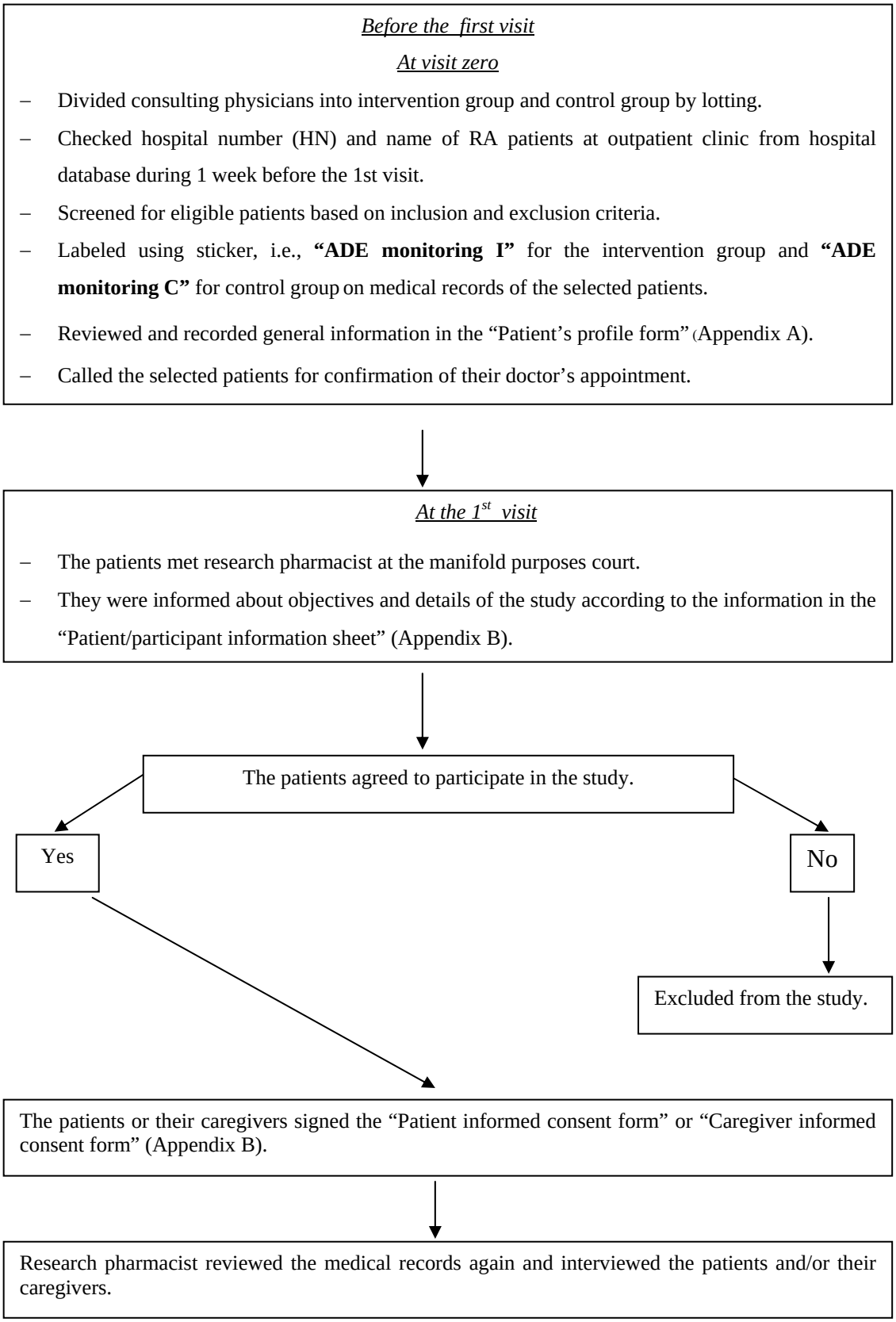

Figure 3 The summary of protocol flow chart.

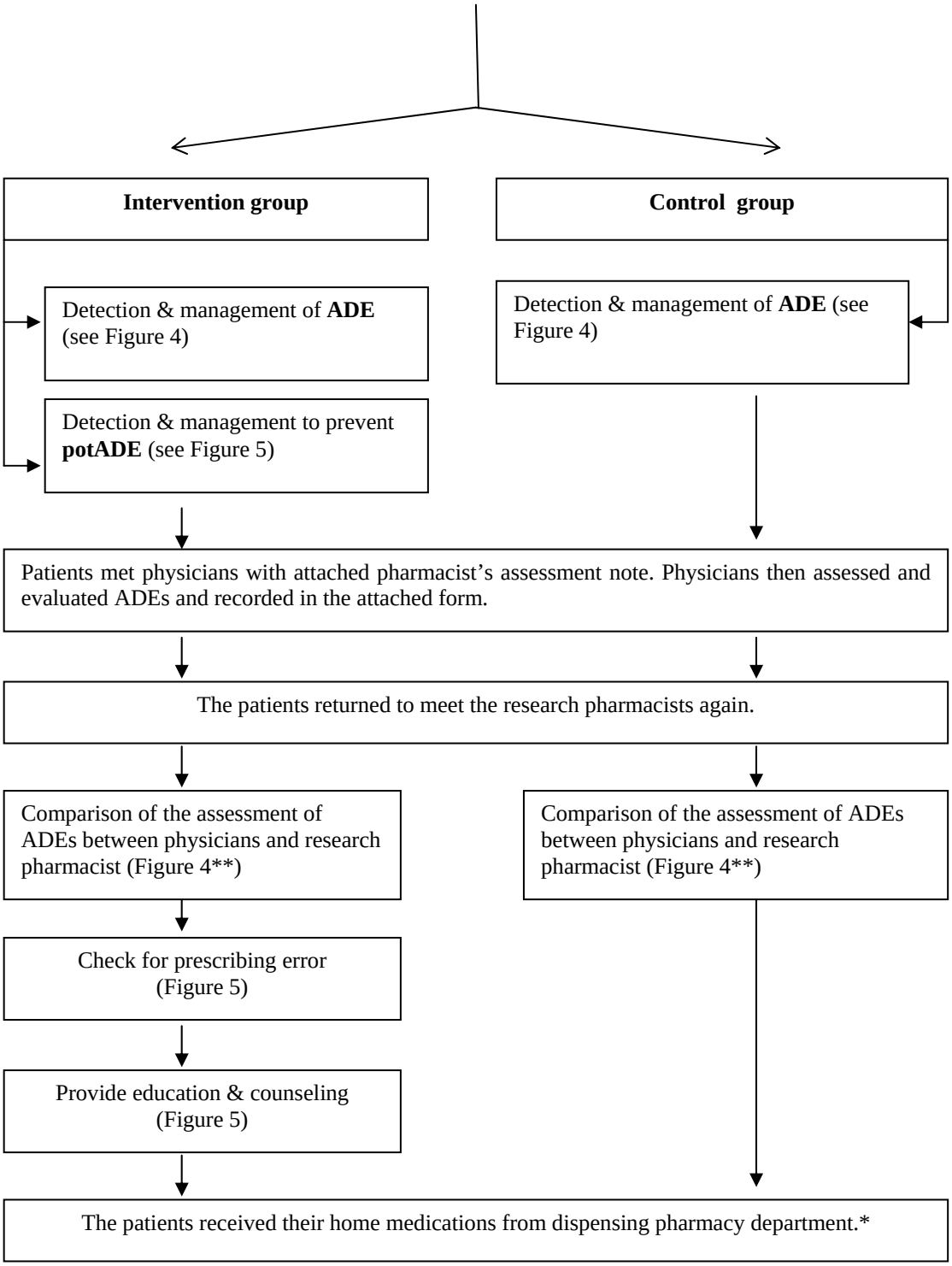

Figure 3 The summary of protocol flow chart (cont.).

Note: * In the case of new drug prescription, the patients were again educated for drugs' indication, dosage, and precaution.

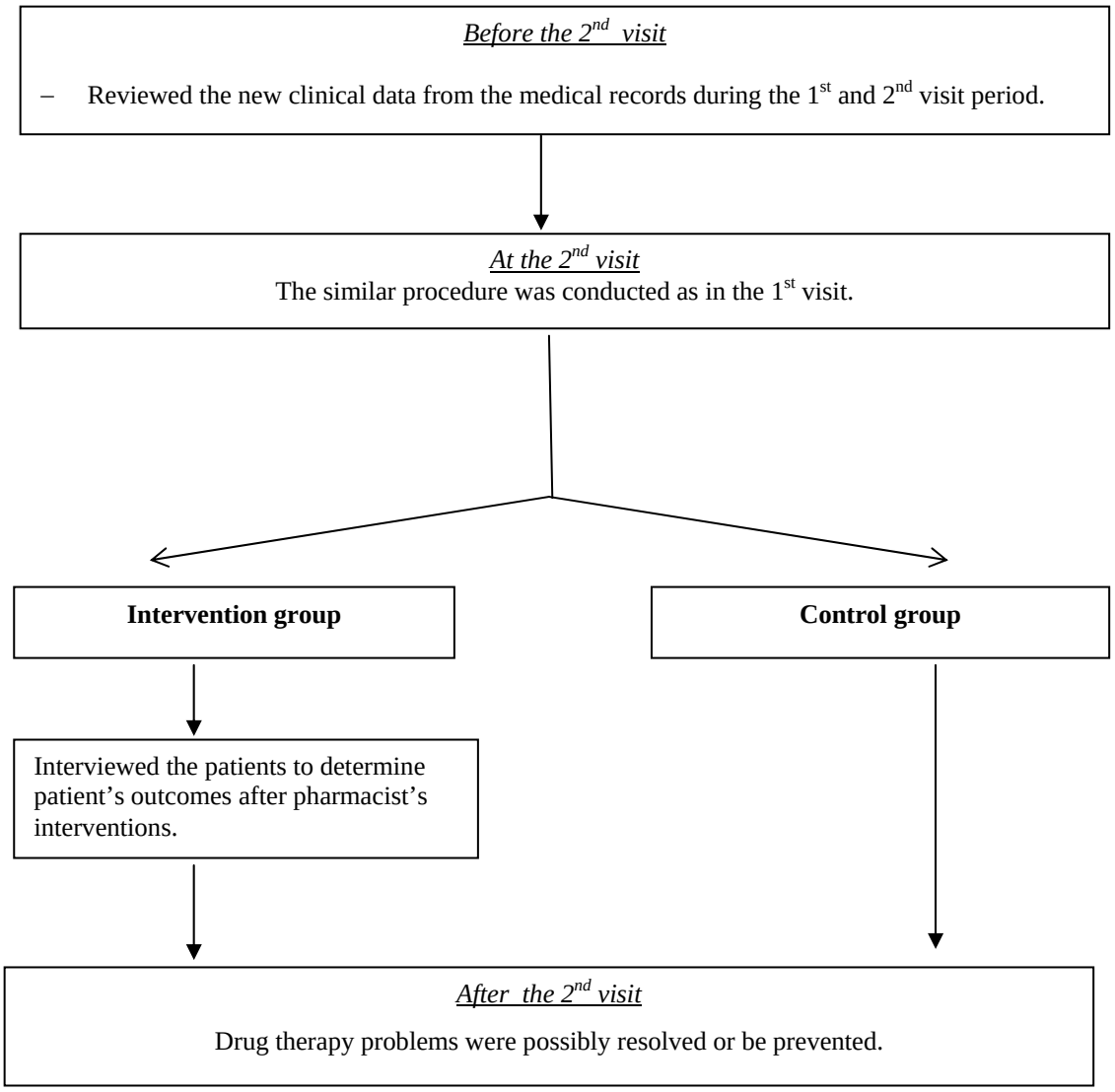

Figure 3 The summary of protocol flow chart (cont.).

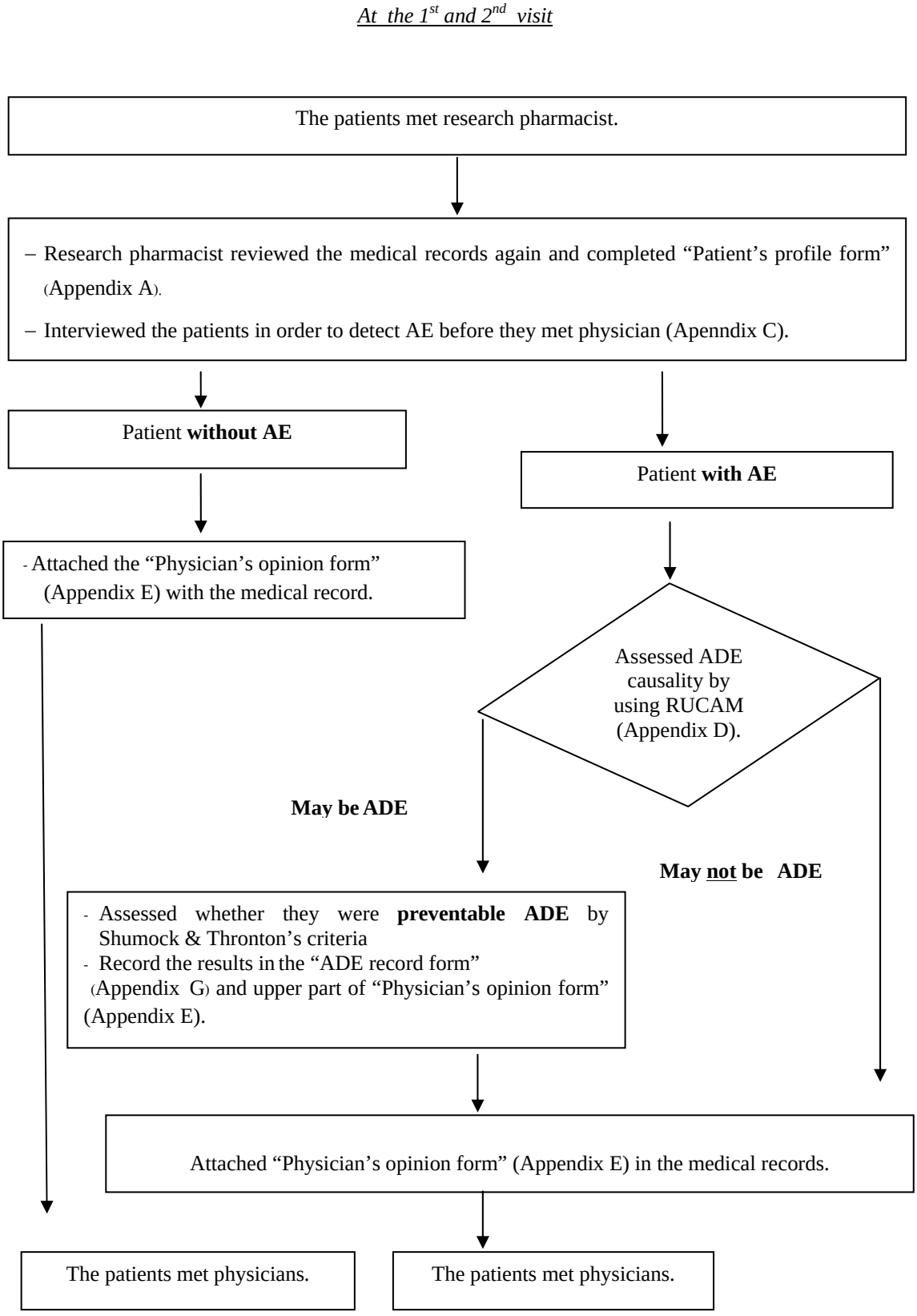

Figure 4 Process of detection and management of ADE.

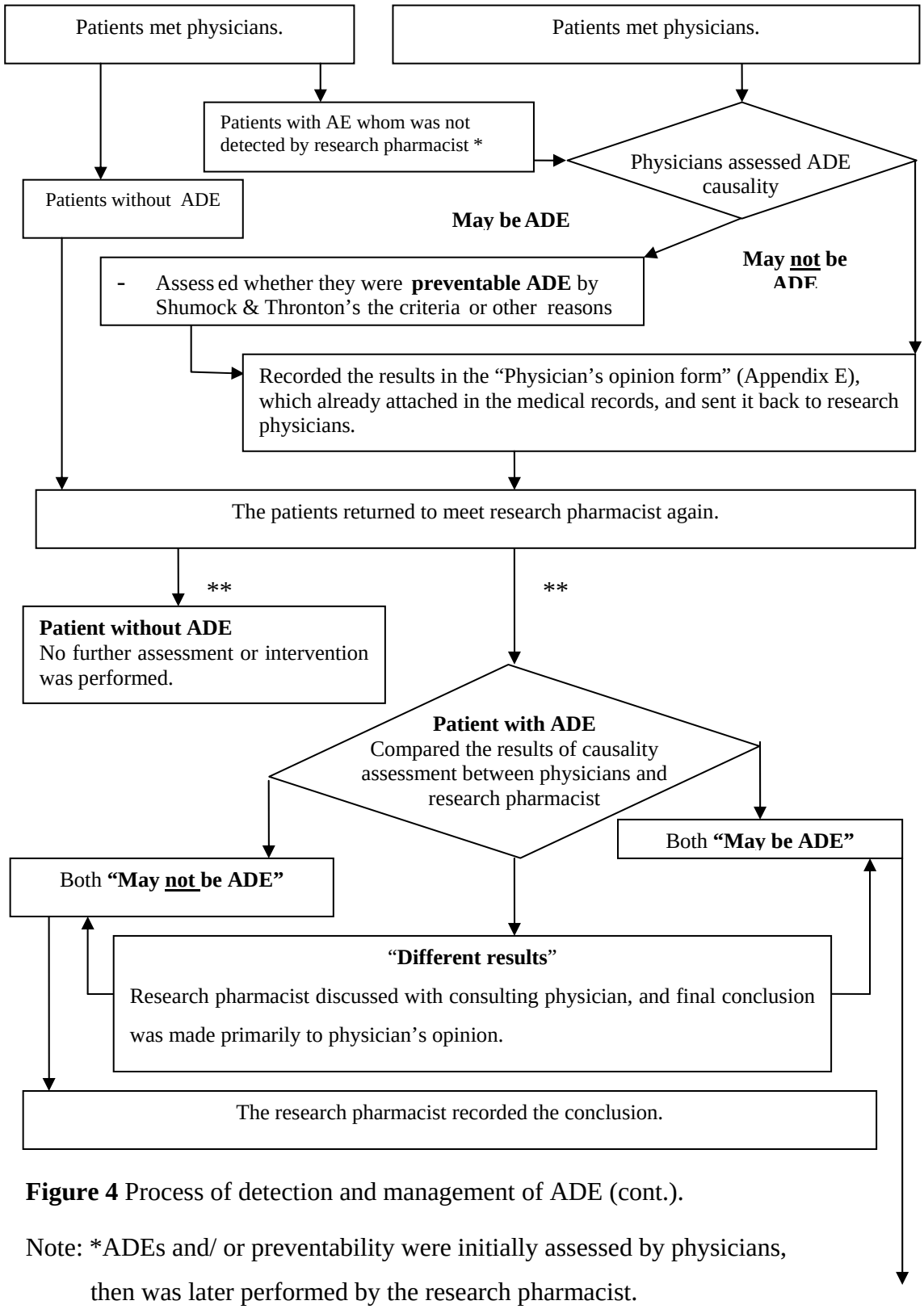

Figure 4 Process of detection and management of ADE (cont.).

Note: *ADEs and/ or preventability were initially assessed by physicians, then was later performed by the research pharmacist.

** see also Figure 3 page 54.

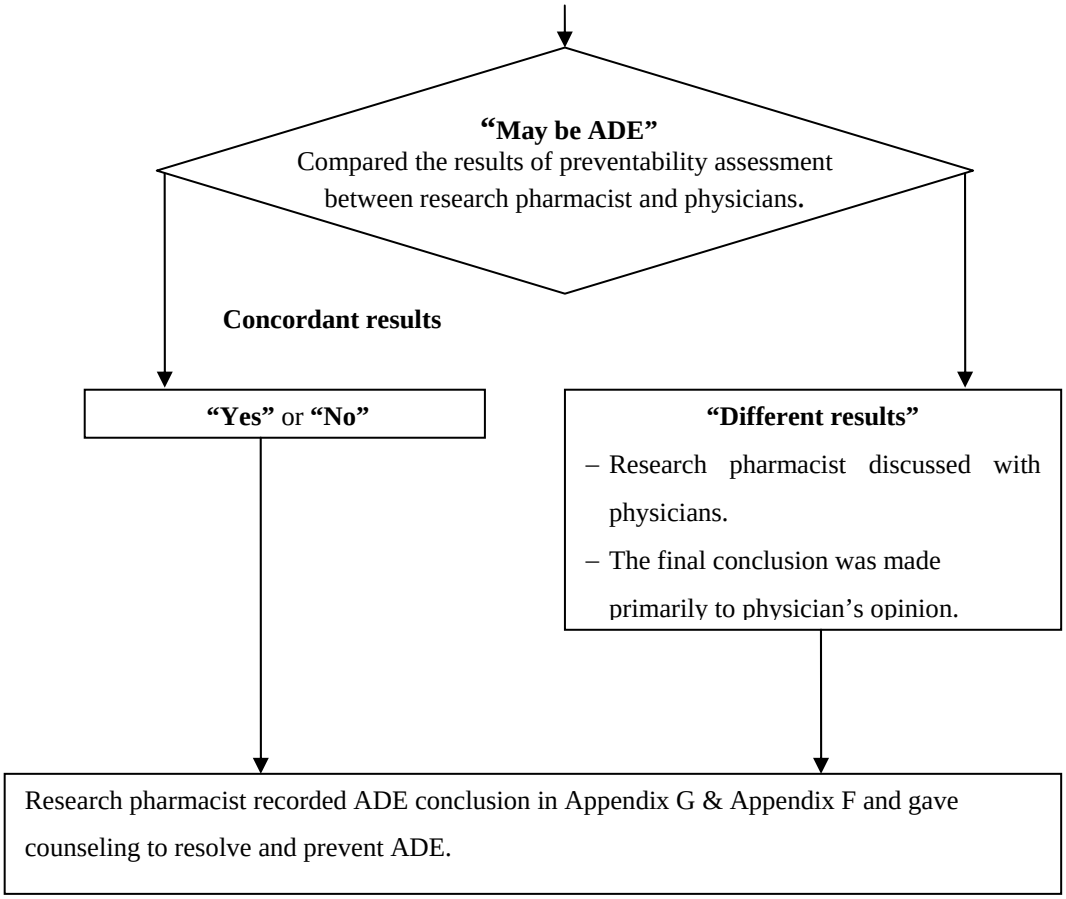

Figure 4 Process of detection and management of ADE (cont.)

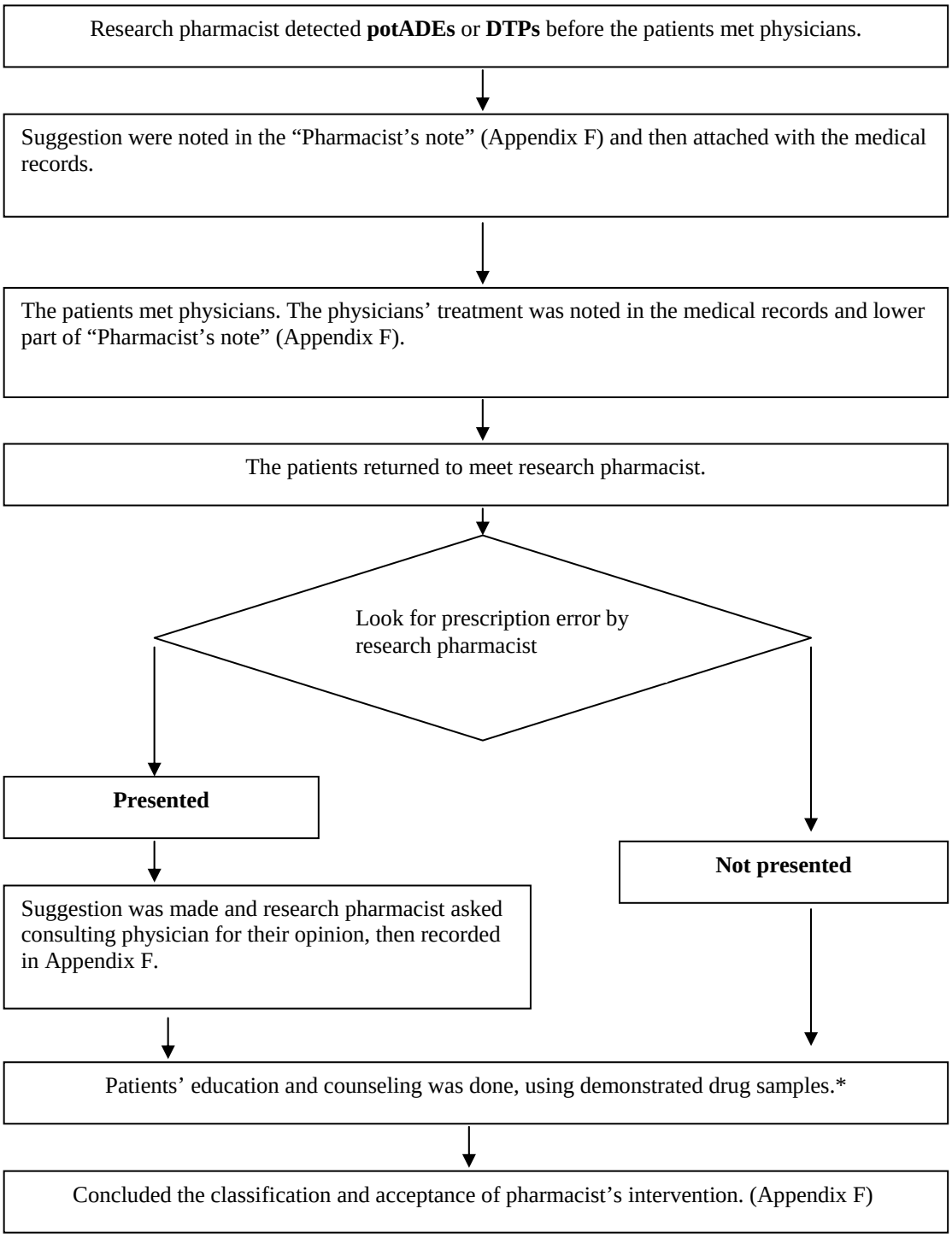

Figure 5 Process of detection & management of potential ADE in the intervention group.

Note: * In the case of new drug prescription, the patient would come back to meet research pharmacist again after receiving the prescribed medications.

7. Data collection

The data were collected and recorded in the data collecting forms as follow:

7.1 Patient's profile consisted of demographic data, medication profile data and laboratory data.

7.2 ADE data

7.2.1 Causality assessment data based on

- Roussel Uclaf Causality Assessment Method (RUCAM) by research pharmacist
- Physicians' clinical decision

7.2.2 Preventability data which were assessed by both research pharmacist and physicians based on Schumock and Thronton's criteria.

7.2.3 Severity of ADE data which were categorized according to the modification of Harwitg and colleagues criteria (76). (Table 11, page 36)

7.2.4 ADE management data which were classified into either required medical treatment or not required medical treatment. Each category comprised of

- no changes in drug use
- change in dose or interval of suspected drug
- discontinuation of suspected drug
- discontinuation of suspected drug and prescription of an alternative drug

7.2.5 Outcome of ADEs were classified as follows (109):

- complete recovery without any treatment or drug change
- complete recovery with treatment or drug changes
- recovery with sequel
- not yet recovered
- death due to ADE
- death due to other causes.

7.3 Pharmacist's intervention data

7.3.1 Pharmacist's intervention classification was adapted from Janpraparn (110) and was categorized as follows:

- Addition of drugs
- Changing dose
- Clarification or correction of order
- Cessation of drugs
- Additional monitoring or other therapy
- Recommendation of alternative drug therapy
- Changing amount of drug
- Changing frequency of administration
- Changing time of administration

7.3.2 The acceptance of pharmacist's intervention were adapted from Kraitep (111) and were categorized as follows:

– Accepted:

Drug therapy and/or prescribing error were adjusted or corrected, according to pharmacist's suggestion noted in "Pharmacist note" (Appendix F).

– Partially accepted :

Drug therapy and/or prescribing error were partially adjusted or corrected according to pharmacist's suggestion, or the suggestion was accepted but actions were not changed at that time of intervention.

– Rejected:

Drug therapy and/or prescribing errors were not adjusted or corrected according to pharmacist's suggestion.

8. Data analysis

The data were analyzed by using the Statistical Package for Social Science (SPSS) version 14.0. Descriptive data including demographic data and characteristics of ADE in intervention and control group were presented and compared. The difference of categorical data was tested by Chi-square test. The normal distribution of continuous data was tested by Kolmogorov-Smirnov statistics. If the continuous data were normally distributed, unpaired *t*-test is used. On the other hand, Mann-Whiney U test would be used if the data were not in normal distribution. Rate of

ADEs and pADE per 100 patients between intervention group and control group were compared by Chi-square test, and between the first and the second visit in each group were tested by McNemars Change Test. All *p*-value were two tailed and less than 0.05 were considered statistically significant.

8.2 Characteristics of ADEs were presented as:

8.2.1 The incidence of ADEs

8.2.2 The rate of pADEs

8.2.3 Drug group and subgroup causing ADEs

8.2.4 Level of severity affecting various organ system

8.2.5 Management of ADEs

8.2.6 Outcome of ADEs.

8.3 Characteristic of pharmacist's intervention

8.3.1 Number of pharmacist's intervention in each patient

8.3.2 Classification of pharmacist's intervention and the result of physicians' acceptance

CHAPTER IV

RESULTS

The study was established in RA outpatients at Ramathibodi Hospital during 30th April to 30th August 2007. During the period of study, 153 RA outpatients were screened and were invited to participate in the study. Before staring the study, they were asked to sign the informed consents (Appendix B). However, eleven of them did not complete the entire study because ten of them missed their appointed time at the 1st visit date for a period longer than the time scheduled to the 2nd visit and the other decided to receive therapy at nearby hospital. Therefore 142 participants completed the study of these participants 70 patients were designed as control group and 72 patients were assigned as intervention group.

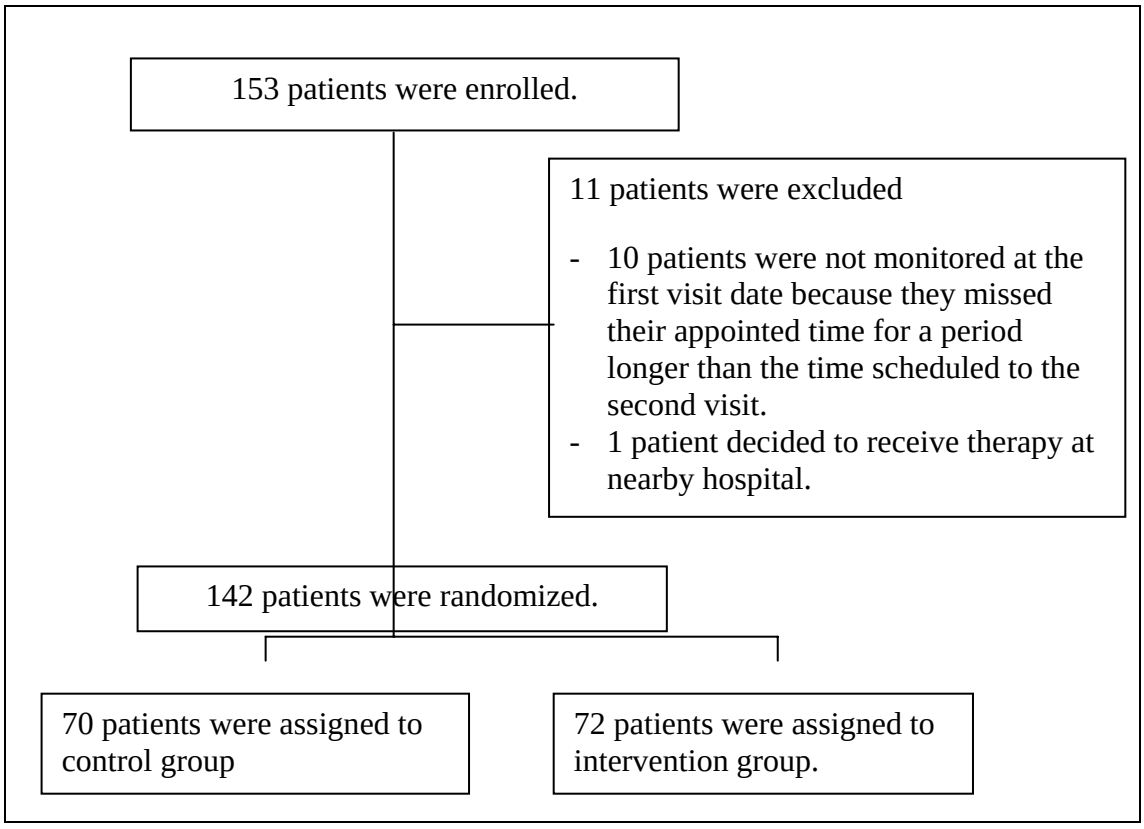

Figure 6 Classification of RA outpatients in the study.

Demographic data in control and intervention group

Of these 142 patients, majority of them were female. Ninety percent were in control group and 86.1% were in intervention group. The mean ± SD of age was 50.0 ± 13.0 years in the control group and 51.4 ± 12.6 years in the intervention group. For the level of education, 58.6% and 51.4% of control group and intervention group had education in primary level. Most patients in both groups were non alcohol user and smoker. Patients were mainly diagnosed of RA for 1-5 years, 51.4% of the control group and 52.8% of the intervention group. The number of patients who had experienced in ADEs were 64.3% in the control group and. 52.8% in the intervention group, respectively. Approximately 56% of the control group and 43% of the intervention group suffered from only RA. It was found that each patient of both groups had more than one concomitant disease, i.e., 1.91 and 1.97 diseases per patient of the control group and the intervention group, respectively. Hypertension was the most common disease found concomitantly with RA, 31.4% of the control group and 27.8% of the intervention group. The mean ± SD of items of medication prescribed in control group and intervention group were 7.4 ± 2.5 and 8.5 ± 2.8 items, for details of patient's demographic data, these are presented in Table 15.

Table 15 The difference of patient characteristics compared between the intervention and control group.

Characteristics	Control group (n=70)	Intervention group (n=72)	p-value
Gender, No. (%)			0.475
Male	7 (10.0)	10 (13.9)	
Female	63 (90.0)	62 (86.1)	
Age (years)			0.532
Mean ± SD	50.0 ± 13.0	51.4 ± 12.6	
Median / range	49.0 / 20-84	52.0 / 25-80	
Education, No (%)			0.878
No education	2 (2.9)	1 (1.4)	
Primary school	41 (58.6)	37 (51.4)	
Secondary school	9 (12.9)	12 (16.7)	
University	18 (25.8)	22 (30.6)	
Social history, no (%)			
Current smoking	8 (11.4)	3 (4.2)	0.126
Current alcohol drinking	4 (5.7)	5 (6.9)	1.000
Duration of RA, No (%)			0.823
< 1 year	4 (5.7)	3 (4.2)	
1-5 year	36 (51.4)	38 (52.8)	
> 5 year	30 (42.9)	31 (43.1)	
History of ADEs, no (%)			0.164
Experienced patients	45 (64.3)	38 (52.8)	
Non-experienced patients	25 (35.7)	34 (47.2)	
Average No. of concurrent disease / patient	1.91	1.97	0.131
Concurrent disease in each patient, No.(%)			
Only RA	39 (55.7)	31 (43.1)	
Two	10 (14.3)	18 (25.0)	
Three	12 (17.1)	18 (25.0)	
> Three	9 (12.9)	5 (7.0)	
Concurrent disease, no (%)			
Hypertension	22 (31.4)	20 (27.8)	
Osteoarthritis	5 (7.1)	13 (18.1)	
Dyslipidemia	10 (14.3)	5 (6.9)	
Diabetic mellitus	2 (2.9)	8 (11.1)	
Thyroid disease	4 (5.7)	3 (4.2)	
Kidney disease	4 (5.7)	3 (4.2)	
Others	12 (17.1)	16 (22.2)	
Number of prescribed medications			
Mean ± SD	7.4 ± 2.5	8.5 ± 2.8	0.03*
DMARDs used	68 (97.1)	72 (100.0)	0.241
NSAIDs used	45 (64.3)	43 (59.7)	0.575
Corticosteroid used	37 (52.7)	42 (58.3)	0.511

S.D. = standard deviation

Comparison data

1. Demographic data between the intervention and the control group

The normal distribution of age was tested by Kolmogorov-Smirnov statistics in each group and the results were normal distribution data. Then, the data were tested with Pearson Chi-square, except for the difference of age between the two groups. The number of prescribed medications was tested with the unpaired *t*-test. The difference of frequency distribution in most parameters between the two groups as shown in Table 15 (page 62) were not statistically significant except for the number of prescribed medications ($p = 0.03$).

2. The incidence of ADEs

All patients assessed for any ADEs using RUCAM (Appendix D). Forty two patients (24 controls, 18 interventions) and 50 patients (30 controls, 20 interventions) were detected at least one ADE at the 1st visit and at the 2nd visit, respectively. The incidence of ADEs in the control group was increased from 34.3% at the 1st visit to 42.9% at the 2nd visit while the incidence of the intervention group was increased from 25.0% to 27.8%.

Total 118 ADEs were detected during the study period. These ADEs were considered as preventable or non-preventable according to Schumock and Thornton's set of question (74). The rate of pADEs are presented in Table 16. There were 55 ADEs appeared in 42 patients at the 1st visit and 63 ADEs in 50 patients at the 2nd visit. At the 1st visit, 16 events in control group were classified as pADEs, while 12 pADEs were able to be detected in the intervention group. At the 2nd visit, there were 23 pADEs in the control group whereas there were 16 pADEs in the intervention group.

The overall incidence of ADE and pADE rate per 100 patients are shown for both visits and both groups in Table 16. In the before and after comparison, the incidence of ADE and the pADE rate per 100 patient in the intervention group increased slightly in the intervention group by 2.8% (25 to 27.8) and 5.5% (16.7 to 22.2, $p = 0.37$) respectively from the 1st visit to the 2nd visit. The incidence of ADE

and the pADE rate per 100 patient in the control group also increased from the 1st visit to the 2nd visit from by 8.6% (34.3 to 42.9) and 10.0% (22.9 to 32.9, p = 0.11).

When the intervention group was compared with the control group at the 2nd visit, the difference of incidence of ADE was 15.1% (p = 0.06) whereas at the 1st visit was 9.3% (p=0.2). The difference of the pADE rate per 100 patients between the intervention group and the control group at the 2nd visit was 10.7% (p = 0.08) whereas at the 1st visit was 6.2% (p = 0.29).

Table 16 The incidence of ADEs and preventable ADEs per 100 patients compared between the control group and the intervention group.

	Control group		**Intervention group**	
	1st visit	**2nd visit**	**1st visit**	**2nd visit**
Number of patients	70	70	72	72
Patients with ADE	24	30	18	20
All ADEs	33	38	22	25
pADEs	16	23	12	16
Incidence of ADE (%)	34.3	42.9*	25	27.8*
pADE rate per 100 patients	22.9	32.9**	16.7	22.2**

*p = 0.06 for comparison between the intervention and the control group

**p=0.08 for comparison between the intervention and the control group

Characteristics of ADEs in each group

1. Drug groups and treatment regimen

Table 17 shows drug groups that were mainly prescribed in RA patients. Almost of patients received DMARDs for treatment (control group vs. intervention group; 97.1% vs. 100.0%) followed by NSAIDs (control group vs. intervention group; 64.3% vs. 59.7%), and corticosteroids (control group vs. intervention group; 52.7% vs. 58.3%).

Table 17 Drug groups that were mainly prescribed in RA patients.

Drug groups	Control group (%), n=70	Intervention group (%), n=72
DMARDs	68 (97.1)	72 (100.0)
NSAIDs	45 (64.3)	43 (59.7)
Corticosteroids	37 (52.7)	42 (58.3)

The three combination therapy comprised of DMARDs, NSAIDs and corticosteroids was the majority of the treatment used not only in the control group but also in the intervention group followed by two combination therapy comprised of DMARDs and NSAIDs or DMARDs and corticosteroids. Table 18 shows these treatment regimens.

Table 18 Treatment regimens in RA patients.

Treatment regimen	No. of patient (%)		
	Control group	Intervention group	Total
DMARDs + NSAIDs + corticosteroids	24 (34.4)	24 (33.3)	48 (33.8)
DMARDs + NSAIDs	20 (28.6)	19 (26.4)	39 (27.5)
DMARDs + corticosteroids	12 (17.1)	18 (25.0)	30 (21.1)
Only DMARDs	12 (17.1)	11 (15.3)	23 (16.2)
Only NSAIDs	1 (1.4)	0	1 (0.7)
Only corticosteroids	1 (1.4)	0	1 (0.7)
Total	70 (100.0)	72 (100.0)	142 (100.0)

2. Drug group and subgroup causing ADEs

One hundred and eighteen ADEs were found in this study, the most frequently cause were DMARDs (81 events; 68.6%) not only in the control group (47 events; 39.8%) but also in the intervention group (34 events; 28.8%). NSAIDs resulted in 20 events (16.9%) of ADEs followed by corticosteroids (prednisolone 7 events; 6.0%). Furthermore, the others (10 events; 8.5%) consisted of tramadol (3 events),

glibenclamide (1 event), pyrazinamide (1 event), theophylline (1 event), glucosamine (1 event), orphenadrine (1 event), calcium carbonate (1 event), and aspirin grain I (1 event). The number and percentage of drug group causing ADEs in each group are showed in Table 19.

Table 19 Drug groups causing ADEs in the control and the intervention group.

Drug groups	**Control group, events (%)**	**Intervention group, events (%)**	**Total, events (%)**
DMARDs	47 (39.8)	34 (28.8)	81(68.6)
NSAIDs	13 (11.0)	7 (5.9)	20 (16.9)
Corticosteroids	4 (3.4)	3 (2.6)	7 (6.0)
Others	7 (5.9)	3 (2.6)	10 (8.5)
Total	**71 (60.1)**	**47 (39.9)**	**118 (100.0)**

When ADEs were further classified by sub-group of DMARDs and NSAIDs (Table 20). Methotrexate (30.9%) was DMARD the most frequently implicated in ADE occurrence followed by chloroquine (21.0%) and hydroxychloroquine (19.8%), respectively. And, naproxen was most commonly implicated as the cause of ADEs (10 events; 50%).

Table 20 Sub-group drugs of DMARDs and NSAIDs.

Drug groups		**No of events (%)**		
		Control group	**Intervention group**	**Total**
DMARDs	Methotrexate (MTX)	17 (21.0)	8 (9.9)	25 (30.9)
	Chloroquine (CQ)	9 (11.1)	8 (9.9)	17 (21.0)
	Hydroxychloroquine (HCQ)	11 (13.6)	5 (6.2)	16 (19.8)
	Sulfasalazine (SSZ)	4 (4.9)	7 (8.6)	11 (13.5)
	Leflunomide (LEF)	4 (4.9)	1 (1.2)	5 (6.1)
	Gold injection	1 (1.2)	3 (3.7)	4 (4.9)
	Azathioprine	1 (1.2)	0	1 (1.2)

Table 20 Sub-group drugs of DMARDs and NSAIDs (cont.).

Drug groups		No of events (%)		
		Control group	**Intervention group**	**Total**
	Cyclphosphamide (CYP)	0	1 (1.2)	1 (1.2)
	Etanercept inj	0	1 (1.2)	1 (1.2)
	Total	**47 (58.0)**	**34 (42.0)**	**81 (100.0)**
NSAIDs	Naproxen	6 (30.0)	4 (20.0)	10 (50.0)
	Etoricoxib	1 (5.0)	2 (10.0)	3 (15.0)
	Celecoxib	2 (10.0)	0	2 (10.0)
	Lumiracoxib	2 (10.0)	0	2 (10.0)
	Meloxicam	1 (5.0)	0	1 (5.0)
	Indomethacine	1 (5.0)	0	1 (5.0)
	Piroxicam	0	1 (5.0)	1 (5.0)
	Total	**13 (65.0)**	**7 (35.0)**	**20 (100.0)**

Total 67 pADEs, 34.3% were classified based on Schumock and Thornton's criteria (74). The first and the second most pADEs were the second criterion (34.3%) and the sixth criterion (13.4%). The second criterion was related to the dose, route, and frequency of administration that was inappropriate for the patient's age, weight and disease state. The sixth criterion related to the document presented the toxic drug level. The third criterion was related to omission of therapeutic drug monitoring or other necessary laboratory test, and the seventh criterion was related to poor compliance. In addition, 11 events; 16.4% were determined as pADEs according to physician's opinions (Table 21). For example, gastrointestinal effects, these most effect were common with NSAIDs including discomfort, distress, nausea, vomiting, diarrhea, bleeding and ulceration could be prevented by gastro-protective agent.

Table 21 Preventable ADEs assessed by Schumock and Thornton's criteria.

Criteria	Preventable ADEs (%)		Total (%)
	Control group	Intervention group	
1	1 (1.5)	1 (1.5)	2 (3.0)
2	15 (22.4)	8 (11.9)	23 (34.3)
3	5 (7.5)	2 (3.0)	7 (10.4)
4	1 (1.5)	4 (6.0)	5 (7.5)
5	2 (3.0)	1 (1.5)	3 (4.5)
6	3 (4.5)	6 (9.0)	9 (13.4)
7	5 (7.5)	2 (3.0)	7 (10.4)
Others	4 (6.0)	7 (10.4)	11 (16.4)
Total	**36 (53.7)**	**31 (46.3)**	**67 (100.0)**

3. Level of severity affected system organ disorder

Table 22 and Table 23 summarize the incidence of ADEs classified as system-organ classes according to WHO Collaborating Centre for international drug monitoring (Appendix H). It was found that gastro-intestinal system and skin and appendages were the two main body systems affected by ADEs. The severity of ADEs was presented at different levels suggested by Harwig and colleagues (76) ranged from level 1 to 4.

At the 1st visit, there were 33 events occurred in 25 patients of the control group and 22 events in 16 patients of the intervention group. Severity of ADEs ranged from level 1 to 4, major severity level of ADEs in control group were level 2a (13 events from 33 ADEs in control group; 39.4%) followed by level 1 (10 events; 30.3%), level 2c (6 events; 18.2%), level 3 (3 events; 9.1%), respectively. Level 4 was the most severe level in this study occurred in 1 patient that was involved in endocrine system (hypoglycemia). While the main severity of the intervention group ADEs were level 1 (7 events from 22 ADEs in intervention group; 31.8%) followed by level 2b (5 events; 22.7%), level 2a and level 3 (4 events; 5.7%), level 2c (2 events; 2.8%), respectively. The two main problems of the control group and the intervention group were ADEs involving skin and appendages system (12 from 33 events in control

group; 36.4% and 7 from 22 events in intervention group; 31.8%) and gastro-intestinal system (10 from 33 events in control group; 30.3% and 7 from 22 events in intervention group; 31.8%).

Table 22 ADE problems classified by organ affected according to WHO at the 1st visit.

System disorder	**Level of severity**													
	Control							**Intervention**						
	1	**2a**	**2b**	**2c**	**3**	**4**	**Total**	**1**	**2a**	**2b**	**2c**	**3**	**4**	**Total**
Gastro-intestinal	2	4	-	1	3	-	**10**	2	-	2	1	2	-	**7**
Skin and appendages	6	5	-	1	-	-	**12**	4	-	1	-	2	-	**7**
Vision	1	1	-	-	-	-	**2**	-	-	-	-	-	-	**0**
Central & peripheral nervous	-	1	-	2	-	-	**3**	-	-	-	-	-	-	**0**
Liver and biliary	-	1	-	1	-	-	**2**	-	1	-	1	-	-	**2**
White cell and RES	1	1	-	-	-	-	**2**	-	1	-	-	-	-	**1**
Urinary system	-	-	-	-	-	-	**0**	1	-	1	-	-	-	**2**
Body as a whole-general	-	-	-	-	-	-	**0**	-	1	-	-	-	-	**1**
Endocrine	-	-	-	-	-	1	**1**	-	1	-	-	-	-	**1**
Red blood cell	-	-	-	-	-	-	**0**	-	-	1	-	-	-	**1**
Cardiovascular system	-	-	-	1	-	-	**1**	-	-	-	-	-	-	**0**
Total	**10**	**13**	**0**	**6**	**3**	**1**	**33**	**7**	**4**	**5**	**2**	**4**	**0**	**22**

RES= Reticuloendothelial system

At the 2nd visit, the most severity level of ADEs of control group were level 1 (21 events from 38 all ADEs in control group; 55.3%) followed by level 2a (7 events; 18.4%), level 3 (5 events; 13.2%), level 2c (4 events; 10.5%), level 2b (1 events; 2.6%), respectively. The major problem was ADEs involving gastro-intestinal system (15 events from 38 ADEs in control group; 39.5%) followed by skin and appendages system (10 events; 36.3%). While in the intervention group, the two main severity level of ADEs were level 2a (8 events from 25 ADEs in intervention group;

32.0%) and 2c (7 events; 28.0%) followed by level 1 (5 events; 20.0%), level 3 (3 events; 12.0%), and level 2b (2 events; 8.0%), respectively. The most two common ADEs were similar to the control group that occurred in gastro-intestinal system (7 from 25 events; 28.0%). and skin and appendages system (6 from 25 events; 24.0%).

Table 23 ADE problems classified by organ affected according to WHO at the 2nd visit.

System disorder	**Level of severity**													
	Control							**Intervention**						
	1	**2a**	**2b**	**2c**	**3**	**4**	**Total**	**1**	**2a**	**2b**	**2c**	**3**	**4**	**Total**
Gastro-intestinal	8	2	-	-	5	-	**15**	-	3	-	1	3	-	**7**
Skin and appendages	7	3	-	-	-	-	**10**	4	1	-	1	-	-	**6**
Vision	3	-	1	2	-	-	**6**	-	2	-	-	-	-	**2**
Central & peripheral nervous	-	2	-	1	-	-	**3**	-	-	-	1	-	-	**1**
Liver and biliary	-	-	-	-	-	-	**0**	-	1	-	1	-	-	**2**
White cell and RES	1	-	-	-	-	-	**1**	-	1	-	-	-	-	**1**
Urinary system	-	-	-	-	-	-	**0**	-	-	1	1	-	-	**2**
Body as a whole-general	-	-	-	-	-	-	**0**	-	-	-	1	-	-	**1**
Red blood cell	-	-	-	-	-	-	**0**	-	-	1	-	-	-	**1**
Cardiovascular system	-	-	-	1	-	-	**1**	-	-	-	-	-	-	**0**
Heart rate and rhythm	-	-	-	-	-	-	**0**	1	-	-	1	-	-	**2**
Reproductive	2	-	-	-	-	-	**2**	-	-	-	-	-	-	**0**
Total	**21**	**7**	**1**	**4**	**5**	**0**	**38**	**5**	**8**	**2**	**7**	**3**	**0**	**25**

RES= Reticuloendothelial system

Characteristics of ADEs which classified affected organ system disorder. It was found that the rate of ADEs in gastro-intestinal system of the control group was increased from 14.3% at the 1st visit to 17.1% and the rate of ADEs also was increased from 30.3% to 39.5%. Whereas in the intervention group there was decreased from 9.7% at the 1st visit to 8.3% and the rate of ADEs also was decreased from 31.8% to 28.0%. Abdominal pain/ dyspepsia was mainly found in control group which was

increased from 4 patients at the 1st visit to 10 patients at the 2nd visit and most of these were in level 1. Nausea/ vomiting in intervention group was lessened from 4 patients at the 1st visit to 2 patients at the 2nd visit. Level 3 of both group mostly involved abdominal pain or dyspepsia from NSAIDs.

Hyperpigmentation from antimalarial DMARDs was the most common ADE that affected skin and appendages. The level of severity was mild (level 1), even though the incidence and the rate of ADEs were also increased**.** Alopecia was detected only in the control group which was increased from 2 patients to 5 patients.

Early maculopathy resulted from antimalrial DMARDs except one patient in the intervention group experienced cataracts from taking oral corticosteroid. The severity level of ADEs were level 1 and 2 (Table 25).

Dizziness and headache were reported in control group at the 1st visit and dizziness in intervention group was reported at the 2nd visit. All of them were in level 2 severity. The drugs caused these DEs were DMARDs (MTX, SSZ) and tramadol.

Liver function disorder increased in both group at the 1st visit and remained stable at the 2nd visit in intervention group.

Leucopenia from DMARDs and leukocytosis from oral corticosteroids were reported and these were in level 1 and 2a severity.

ADEs affected white cell system occurred only in the intervention group and was in level 1 and 2 severity. Hematuria and proteinuria occurred in 3 patients who received parenteral gold injection. Serum creatinine was increased due to non-compliance with NSAIDs.

Fatigue was presented in 2 patients of intervention group at the 1st visit and the the 2nd visit, respectively. Levels of severity were level 2a and 2c.

Hypoglycemia from anti-diabetic drugs occurred at the 1st visit in one patient in each group. The severity was level 4 in control group and level 2a in intervention group.

Decreased Hct and MCV were detected only in the intervention group, one patient at the 1st visit and the other at the 2nd visit. One patient who previously

experienced pancytopenia presented with macrocytic anemia. All of them were in level 2b.

Two patients had peripheral edema, one resulted from parenteral gold injection and the other had affected by NSAIDs. The seveity was in level 2c.

Two patients of intervention group complained that they had palpitation at the 2nd visit. One was detected from oral muscle relaxant and the other was from theophylline which was prescribed from another OPD clinic. The severities were 1 and 2c, respectively. At the 1st visit; two patients in intervention group were infected with level 1 severity resulting from DMARDs. All of the number (%) of ADEs was shown in Table 24.

Table 24 ADEs classified by organ system, symptom or reaction in e group at the 1st visit and the 2nd visit.

System / Symptom or Reaction	**No (% of patients)**				**No (% of events)**			
	1st visit		**2nd visit**		**1st visit**		**2nd visit**	
	C (N= 70)	**I** (N= 72)	**C** (N= 70)	**I** (N= 72)	**C** (N=33)	**I** (N= 22)	**C** (N= 38)	**I** (N= 25)
Gastro-intestinal system	10 (14.3)	7 (9.7)	12 (17.1)	6 (8.3)	10 (30.3)	7 (31.8)	15 (39.5)	7 (28.0)
- Oral ulcer or mucositis	3	-	1	-	3	-	1	-
- Nausea / vomiting	1	4	1	2	1	4	1	2
- Diarrhea	1	-	1	-	1	-	1	-
- Constipation	-	-	2	-	-	-	2	-
- Abdominal pain/ dyspepsia	4	1	10	4	4	1	10	4
- Dry mouth	1	1	-	-	1	1	-	-
- Anorexia	-	1	-	1	-	1	-	1
Skin and appendages	11 (15.7)	7 (9.7)	10 (14.3)	6 (8.3)	12 (36.4)	7 (31.8)	10 (26.3)	6 (24.0)
- Alopecia	2	-	5	-	2	-	5	-
- Hyperpigmentation	7	6	5	4	7	6	5	4
- Inject site of reaction	-	1	-	-	-	1	-	-
- Acne	2	-	-	1	2	-	-	1
- Fixed drug eruption	1	-	-	-	1	-	-	-
- Photosensitivity	-	-	-	1	-	-	-	1

Table 24 ADEs classified by organ system, symptom or reaction in e group at the 1st visit and the 2nd visit (cont.).

System / Symptom or Reaction	No (% of patients)				No (% of events)			
	1st visit		2nd visit		1st visit		2nd visit	
	C (N= 70)	I (N= 72)	C (N= 70)	I (N= 72)	C (N=33)	I (N= 22)	C (N= 38)	I (N= 25)
Vision	2 (2.9)	- (0)	6 (8.6)	2 (2.8)	2 (6.1)	- (0)	6 (15.8)	2 (8.0)
- Blurred or double vision	2	-	6	2	2	-	6	2
Central & peripheral nervous	3 (4.3)	- (0)	3 (4.3)	1 (1.4)	3 (9.1)	- (0)	3 (7.9)	1 (4.0)
- Headache	1	-	-	-	1	-	-	-
- Dizziness	2	-	3	1	2	-	3	1
Liver and biliary	2 (2.9)	2 (2.8)	- (0)	2 (2.8)	2 (6.1)	2 (9.1)	- (0)	2 (8.0)
- LFT increased	2	2	-	2	2	2	-	2
White cell and res	2 (2.9)	1 (2.8)	1 (1.4)	1 (2.8)	2 (6.1)	1 (4.5)	1 (2.6)	1 (4.0)
- Leucopenia								
- Leukocytosis	1	1	1	1	1	1	1	1
	1	-	-	-	1	-	-	-
Urinary system	- (0)	2 (2.8)	- (0)	2 (2.8)	- (0)	2 (9.1)	- (0)	2 (8.0)
- Hematurea	-	2	-	-	-	2	-	-
- Proteinuria	-	-	-	1	-	-	-	1
- SCr increased	-	-	-	1	-	-	-	1
Body as a whole-general	-	1 (1.4)	-	1 (1.4)	-	1 (4.5)	-	1 (4.0)
- Fatigue	-	1	-	1	-	1	-	1
Endocrine	1 (1.4)	1 (1.4)	- (0)	- (0)	1 (3.0)	1 (4.5)	- (0)	- (0)
- Hypoglycemia	1	1	-	-	1	1	-	-
Red blood cell	- (0)	1 (1.4)	- (0)	1 (1.4)	- (0)	1 (4.5)	- (0)	1 (4.0)
- Hct, MCV decreased	-	1	-	-	-	1	-	-
- Anemia	-	-	-	1	-	-	-	1
Cardiovascular system	1 (1.4)	- (0)	1 (1.4)	- (0)	1 (3.0)	- (0)	1 (2.6)	- (0)
- Peripheral edema	1	-	1	-	1	-	1	-

Table 24 ADEs classified by organ system, symptom or reaction in e group at the 1st visit and the 2nd visit (cont.).

System / Symptom or Reaction	No (% of patients)				No (% of events)			
	1st visit		2nd visit		1st visit		2nd visit	
	C (N= 70)	I (N= 72)	C (N= 70)	I (N= 72)	C (N=33)	I (N= 22)	C (N= 38)	I (N= 25)
Heart rate and rhythm	- (0)	- (0)	- (0)	2 (2.8)	- (0)	- (0)	- (0)	2 (8.0)
Palpitation	-	-	-	2	-	-	-	2
Reproductive	- (0)	- (0)	2 (2.9)	- (0)	- (0)	- (0)	2 (5.3)	- (0)
- Secondary infection	-	-	2	-	-	-	2	-

4. Management of ADEs

Total 118 ADEs based on the severity level and the management of ADEs are shown in Table 26. In the control group, most of ADEs were in severity level 1. Approximately 15% of all ADEs in the control group required medical treatment but no change drug therapy while 28 % did not require medical treatment and no change drug therapy. In the intervention group, the two main severity levels were in level 1 and level 2a (approximately 25% of each level). Most of ADEs were in level 1 that did not require medical treatment and also were not changed suspected drugs (17.0%). However, almost of ADEs with level 2a did not require medical treatment but required changed dose or interval of suspected drugs (21%).

Table 25 The management of ADEs.

Severity	Management	ADEs 118 events	
		Control group N = 71	**Intervention group N = 47**
1	Require medical treatment - No changes	11 (15.5%)	1 (2.1%)
	Not require medical treatment - Change dose or interval of suspected drug	-	2 (4.3%)
	- No changes	20 (28.2%)	8 (17.0%)
	- Discontinuation of suspected drug	-	-
	- Discontinuation of suspected drug & taking as an alternative drug	-	1 (2.1%)
2a	Require medical treatment - Change dose or interval of suspected drug	1 (1.4%)	1 (2.1%)
	- No changes	-	1 (2.1%)
	Not require medical treatment - Change dose or interval of suspected drug	18 (25.4)	10 (21.3%)
	- No changes	1 (1.4%)	-
2b	Require medical treatment - Discontinuation of suspected drug & taking as an alternative drug	-	1 (2.1%)
	Not require medical treatment - Change dose or interval of suspected drug	-	1 (2.1%)
	- Discontinuation of suspected drug & taking as an alternative drug	1 (1.4%)	5 (10.6%)
2c	Not require medical treatment - Change dose or interval of suspected drug	1 (1.4%)	2 (4.3%)
	- Discontinuation of suspected drug	6 (8.5%)	5 (10.6%)
	- Discontinuation of suspected drug & taking as an alternative drug	3 (4.2%)	2 (4.3%)

Table 25 The management of ADEs (cont.).

Severity	Management	ADEs 118 events	
		Control group N = 71	**Intervention group N = 47**
3	Require medical treatment		
	- Change dose or interval of suspected drug	1 (1.4%)	2 (4.3%)
	- No changes	3 (4.2%)	3 (6.4%)
	- Discontinuation of suspected drug	2 (2.8%)	1 (2.1%)
	- Discontinuation of suspected drug & taking as an alternative drug	2 (2.8%)	-
	Not require medical treatment		
	- Change dose or interval of suspected drug	-	1 (2.1%)
4	Require medical treatment		
	- Discontinuation of suspected drug & taking an alternative drug	1 (1.4%)	-

1. Outcome after ADEs

Patient clinical outcome of total 118 ADEs were monitored and were assessed at the end of the study presented in Figure 7. The majority of ADEs in the control group was able to be completely recovered with treatment or suspected drug change (35.2%). Nineteen ADEs (26.8%) occurring in 17 patients were not yet recovered, most of them involved skin hyperpigmentation (14.1%). There were approximately 18% of ADEs recovered with sequelae and 1% was able to completely recovered without treatment or change in medical therapy. Moreover, 13 ADEs (18.3%) in 12 patients were not able to be assessed because the follow up visit was over the study period.

In the intervention group, the majority of ADEs (27.7%) were not able to be recovered at the end of the study period. Majority involved skin hyperpigmentation (14.1%) as same as the control group. Approximately 25% of ADEs recovered with sequelae, 17% were able to be completely recovered with treatment or suspected drug change equal which were able to be completely recover without treatment or change in

medical therapy. Six ADEs in 5 patients were not assessed because the follow up visit was over the study period. One patient who was referred to dermatology clinic was concluded that she required medical treatment.

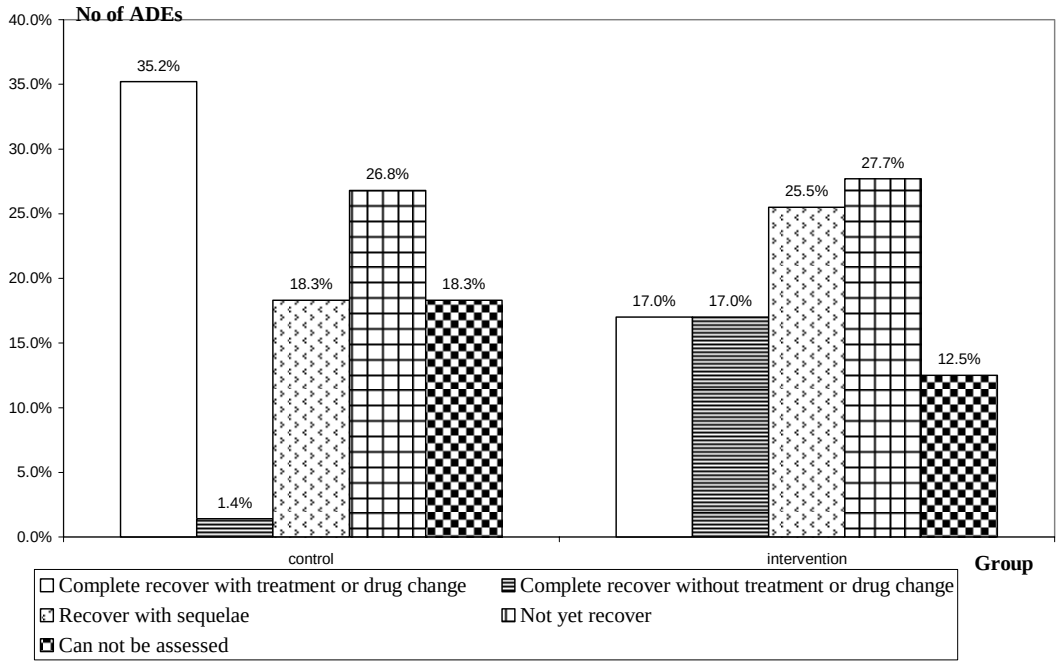

Figure 7 Outcome of ADE occurrences.

Characteristics of pharmacist's intervention

1. Number of pharmacist's intervention in each patient

In total 72 patients in intervention group, there were 28 patients that the research pharmacist performed 42 interventions to physicians during the study. The number of the research pharmacist's interventions ranged from 1-4 interventions per patient as shown in Table 26. Approximately 61% of 28 patients were provided one intervention per one patient.

Table 26 The number of pharmacist's interventions performed per patient.

No of intervention/ patient	No of patient	Percent
1	17	60.7
2	9	32.1
3	1	3.6
4	1	3.6
Total	**28**	**100.0**

2. Classification of Pharmacist's intervention and physician's acceptance

Forty two the research pharmacist's interventions were performed in 28 patients during the study. The interventions involved in managing ME problems, preventing ADEs by detecting potADEs, resolving home-medication problem, suggestion additional monitoring or other therapy (Table 27). Physicians accepted 31 interventions (73.7%), partially accepted 7 interventions (16.7%) and rejected 4 interventions (9.6%). The three most common interventions involved in addition of drug (10 interventions; 23.8%), changing dose (9 interventions; 16.7%), and clarification or correction of order (7 interventions; 16.7%), respectively.

Table 27 Classification of pharmacist's intervention and physician acceptance.

Classification of pharmacist's intervention	**Result of intervention**		
	Accepted (%)	**Partially accepted (%)**	**Rejected (%)**
Addition of drugs	7 (16.7)	3 (7.1)	-
Changing dose	6 (14.1)	2 (4.8)	1 (2.4)
Clarification or correction of order	7 (16.7)	-	-
Cessation of drugs	3 (7.1)	1 (2.4)	1 (2.4)
Additional monitoring or other therapy	3 (7.1)	1 (2.4)	-
Recommendation of alternative drug therapy	2 (4.8)	-	-
Changing amount of drug	1 (2.4)	-	1 (2.4)
Changing frequency of administration	1 (2.4)	-	1 (2.4)
Changing time of administration	1 (2.4)	-	-
Total (n= 42)	**31 (73.7)**	**7 (16.7)**	**4 (9.6)**

Detail of the research pharmacist's intervention about addition of drugs was involved in 10 instances. The addition of drugs for 4 cases of untreated condition (case no. 16, 18, 23 and 28 in 28 patients with 42 interventions that were shown in Appendix I) were accepted. Another was partially accepted (case no. 20) which involved in suggestion of drugs for the resolution of dyspepsia. Physician did not prescribe at the time of doing intervention; however, at the next visit, when the symptom was revealed, the drugs were prescribed to prevent/ resolve the symptom. The addition of drugs for resolution of ADEs was accepted in 3 cases (case no. 8, 10, 27). One case (case no. 7) was partially accepted which involved in suggestion of domperidone to reduce vomiting symptom but still continued SSZ which caused ADE. Physician prescribed domperidone but prescribed other DMARDs in stead of SSZ.

Addition of drug for preventing potADE occurred in case no. 6 in Appendix I and this intervention was partially accepted.

Interventions for improper dosage were performed in 5 cases with ADEs, 3 of 5 were accepted (case no. 20, 27 and 28), one case (case no. 11) was partially accepted and the other case (case no. 21) was rejected. Partially accepted intervention involved in titrating down prednisolone dosage in patient who experienced steroid acne to prevent steroid dependence. At that time of doing intervention, prednisolone was not titrated to low dose but this was done at the next visit. A rejected intervention was the suggestion of continuing MTX dose and also counseling the right dosage to the patient who experienced ADE from poor compliance. Physician held on MTX because the patient had infected wound at that time.

Seven interventions of clarification or correction of order were all accepted. All of them were prescribing error. Four cases (case no. 14, 17, 19 and 26) involved in transcribing process between medication order sheets and prescriptions. Two cases (case no. 1 and 3) were errors with re-medication process in medication order sheet. Another case (case no. 9) was error with printed order by computer on line system.

Three interventions of cessation of drugs were accepted. These problems were unnecessary drug use (case no. 11), 2 potADEs from duplication of drug therapy (case no. 12) and dosage too high in renal impairment patient (case no. 23). The partially accepted interventions in ADE problem was suggest on to hold MTX and nimesulide because of increasing SGPT. Physician held on MTX but decreased nimesulide dose (case no.12). A rejected intervention was duplication of calcium channel blockers (case no. 13). Physician gave the reason that this problem should be resolved at hypertension clinic.

Three accepted interventions of additional monitoring or other therapy involved in 2 untreated indications (case no. 11 and no. 15) and the other (case no. 2) related to potADE requiring additional monitoring. A partially accepted intervention (case no. 5) was suggestion on additional monitoring in palpitation symptom that physician decided to send the patient to cardiologist at next visit.

The other five accepted intervention were recommendation of alternative drug therapy (case no. 1, and no. 4), changing amount of drug (case no. 2), changing frequency of administration (case no. 28) and changing time of administration (case no. 6). Lastly, the two rejected interventions were suggestions on increasing amount of drug for co-morbidity (case no. 25) and addition of drug for untreated indication (case no. 28). Case no.25 had not enough antihypertensive drugs until appointment time at hypertension clinic. Physician did not prescribe it at that time and gave the reason that the patient had appointment time with hypertension clinic at next 3 days. Case no. 28, patient received steroid dose for p.r.n. (as-needed) but she took it every day thus there was not enough drug until the next visit. Research pharmacist suggested physician to increase the amount of drug for every day but physician did not accept by giving the result that patient had steroid dependence.

Intervention for managing ADEs and outcome

Ten ADEs were resolved by the research pharmacist's interventions during the study. Among these ADEs 10 interventions to physicians for 9 patients and another one intervention to patient. These were GI discomfort (case no. 7, 8, 10 and 27), anorexia (case no. 20, 21), hyperpigmentaion (case no. 27, 28), steroid acne (case no. 11) and increased LFT (case no. 12).

Of all 10 ADEs that were managed by the research pharmacist's interventions to physicians were accepted 9 events and 1 event was rejected. The details are also shown in Appendix I. The rejected intervention involved in noncompliance with incorrect administration. The patient took drug overdose and she experienced anorexia. The research pharmacist suggested to continue the drug and counseled patient to take right dosage. Physician quitted the suspected drug (MTX) because of patient's skin infection.

Intervention for managing potential ADEs (potADEs) and outcome

Eleven potADEs were prevented by the research pharmacist. Nine interventions suggested to physicians and 2 interventions to patients. PotADEs comprised of GI discomfort (case no. 11, 12, 19 and 26), nephrotoxicity (case no. 2

and 23), neutropenia (case no. 14), steroid induced osteoporosis (case no. 6), hypotension (case no.13), and ophthalmic drug effect which resulted from patient missed to check-up with ophthalmologist for early detection of eye maculopathy from hydrochloroquine**.**

Of all 9 potADEs that were managed by the research pharmacist's interventions to physicians, were accepted by 8 events and was rejected by one event. The details are shown in Appendix I. The rejected intervention involved in duplication of drug therapy. Physician gave the reason that it was non-serious problem resulting from other clinic and should be managed by former prescribed physician.

Managing with non-compliance

Although the aims of the present study were not to determine non-compliance problems, 21 patients with non compliance of which not only affected ADEs but also affected medication therapy were detected and determined. Fours types of patient's non-compliance are presented in Table 28.

Table 28 Types of patient's non-compliance.

Type	Number (%)
• Incorrect administration	14 (66.7)
• Refuse to take medication	4 (19.0)
• Delay of follow up	2 (9.5)
• Forget to take doses	1 (4.8)
Total	**21 (100.0)**

Four patients with non-compliance problems were resolved by interventions to physicians that are shown in Appendix I (case no. 2, 6, 14, 21). Moreover, 17 patients were counseled and educated by the research pharmacist.

Incorrect administration problem was found in 14 patients who 3 cases of them were resolved by intervention to physicians (case no. 2, 6, 21) and other 11 patients were intervened by the research pharmacist. Eight from 11 patients did not read drug labels at the present date. They took medicine as the first received dose that

affected to over or under dose. Other one from 11 patients had problem with complicated drug label. Her problem was step-up SSZ regimen which one tablet once daily at 1st week, then one tablet twice daily and one tablet t.i.d. for continuous dose, but she took right dose at 1st week , took one tablet twice daily for 3 days at 2nd week. The research pharmacist resolved by counseled with the use of calendar bookmark for patient's right dose taking between step-up regimen periods. The other case had experience of steroid ADEs, he took medicine under dose that caused uncontrolled inflammatory condition. And last case, patient experienced ADEs (increased SCr) from NSAIDs overdose because she received piroxicam 20 mg (tablet form) instead of 10 mg (capsule form) for control pain. Unfortunately she never knew that also the two different strength form and different preparation are same drug, she took new received drug (piroxicam 20 mg tablet) and old received drug which still remained at home (piroxicam 10 mg capsule) together. The research pharmacist notified at medication chart to counsel her whenever the dose or any drug preparation was changed.

Refuse to take medication problem was found in 4 patients from 4 different causes. First case, patient quitted all medicine because of palpitation occurring until the appointment visit. Palpitation sign still remained and RA condition was worsened. The research pharmacist educated the patient that if any adverse effect occurred she should stop and should not delay to bring the medicine to consult with the doctor. Second, patient denied calcium tablet receiving because she mistook that calcium might cause hypercalcemia. Third, patient had previous maculopathy from HCQ. When the drug was re-prescribed, she refused to take it. Of both cases, the research pharmacist counseled and educated about importance of continuous taking medicine, not stop medicine before consulting with the doctor. Fourth, patient had been problem with glucosamine capsule dosage form at previous visit, thus physician changed to sachet dosage form. He complained that it too expansive to pay for medicine which was original trade name. the research pharmacist consulted physician before advised patient to buy the other trade name which had lower price at drug store.

Two delay of follow up problems, one was resolved by intervention to physician (case no. 2) and other case with potADE was intervened to patient involved

in she took HCQ but missed annual eye examination for prevention early eye maculopathy. The research pharmacist educated her for the importance of it.

Last non-compliance problem was forget to take PPI dose for reduce GI discomfort from NSAIDs. Patient often forgot to take medicine before meals and she did not know whether to take the drug before or after meals as soon as remember. The research pharmacist counseled and checked remaining medicine at later visit.

CHAPTER V
DISCUSSION

Overall, 142 participants completed the study. There were assigned into the control group 70 patients and the intervention group 72 patients. Majority of both groups were female and the average age was over 50 years. This was the general hemographic of RA population which is two to three times more prevalent in women than in men and usually presenting in the fifth or sixth decade of age (32). More than 50% of both groups were educated lower than secondary school. These suggested that giving drug information by only labeling or leaflets might not be adequate for them. The education and counseling about RA drugs, disease, observable some ADEs by themselves and the advice on compliance aids such as special medication container, calendar to remind medicine intake should be provided in the future.

Smoking and alcohol consumption were found in small fraction of patients because majority of them were females, who did not smoke and/or drink alcohol. Patients were mainly diagnosed of RA for longer than a year. Approximately 50% had suffered from only RA disease.

Hypertension was the most common disease that found concomitant in both groups. Not surprisingly, almost 100% of patients received DMARDs for treatment and the three combination therapy consisted of DMARDs, NSAIDs, and corticosteroids was the majority of the treatment. Resulting from multiple co-morbid conditions in both groups, polypharmacy (i.e., no. of prescribed drugs the present study were approximately 7-8 items) was common among patients in this study. Thus, there were higher than 50% of experienced patients with history of ADEs.

Consequently, the patients in both groups had several patient-related risk factors of ADEs including gender (female higher than male), middle ages, polypharmacy, history of ADEs and concurrent diseases (112), participant balance on important background characteristics between both groups was good. Most characteristics of control and intervention group in the present study including age,

gender, education, social history, duration of RA, History of ADEs, concurrent disease demonstrated no statistically significant differences except the number prescribed medications. Although, the difference of prescribed medication items may result in the difference of occurring ADEs, some studies found that prescribing medication was controversial risk factor (85, 113-119).

In this study, the incidence of patients who experienced ADEs in the control group was highly increased about 8.6% whereas the incidence in the intervention group was slightly increased about 2.8% at the 2nd visit. Although, the increased incidence of ADEs in each group was not statistically significant; surprisingly, the incidence of ADEs in control group were higher than in the intervention group at the 2nd visit (p value = 0.06). This study did not present the incidence of pADEs because each patient had opportunity to have pADE or non pADE in the same visit. The rate of all ADEs and pADEs were increased in both groups after 2 visits. When calculating pADE rate per 100 patients, it was found that the rate in the control group were higher than in the intervention group at the 2nd visit (p value = 0.08). Despite the results showed that the difference of incidence of pADEs including the rate per 100 patients between control group and intervention group at the 2nd visit were not statistically significant, the pharmacist's interventions seem to have some impact on ADE reduction in outpatients with RA. These might be due to small sample size which limited power of detection. Other explanations of these results were the nature of ADEs in RA patient. Some ADEs were detected by patient's report, for example GI discomfort, anorexia. At the 1st visit, with any reason for example some patients did not know the side effect of the prescribed medications, some ignored to report when they had mild symptom. When coming to the 2nd visit, they were educated by the research pharmacist during the 1st visit and/or they had severe symptom, they then reported in the 2nd visit. Therefore, ADEs might be increasingly detected. Some particular ADEs were long term effects and also required laboratory test or other investigations to confirm. For example, Bull's eye maculopathy required eye examination or alopecia required dermatologist's diagnosis, and these ADEs may be

possibly evaluated in the 2nd visit in stead of the 1st visit. It might be these results; ADEs rate was higher in the 2nd visit than the 1st visit.

Systematic review of the incidence and characteristics of pADEs in ambulatory care presented that ADEs in ambulatory care are common, with 21% being preventable (77). A meta-analysis and systematic review suggested that pharmacist-led intervention based on chart review report higher ADE rate among inpatients (120). And many studies have proved that ADEs were reduced in hospitalized patients by pharmacists (121). Systematic review of the roles and impacts of pharmacists in ambulatory settings showed improvement in outcomes for patients with hypertension, hypercholesterolemia, chronic heart failure, and diabetes mellitus (91). Moreover, the role of pharmacist in other chronic disease management had been studied, for instance, in thyroid clinic (122). In Thailand, there are limited studies which estimated role of pharmacist in chronic disease with outpatient (22, 23, 25-29, 123, 124). It was difficult to directly compare the incidence and the rate of ADEs in the present study with previous studies because of discrepancies of ADE's definitions, method of ADE detection, population, sample size and duration of monitoring. Although the direct comparison between the pADE rates in the present study and previous studies are difficult, there were 2 studies with the role of pharmacist intervention were compared in outpatient clinics. One study was studies in outpatient with hypertension (107) and another was established in ambulatory oncology patients (110), respectively. Both studies had common demographic data's participants similar to the present study such as midlife, mostly female and mainly not educated higher than secondary school. It was noted that main education level of both studies was secondary school whereas the present study was primary school. Moreover, there were 3 participants in the present study had no education. Other reasons, the similar of average prescription medications in Murray's study (107) were approximately 8.6 items study was approximately 7.9 items. Chemotherapy agents used in oncology patients had common ADEs related to DMARDs used in RA patients, thus pharmacist participation in Janpraparn's oncology outpatients study (110) at Ramathibodi Hospital was compared with the present study. Murray's data were pooled from 2 RCTs then were stratified into complicated

hypertension subgroup (participants who had other cardiovascular disease co-morbidity) and uncomplicated hypertension subgroup (only hypertension disease). Although, the risk of any events was 34%, the overall mean number of ADEs per uncomplicated hypertension participant at 12 months follow-up period was not significant. These resulted from some ADEs characteristic in uncomplicated hypertension subgroup in Murray's study may be similar to RA participant in the present study. For example, mild ADEs with detected by only patient interview and/ patient ignored to informed. Other reason Murray's study was designed to 12 months follow-up period which clinical pharmacist had time to intervene to physician and educate or counsel patient more than one visit. The results of clinical pharmacist intervention seem to have impact to reduce ADEs in sprite of the difference was not significant. On the other hand, the present study spent only one time to intervene, educate and counsel at the 1st visit, then; ADEs at the 2nd visit were compared. Some patients who were educated ADEs knowledge from clinical pharmacist may informed at the 2nd visit. And last reason, some ADEs at the 1st visit that confirmed by laboratory data or other clinic (such as dermatologic clinic for hair or skin disorder) may concluded these ADEs at the 2nd visit. Therefore, ADEs at the 2nd visit were detected increasingly not only control group but also intervention group. In contrast, the present study showed that the incidence ADEs in intervention group was seem to be lower than in control group ($p = 0.06$ at the 2nd visit vs. $p = 0.2$ at the 1st visit) like as the rates per 100 patients at the 2nd visit ($p = 0.08$ at the 2nd visit vs. $p = 0.29$ at the 1st visit). The explanation of these situation might result from the study period was also too shorten and small sample size to see the impact of pharmacist intervention on prevention of ADEs for RA outpatients significantly.

The majority of pADEs found in the present study was corresponding to other study (104). These involved inappropriate dose, route and frequency of administration for the patient. Although in the present study were classified pADEs based on Schumock and Thornton's criteria, there were 11 events in both groups classified by other reasons. The reasons of adding of these criteria because the suspected drugs were already prescribed together the protecting drugs. For example,

gastro-protective agent was prescribed to prevent gastrointestinal effect, the most common problem from tNSAIDs.

In the present study, 68.6% of ADEs were most frequently caused by DMARDs. Patients using 3 combinations of therapy (12.7% of both groups at the 1st visit and 16.2% at the 2nd visit, respectively) experienced ADEs in higher than others correspond to the four recent systematic-reviews revealed that combination therapy was more effective than monotherapy but resulting in many withdrawals for toxicity (7-10).

The present study classified severity level of ADEs to 7 levels according to Hartwig and colleagues' criteria, several studies did not classify as the present study. As a result, the comparison between the present study and the previous studies was difficult in term of severity level of ADEs. It was founded that gastro-intestinal system and skin and appendages were two main body systems affected by ADEs. Fortunately, the severity levels were categorized mainly in level 1, level 2a and level 2b. The suspected drug could be justified by changing dosage or adding alternative drug to control pain and slow progression of RA. The highest severity level was classified as level 4, the patient in control group had to be admitted due to hypoglycemia from antidiabetic drug. Moreover, majority of ADEs that patients experienced in this study were related to drugs that they received. For example, Hyperpigmentation and eye maculopathy resulted from antimalarial DMARDs (CQ, HCQ). Hematuria and proteinuria were found in gold injection DMARDs regimen. Nausea, vomiting or other GI disorders were common found in SSZ or tNSAIDs regimen. In addition to, alopecia, fatigue, blood disorders were common in patient who received MTX, CYP that were consistent with oncology outpatients who had MTX, CYP in their regimen (110). They might suggested that common drugs used in RA had potential toxicity and required careful monitoring as regimens used in cancer.

Clinical outcome after patients developed ADEs were re-monitored and were assessed by interviewing patients at the next visit, medical record review or telephone calling after the end of the data collection period. Over 50% of patients in both groups completely recovered from ADEs or recovered with squelae.

Approximately 30% in both groups were not yet recovered because they were in uncontrolled status and the physicians did not stop suspected drugs. The outcome of 12 patients in control group and 5 patients in intervention group were not evaluated because the follow up visits were over the study period. Most of them involved in hyperpigmentation which required long time period to assess patient outcome. Accordingly, the study period should be longer than 4 month period in further study.

Classification of pharmacist's intervention provided by research pharmacist was dependent on type of identified problems, in which sometimes might be varied according to individual patient's condition. The research pharmacist made recommendation commonly most addition of drugs to prevent/resolve ADEs. Clarification or correction of order was accepted 100% for resolving prescribing errors. According to 4 rejected interventions, 2 cases involved with other outpatient clinics but were detected in RA outpatient clinic in the present study. Physicians justified that they were not critical problems and should be resolve at the non RA clinic. In addition, not only drugs used in RA but also drugs for concurrent diseases frequently affected treatment or organ function. Therefore, clinical pharmacist should be reminded and suggested necessary laboratory, such as CBC, renal function, liver function for ADE monitoring. Although, physicians in this study are rheumatologists or rheumatology fellows, the average number of patient on AIR unit was rather high. Physicians were able to spend approximately 5-10 minutes per patient to treat and prescribed medication. As a result, some ADEs that were detected by patient interview such as constipation, anorexia, insomnia were not detected. If clinical pharmacist provided education and counseling to patients, it would be prevented and resolved ADEs and increased good compliance in order to help patients get most benefit from medication.

Overall research pharmacist's interventions were absolutely accepted 73.7%, partially accepted 16.7% and were not accepted 9.6%. Closely, Alttavela et al. (125) showed that acceptance rate on primary care unit was 69.7%. As a result, most problems were resolved with positive clinical outcome after clinical pharmacist's interventions. Approximately 90% of research pharmacist's intervention with

prevented/ resolved ADEs and reminded potADEs were good acceptance. This support role of clinical pharmacist in prevented/resolved ADEs on RA outpatients.

In the present study, 10 potADEs were found 12.5% (total 72 patients in intervention group) and 9 interventions were reminded to physicians and 2 interventions to patients. PotADEs in the present study were lower than in oncology outpatient study (110) that were found 13.2%. of 16 interventions (total 121 intervened patient). The possible reason was the research pharmacist in the present study spent about 15 minutes per patient to detect ADEs, potADEs or other problems in outpatient clinic. On the other hand; oncology outpatient clinic, research pharmacist was able to spent more time to detect and prevent any potential problems while patients were administrated chemotherapy.

Identification and correction of MEs can reduce harm to patients. It was another important part of pharmacist intervention to prevent ADEs. Prescribing error occurred in 8 patients from 72 patients (11.1%) in intervention group. Prescribing errors in this study mainly resulted from handwriting and re-medication by manual transcribing. The preprinted order by computer on-line prevented error from handwriting and transcribing. However, computer on-line delivery still found prescribing errors related to mild skill user. Some strategies to reduce this problem were training new staff before using this program and reviewing skill technique at least once a year.

Not only system errors with prescribing errors but also dispensing errors, it was found 2 patients from 72 patients at previous visit (2.8%) involving in unavailable NSAIDs dosage form in Thailand now. One case, physician was not informed this problem at previous visit and did not prescribe alternative NSAIDs to control patient's pain. Another received short acting dosage form instead of long acting form, fortunately it did not control pain during night time. These results confirmed that pharmacist review chart and interview patient had benefit for resolving error. The present study found that dispensing errors which lower than study in the intensive care unit (86). The possible reason of the present study did not designed to re-check labels after patient received medicine from dispensing department. Dispensing errors that

were detected in the present study were errors from previous visit time. Another reason was prescribing ordered in the intensive care might complicate than outpatient clinic.

Although the present study was not designed to detect to noncompliance, there were 21 of 72 patients (29.2%) in intervention group had noncompliance. Four problems were resolved by research pharmacist who intervened to physician. Approximately 80% of non-compliance problems were found by the research pharmacist revised the cause of problems and counsel to patients. The main cause of the noncompliance related to lack of knowledge and ignored importance of reading the labels before taking drugs which might change according to prescribing order in each visit. Moreover, approximately 50% of participants in the present study were educated in primary school. Therefore, the skills of read, learn understanding about necessary drug information for patient were interesting to evaluate in the future. Some patients refused to take medication because they did not understand they refused to take DMARDs because they had previous ADEs with DMARDs. These confirmed that the major roles of clinical pharmacist in RA patients were not limited in the part of prevent ADEs, clinical pharmacist should play roles in other parts such as managing noncompliance to encourage treatment.

Although the present study was designed as a prospective controlled study and could confirm of the probability and preventability of ADEs by physicians, the present study still had several limitations as follows:

1. The sample size was calculated using the percentage of reported pADE from the preliminary study. At least 189 patients should be sampled for 80% of power of test. Unfortunately, only 153 patients were enrolled and only 142 participants could completed the study that affected to decrease the power of 1-β from 80% to 67%. The power to measure the effect of clinical pharmacist on the incidence and the rate of pADEs in outpatient with RA was limited.

2. Four months for data collection periods and only 2 visit times to follow up were hardly to see the end outcome after managing ADEs and some ADE was not be able to confirm during the time of study period, for example chloroquine induced

eye maculopathy which required eye examination. The appointment time at ophthalmologist for a period longer than the time of study period.

3. There were 4 clinics per week for RA outpatient servicing and 3 hours per clinic day therefore research pharmacist needed to spend approximately 15 minutes per patient to detect ADEs before they met physicians. The study was designed at least 2 visit to follow up per patient. In addition to, the patients in the intervention group must return to meet the research pharmacist again after met physicians. Therefore, some participants in the study were not randomized at each appointment time resulting from limited time at the outpatient clinic.

4. The place which the research pharmacists met patients located nearby RA outpatient clinics. It is convenient for the research pharmacist to consult physicians and check prescription for preventing potADEs from ordering error before patient took the prescriptions to dispensing pharmacy department. However, it was settled at the manifold purpose court which affected from any disturbance. One might argue that the private area of OPD would be better to make an appointment and counsel the patients.

CHAPTER VI
CONCLUSION

The present study was performed with a prospective controlled design in order to evaluate the effect of clinical pharmacist's participation on detection and management of ADEs and potential ADEs (potADEs), checking prescribing error and providing education and counseling in RA outpatient, who were appointed to medical clinics at Ramathibodi Hospital during 30th April to 30th August 2007, 153 patients were recruited, 142 patients completed the study. Participants were randomly divided into the intervention group (n = 72) and the control group (n = 70). The primary outcome was the reduction in rate of preventable ADEs (pADEs) by comparison patients receiving stand care including pharmacist's participation with patients receiving only standard care. Classification of the research pharmacist's intervention and percentage of physician's acceptance were the secondary outcomes. The results of the study were concluded as follows:

1. Demographic data between the intervention group and the control group are not statistically significant except for the mean number of prescribed medications in intervention group was higher than the control group.

2. The incidence of ADE was compared between the control group and the intervention group, at the 2nd visit the difference was 15.1% (p = 0.06) whereas the 1st visit was 9.3% (p = 0.2).

3. The difference of the rates per 100 patients between the intervention group and the control group at the 2nd visit was 10.7% (p = 0.08) whereas at the 1st visit was 6.2% (p = 0.29).

4. In total 72 patients in intervention group, there were 28 patients that the research pharmacist performed 42 interventions to physician during the study period. Approximately 61% were 1:1 intervention per patient.

5. The forty two pharmacist's interventions were classified as 9 categories. Of these, 73.7% were accepted, 16.7% were partially accepted and 9.6% were rejected.

6. The three most common interventions involved in addition of drug (10 interventions; 23.8%), changing dose (9 interventions; 16.7%), and clarification or correction of order (7 interventions; 16.7%), respectively. The 3 categories that were accepted 100% by physicians included clarification or correction of order, recommendation of alternative drug therapy and changing time of administration.

7. Ten from 42 interventions related to ADEs and 90% of ADEs inervention were resolved by the research pharmacist's interventions to physicians during the study period.

8. Eleven potADEs were intervened for preventing of ADEs and 88.9% were physicians' acceptations.

9. Twenty one patients with noncompliance problem were found, 4 cases were resolved by the research pharmacist intervened to physicians, others were managed by counseling to patients. Incorrect administration was the most non-compliance problems with approximately 67% of all non-compliance problems.

The finding of the present study demonstrated that clinical pharmacist can play a major role in ambulatory RA clinic in the part of identifying, preventing and resolving ADEs and notifying system errors involving in prescribing and/ or dispensing process. Reminding, suggestion to physicians and providing education and counseling to the patients were the strong strategies which clinical pharmacist should continue performing for the safety and resolving any problems related to drugs.

Furthermore, the number of sample size and the too short study period limited to evaluate the effect of clinical pharmacist's participation on this study, future studies should be conducted as multi-center setting and/ or increasing the length of study period. In addition, cost saving resulting from clinical pharmacist participation should be further investigated.

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APPENDICES

APPENDIX A

แบบบันทึกข้อมูลผู้ป่วย (Patient's Profile) (Form I)

Date visit	F/U

Code: CI …….. . CO…….. I…….

Initial……HN…… [1] Sex O F O M
Date of birth……/……/…….[2] Age…….yr Wt…….....kg. Ht……cm.
Address……Tel……
Clinic O Gen med (Monday) O Allergy and arthritis (Tuesday)
O Gen med (Wednesday) O Arthritis (Thursday)

---

[3] Education O primary school O high school O college O post-graduate
O others…….
[4] History of ADEs O not known O none O known (record in the following table)

Drugs	Symptom	Resolve

[5] Current Disease
1…… . date…….
2…… ..date…….
3…….....date…….
4…….....date…….
5…….....date…….
6……date ……
7……date ……
[6] Alcohol..... O None O Current .....bottle/day , duration……yr
O Past, but give up drinking.....yr
[7] Cigarette O None O Current ……..roll/day, duration……yr
O Past, but give up smoking …….yr
[8] Non-prescription drug O No O Yes .....
……...
[9] Duration of RA……..
[10] Past of illness

Date	**Events**

Medication Profile Data (Form II)

Visit No O 1st O 2nd Date……/……/……
Physician……

Drug & regimen	Indication	Start	Remark

[1] suspected ADEs symptom O No O Yes…….
……

[2] DTPs

Problems	Assessment	Follow up

Laboratory Data (Form III)

Hematology

Lab test	Normal value						
Hb g/dL	13-18						
Hct %	40-54						
MCV fL	80-99						
MCH pg	27-31						
MCHC g/dL	33-37						
WBC x 10^3 cells/μL	4-10						
Neu %	40-74						
Lym %	19-48						
Mono %	3-9						
Eos %	0-7						
Baso %	0-2						
RBC x 10^6 cells//μL	4.5-6						
Anisocytosis							
Poikilocytosis							
Microcytosis							
Macrocytosis							
Hypochromia							
Polychromasia							
Plt x 10^3 cells//μL	140-450						
Plt smear							
RDW %	11.5-14.5						
ESR mm/hr	1-10 (m) 4-20 (f)						
RF							

Blood chemistry

Lab test	Normal value						
BUN mg/dL	7-17						
SCr mg/dL	0.6-1.2						
Na^+ mmol/L	135-147						
K^+ mmol/L	3.6-4.6						
Cl^- mmol/L	101-111						
Ca^{2+} mg/dL	8.8-10.0						
T. bili mg/dL	0.2-1.2						
D. bili mg/dL	0.1-0.5						
SGOT μ/L	5-40						
SGPT μ/L	5-40						
Alk Phos μ/L	40-105						
GGT μ /L	7-50						
TG mg/dL	30-90						
Chol mg/dL	$\leq$ 200						
LDL mg/dL	< 160						
HDL mg/dL	40-60						
Uric acid mg/dL	4.4-8.1						

Urinalysis

Lab test	Normal value						
Color/Transparency							
Sp. gr.							
pH							
Blood							
WBC/HPF							
RBC/HPF							
Cast Hyaline/LPF Granular/LPF							
Epi.Sq./HPF							

Others

Lab test	Normal value						

Eye vision

Date	Anti malarial drugs	Dose	Start	Report

APPENDIX B

เอกสารชี้แจงข้อมูล/คำแนะนำแก่ผู้เข้าร่วมการวิจัย
(Patient/Participant Information Sheet)

ชื่อโครงการ บทบาทเภสัชกรคลินิกในการป้องกันการเกิดเหตุการณ์ไม่พึงประสงค์จากการใช้ยาชนิดที่ป้องกันได้ของผู้ป่วยนอกโรคข้ออักเสบรูมาตอยด์ ณ โรงพยาบาลรามาธิบดี

ชื่อผู้วิจัย พญ. ทิชา ลิ้มสุวรรณ, ผศ. ดร. ปราโมทย์ ตระกูลเพียรกิจ, รศ. ดร. สุวัฒนา จุฬาวัฒนทล, ภญ. เอื้อมพร ศิริเขตกร, ภญ. สุธาทิพย์ สมจริต, ศ. พญ. สุชีลา จันทร์วิทยานุชิต

สถานที่วิจัย คลินิกโรคข้อ, คลินิกโรคภูมิแพ้, คลินิกอายุรกรรมทั่วไป หน่วยโรคภูมิแพ้อิมมูโนวิทยาและโรคข้อ ภาควิชาอายุรศาสตร์ คณะแพทยศาสตร์ โรงพยาบาลรามาธิบดี

บุคคลและวิธีการติดต่อเมื่อมีเหตุฉุกเฉินหรือความผิดปกติที่เกี่ยวข้องกับการวิจัย

1. ศ. พญ. สุชีลา จันทร์วิทยานุชิต
   สถานที่ที่ติดต่อได้: หน่วยโรคภูมิแพ้ อิมมูโนวิทยาและโรคข้อ ภาควิชาอายุรศาสตร์ คณะแพทยศาสตร์ โรงพยาบาลรามาธิบดี โทร 02-2011477
2. พญ. ทิชา ลิ้มสุวรรณ
   สถานที่ที่ติดต่อได้: หน่วยโรคภูมิแพ้ อิมมูโนวิทยาและโรคข้อ ภาควิชาอายุรศาสตร์ คณะแพทยศาสตร์ โรงพยาบาลรามาธิบดี โทร 02-2011477

ผู้สนับสนุนการวิจัย บัณฑิตวิทยาลัย มหาวิทยาลัยมหิดล

ความเป็นมาของโครงการ

โรคข้ออักเสบรูมาตอยด์ เป็นโรคที่ทำให้เกิดความเจ็บปวดเรื้อรัง มีการทำลายของข้อ เกิดปัญหาในการทำงานและทำกิจวัตรประจำวัน ซึ่งความรุนแรงของโรคเป็นมากสลับเป็นน้อยและขณะนี้ยังเป็นโรคที่รักษาไม่หายขาด การรักษาในปัจจุบันใช้หลายวิธีร่วมกันประกอบด้วย การให้ยาร่วมกันระหว่างยาต้านอักเสบชนิดไม่ใช่สเตอรอยด์ ร่วมกับยาต้านรูมาติสซั่มที่ปรับเปลี่ยนการดำเนินโรค ที่ช่วยปรับเปลี่ยนและชะลอการดำเนินของโรค และ/หรือการให้สเตอรอยด์หรือยาอื่นๆ

ร่วมด้วย ซึ่งยาเหล่านี้แม้จะมีประสิทธิภาพในการควบคุมการดำเนินไปของโรคแต่ก็จำเป็นต้องเฝ้าระวังและติดตามเหตุการณ์ไม่พึงประสงค์จากการใช้ยาหลายประการ เนื่องจากยาที่ใช้ในโรคข้ออักเสบรูมาตอยด์ มีโอกาสเกิดเหตุการณ์ไม่พึงประสงค์ได้สูง รวมทั้งผู้ป่วยส่วนใหญ่อยู่ในวัยกลางคนถึงสูงอายุ และเนื่องจากโรคข้ออักเสบรูมาตอยด์เป็นโรคเรื้อรัง มีโอกาสโรคกำเริบได้ซ้ำ ดังนั้นผู้ป่วยมีโอกาสที่จะซื้อยาอื่นหรือผลิตภัณฑ์อื่นมาใช้เองนอกเหนือจากที่ได้รับจากโรงพยาบาล การที่เภสัชกรซึ่งเป็นผู้เชี่ยวชาญทางยามีส่วนร่วมในการดูแลผู้ป่วย น่าจะช่วยแก้ไข ป้องกัน และลดระดับความรุนแรงของอาการไม่พึงประสงค์ได้ รวมทั้งป้องกันการเข้ารักษาตัวในโรงพยาบาลเนื่องจากเหตุการณ์ไม่พึงประสงค์จากการใช้ยา รวมทั้งมีบทบาทในการให้ความรู้และให้คำปรึกษาแนะนำแก่ผู้ป่วยโดยเน้นเกี่ยวกับข้อบ่งใช้ วิธีใช้ยา และอาการข้างเคียง ตลอดจนการเฝ้าระวังอาการข้างเคียงของยาที่ได้รับ โดยเน้นที่ยาต้านอักเสบชนิดไม่ใช่ สเตอรอยด์และยาต้านรูมาติสซั่มที่ปรับเปลี่ยนการดำเนินโรค ซึ่งเป็นยาที่ผู้ป่วยส่วนใหญ่ได้รับ เมื่อดำเนินการร่วมกับทีมแพทย์และพยาบาลก็จะก่อให้เกิดประสิทธิภาพและความปลอดภัยของการใช้ยาในผู้ป่วยนอกโรคข้ออักเสบรูมาตอยด์มากยิ่งขึ้น

วัตถุประสงค์

1. เพื่อลดเหตุการณ์ไม่พึงประสงค์จากยาชนิดที่ป้องกันได้ (preventable ADEs) และป้องกันเหตุการณ์ไม่พึงประสงค์จากการใช้ยาที่คาดว่าจะเกิดขึ้น (potential ADEs) ในผู้ป่วยนอกโรคข้ออักเสบรูมาตอยด์ รพ. รามาธิบดี
2. เพื่อประเมินการยอมรับของแพทย์ที่มีต่อบทบาทของเภสัชกรคลินิก ในการให้ข้อเสนอแนะการป้องกัน/แก้ไข ADEs หรือปัญหาที่คาดว่าจะเป็นสาเหตุของการเกิดเหตุการณ์ไม่พึงประสงค์จากการใช้ยาในคลีนิคผู้ป่วยนอกโรคข้ออักเสบรูมาตอยด์ รพ. รามาธิบดี

รายละเอียดที่จะปฏิบัติต่อผู้เข้าร่วมการวิจัย

1. ก่อนผู้ร่วมวิจัยพบแพทย์ ผู้วิจัยสัมภาษณ์รายละเอียดเกี่ยวกับข้อมูลพื้นฐาน ชื่อ อายุ อาชีพ การศึกษา ที่อยู่ที่สามารถติดต่อได้สะดวก อาการของโรค ยาและวิธีการใช้ยาที่ได้รับจากแพทย์ รวมถึงจากแหล่งอื่นๆ (ถ้ามี) ประวัติการแพ้ยา การใช้อาหารเสริม ประวัติการสูบบุหรี่ หรือดื่มอัลกอฮอล์ (ถ้ามี)
2. ประเมินเหตุการณ์ไม่พึงประสงค์จากยา หรือเหตุการณ์ไม่พึงประสงค์จากการใช้ยาที่คาดว่าจะเกิดขึ้น เสนอปัญหาที่คาดว่าจะเกิดจากการใช้ยาและข้อเสนอแนะจากเภสัชกรต่อแพทย์
3. ผู้ร่วมวิจัยพบแพทย์ รับการตรวจจากแพทย์และรับยาที่ห้องจ่ายยาตามขั้นตอนปกติ

4. ผู้ร่วมวิจัยบางราย อาจต้องกลับมาพบผู้วิจัยอีกครั้ง เพื่อให้คำปรึกษาและแนะนำวิธีใช้ยา รวมทั้งการป้องกันและสังเกตเหตุการณ์ไม่พึงประสงค์จากกยาที่ผู้ป่วยได้รับ หลังรับยาจากห้องจ่ายยาแล้ว
5. หากผู้ร่วมวิจัยไม่มารับการตรวจตามนัด ผู้วิจัยจะโทรศัพท์ไปสอบถามอาการเพื่อติดตามผล

ประโยชน์และผลข้างเคียงที่จะเกิดแก่ผู้เข้าร่วมการวิจัย

ประโยชน์ที่คาดว่าจะเกิดจากงานวิจัยนี้ ได้แก่

1. สามารถลดเหตุการณ์ไม่พึงประสงค์จากการใช้ยา และป้องกันเหตุการณ์ไม่พึงประสงค์จากการใช้ยาที่คาดว่าจะเกิดขึ้นในผู้ป่วยโรคข้ออักเสบรูมาตอยด์
2. พัฒนาความรู้เกี่ยวกับการใช้ยาและข้อปฏิบัติตนเพื่อความร่วมมือในการใช้ยาของผู้ป่วย เพื่อสนับสนุนผลการรักษา

ถ้าท่านมีปัญหาข้องใจหรือรู้สึกกังวลใจกับการเข้าร่วมในโครงการวิจัยนี้ ท่านสามารถติดต่อกับประธานกรรมการจริยธรรมการวิจัยในคน สำนักงานวิจัยคณะฯ อาคารวิจัยและสวัสดิการ คณะแพทยศาสตร์โรงพยาบาลรามาธิบดี

หนังสือยินยอมโดยได้รับการบอกกล่าวและเต็มใจ

(Informed Consent Form)

ชื่อโครงการ บทบาทเภสัชกรคลินิกในการป้องกันการเกิดเหตุการณ์ไม่พึงประสงค์จากการใช้ยาชนิดที่ป้องกันได้ ของผู้ป่วยนอกโรคข้ออักเสบรูมาตอยด์ ณ โรงพยาบาลรามาธิบดี

ชื่อผู้วิจัย พญ. ทิชา ลิ้มสุวรรณ, ผศ. ดร. ปราโมทย์ ตระกูลเพียรกิจ, รศ. ดร. สุวัฒนา จุฬาวัฒนทล, ภญ. เอื้อมพร ศิริเขตกร, ภญ. สุธาทิพย์ สมจริต, ศ. พญ. สุชีลา จันทร์วิทยานุชิต

*ชื่อผู้เข้าร่วมการวิจัย ----------

อายุ ----------เลขที่เวชระเบียน ----------

คำยินยอมของผู้เข้าร่วมการวิจัย

ข้าพเจ้า นาย/นาง/นางสาว ---------- ได้ทราบรายละเอียดของโครงการวิจัยตลอดจนประโยชน์ และข้อเสี่ยงที่จะเกิดขึ้นต่อข้าพเจ้าจากผู้วิจัยแล้วอย่างชัดเจน ไม่มีสิ่งใดปิดบังซ่อนเร้นและยินยอมให้ทำการวิจัยในโครงการที่มีชื่อข้างต้น และข้าพเจ้ารู้ว่าถ้ามีปัญหาหรือข้อสงสัยเกิดขึ้นข้าพเจ้าสามารถสอบถามผู้วิจัยได้ และข้าพเจ้าสามารถไม่เข้าร่วมโครงการวิจัยนี้เมื่อใดก็ได้ โดยไม่มีผลกระทบต่อการรักษาที่ข้าพเจ้าพึงได้รับ นอกจากนี้ผู้วิจัยจะเก็บข้อมูลเฉพาะเกี่ยวกับตัวข้าพเจ้าเป็นความลับและจะเปิดเผยได้เฉพาะในรูปที่เป็นสรุปผลการวิจัย การเปิดเผยข้อมูลเกี่ยวกับตัวข้าพเจ้าต่อหน่วยงานต่างๆที่เกี่ยวข้อง กระทำได้เฉพาะกรณีจำเป็นด้วยเหตุผลทางวิชาการเท่านั้น

ลงชื่อ..... (ผู้เข้าร่วมการวิจัย)

..... (พยาน)

..... (พยาน)

วันที่ .....

คำอธิบายของแพทย์หรือผู้วิจัย

ข้าพเจ้าได้อธิบายรายละเอียดของโครงการ ตลอดจนประโยชน์ของการวิจัย รวมทั้งข้อเสี่ยงที่อาจจะเกิดขึ้นแก่ผู้เข้าร่วมการวิจัยทราบแล้วอย่างชัดเจนโดยไม่มีสิ่งใดปิดบังซ่อนเร้น

ลงชื่อ.....(แพทย์หรือผู้วิจัย)

วันที่.....

หมายเหตุ : กรณีผู้เข้าร่วมการวิจัยไม่สามารถอ่านหนังสือได้ ให้ผู้วิจัยอ่านข้อความในหนังสือยินยอมฯ นี้ให้แก่ผู้เข้าร่วมการวิจัยฟังจนเข้าใจดีแล้ว ละให้ผู้เข้าร่วมการวิจัยลงนามหรือพิมพ์ลายนิ้วหัวแม่มือรับทราบในการให้ความยินยอมดังกล่าวข้างต้นไว้ด้วย

* ผู้เข้าร่วมการวิจัย หมายถึง ผู้ยินยอมตนให้ทำวิจัย

หนังสือยินยอมโดยได้รับการบอกกล่าวและเต็มใจสำหรับผู้เข้าร่วมการวิจัยที่ไม่สามารถแสดงความยินยอมได้ด้วยตนเอง

(Caregiver Informed Consent Form)

ชื่อโครงการ บทบาทเภสัชกรคลินิกในการป้องกันการเกิดเหตุการณ์ไม่พึงประสงค์จากการใช้ยาชนิดที่ป้องกันได้ของผู้ป่วยนอกโรคข้ออักเสบรูมาตอยด์ ณ โรงพยาบาลรามาธิบดี

ชื่อผู้วิจัย พญ. ทิชา ลิ้มสุวรรณ, ผศ. ดร. ปราโมทย์ ตระกูลเพียรกิจ, รศ. ดร. สุวัฒนา จุฬาวัฒนทล, ภญ. เอื้อมพร ศิริเขตกร, ภญ. สุธาทิพย์ สมจริต, ศ. พญ. สุชีลา จันทร์วิทยานุชิต

*ชื่อผู้เข้าร่วมการวิจัย .....

อายุ .....เลขที่เวชระเบียน .....

คำยินยอมของผู้มีอำนาจกระทำการแทนผู้เข้าร่วมการวิจัย

ข้าพเจ้า นาย/นาง/นางสาว ..... ซึ่งเป็นผู้มีอำนาจกระทำการแทนนาย/นาง/นางสาว/ด.ช./ด.ญ. ..... ในฐานะ.....ได้ทราบรายละเอียดของโครงการการวิจัยตลอดจนประโยชน์ และข้อเสี่ยงที่จะเกิดขึ้นต่อผู้เข้าร่วมการวิจัยจากผู้วิจัยแล้วอย่างชัดเจนไม่มีสิ่งใดปิดบังซ่อนเร้นและยินยอมให้ทำการวิจัยในโครงการที่มีชื่อข้างต้น และข้าพเจ้ารู้ว่าถ้ามีปัญหาหรือข้อสงสัยเกิดขึ้นข้าพเจ้าสามารถสอบถามผู้วิจัยได้ และข้าพเจ้าสามารถไม่ให้ผู้เข้าร่วมการวิจัยเข้าร่วมโครงการวิจัยนี้เมื่อใดก็ได้ โดยไม่มีผลกระทบต่อการรักษาที่ผู้เข้าร่วมการวิจัยได้รับ นอกจากนี้ผู้วิจัยจะเก็บข้อมูลเฉพาะเกี่ยวกับตัวผู้เข้าร่วมการวิจัยเป็นความลับและจะเปิดเผยได้เฉพาะในรูปที่เป็นสรุปผลการวิจัย การเปิดเผยข้อมูลเกี่ยวกับตัวผู้เข้าร่วมการวิจัยต่อหน่วยงานต่างๆที่เกี่ยวข้อง กระทำได้เฉพาะกรณีจำเป็นด้วยเหตุผลทางวิชาการเท่านั้น

ลงชื่อ..... (ผู้มีอำนาจกระทำการแทน)

..... (พยาน)

..... (พยาน)

วันที่ .....

คำอธิบายของแพทย์หรือผู้ทำวิจัย

ข้าพเจ้าได้อธิบายรายละเอียดของโครงการ ตลอดจนประโยชน์ของการวิจัย รวมทั้งข้อเสี่ยงที่อาจจะเกิดขึ้นแก่ผู้เข้าร่วมการวิจัยให้ผู้มีอำนาจกระทำการแทนทราบแล้วอย่างชัดเจนโดยไม่มีสิ่งใดปิดบังซ่อนเร้น

ลงชื่อ..... (แพทย์หรือผู้วิจัย)

วันที่.....

---

* ผู้เข้าร่วมการวิจัย หมายถึง ผู้ยินยอมตนให้ทำวิจัย

APPENDIX C

Check list of ADE Form

Initial……HN…….....

Sign & Symptom	Results			
	1st Visit		2nd Visit	
Headache	**O no**	**O yes**	**O no**	**O yes**
Dizziness or lightheadedness	**O no**	**O yes**	**O no**	**O yes**
Alopecia	**O no**	**O yes**	**O no**	**O yes**
Blurred or double vision	**O no**	**O yes**	**O no**	**O yes**
Conjunctivitis	**O no**	**O yes**	**O no**	**O yes**
Metallic taste	**O no**	**O yes**	**O no**	**O yes**
Oral ulcer / mucositis	**O no**	**O yes**	**O no**	**O yes**
Dry mouth	**O no**	**O yes**	**O no**	**O yes**
Nausea / vomiting	**O no**	**O yes**	**O no**	**O yes**
Diarrhea	**O no**	**O yes**	**O no**	**O yes**
Constipation	**O no**	**O yes**	**O no**	**O yes**
Abdominal pain	**O no**	**O yes**	**O no**	**O yes**
Anorexia	**O no**	**O yes**	**O no**	**O yes**
Weight loss	**O no**	**O yes**	**O no**	**O yes**
Palpitation	**O no**	**O yes**	**O no**	**O yes**
Rash / itching	**O no**	**O yes**	**O no**	**O yes**
Photosensitivity	**O no**	**O yes**	**O no**	**O yes**
Dark skin	**O no**	**O yes**	**O no**	**O yes**
Local reaction at injection site	**O no**	**O yes**	**O no**	**O yes**
Pale	**O no**	**O yes**	**O no**	**O yes**
Jaundice	**O no**	**O yes**	**O no**	**O yes**
Lack of energy/ fatigue	**O no**	**O yes**	**O no**	**O yes**
Insomnia	**O no**	**O yes**	**O no**	**O yes**
Edema	**O no**	**O yes**	**O no**	**O yes**
Peripheral neuropathy	**O no**	**O yes**	**O no**	**O yes**
Arthritis	**O no**	**O yes**	**O no**	**O yes**
Hematuria	**O no**	**O yes**	**O no**	**O yes**
Black stool	**O no**	**O yes**	**O no**	**O yes**
Others…….	**O no**	**O yes**	**O no**	**O yes**
Others…….	**O no**	**O yes**	**O no**	**O yes**

Comment……
……
……...

APPENDIX D

แบบประเมินความน่าจะเป็นของเหตุการณ์ไม่พึงประสงค์จากการใช้ยาของ RUCAM

Criteria	Score
1.Time to onset	
Highly suggestive	+3
Suggestive	+2
Compatible	+1
Inconsistent	0
2. Course of the reaction	
Highly suggestive	+3
Suggestive	+2
Compatible	+1
Against the role of the drug	−2
Inconclusive or not available	0
3. Risk factors for drug reaction	
Presence (a = one additional point for every validated risk factor)	+1[a]
Absence	0
4. Concomitant drug(s)	
Time to onset incompatible	0
Time to onset compatible but unknown reaction	−1
Time to onset compatible and known reaction	−2
Role proven	−3
None or no information	0
5. Non drug-related cause(s)	
Ruled out	+2
Possible or not (depending on the nature of reaction)	+1 to −2
Investigated probable	−3
6. Previous information on drug	
Reaction unknown	0
Reaction published but unlabelled	+1
Reaction labelled	+2
7. Response to rechallenge	
Positive	+3
Compatible	+1
Negative	−2
Not available or not interpretable	0
Or plasma concentration of drug known to be toxic	+3
Or validated laboratory test with high specificity, sensitivity and predictive value	
Positive	+3
Negative	−3
Not interpretable or not available	0
Total **(> 8 = Highly probable 6-8 = Probable 3-5 = Possible** **1-2 = Unlikely < 1 = Exclude)**	

APPENDIX E

PHYSICIAN'S OPINION FORM

Initial……HN.……Date…/……/…..

**** ส่วนที่ เภสัชกร กรอกรายละเอียด ****

Suspected drugs	Symptoms	Lab abnormality

**** ส่วนที่ แพทย์ลงผลการประเมิน ****

Finding…….....
…….

1. Suspected drug (ระบุชื่อยา)…… (ระบุอาการ)…….
( ) highly probable ( ) probable ( ) possible ( ) unlikely ( ) exclude (√ หน้าตัวเลือก)
Preventability (สามารถเลือกได้ ≥ 1 ข้อ หรือ ระบุเหตุผลอื่นๆ)
( ) no ( ) yes criteria no…… or ( ) other reasons (please specify) .....
…….

2. Suspected drug (ระบุชื่อยา)…… (ระบุอาการ)……
( ) highly probable ( ) probable ( ) possible ( ) unlikely ( ) exclude (√ หน้าตัวเลือก)
Preventability (สามารถเลือกได้ ≥ 1 ข้อ หรือ ระบุเหตุผลอื่นๆ)
( ) no ( ) yes criteria no…… or ( ) other reasons (please specify)…….
……...

3. Suspected drug (ระบุชื่อยา)…… (ระบุอาการ)……..
( ) highly probable ( ) probable ( ) possible ( ) unlikely ( ) exclude (√ หน้าตัวเลือก)
Preventability (สามารถเลือกได้ ≥ 1 ข้อ หรือ ระบุเหตุผลอื่นๆ)
( ) no ( ) yes criteria no…… or ( ) other reasons (please specify)……
……...

ที่	เกณฑ์การประเมิน preventable ADEs
1	ยาที่สงสัยว่าเป็นสาเหตุของเหตุการณ์อันไม่พึงประสงค์นั้น ผู้ป่วยได้รับอย่างไม่เหมาะสมกับโรคหรือภาวะทางคลินิกของผู้ป่วย
2	ขนาดยา วิถีการบริหารยา ความถี่ ของการบริหารยาไม่เหมาะสม กับอายุ น้ำหนัก และสภาวะของโรคของผู้ป่วย
3	ไม่ได้ทำการตรวจวัดระดับยาหรือค่าทางห้องปฏิบัติการที่จำเป็นในการประเมินการรักษา
4	ผู้ป่วยเคยมีประวัติการแพ้หรือเกิดอาการจากยาดังกล่าวมาก่อน
5	เกิดปฏิกิริยาระหว่างยาที่เกี่ยวข้องกับ ADEs ที่เกิดขึ้น
6	มีการบันทึกค่าระดับยาหรือค่าการทดสอบทางห้องปฏิบัติการที่บ่งบอกถึงความเป็นพิษของยา
7	มีการใช้ยาที่ไม่เป็นไปตามที่แพทย์สั่ง (poor compliance)

……**Physician's assessor**

Pharmacist' s opinion	Conclusion

1. Suspected drug (ระบุชื่อยา)…… (ระบุอาการ)……
( ) highly probable ( ) probable ( ) possible ( ) unlikely ( ) exclude (√ หน้าตัวเลือก)
Preventability (สามารถเลือกได้ ≥ 1 ข้อ หรือ ระบุเหตุผลอื่นๆ)
( ) no ( ) yes criteria no…… or ( ) other reasons (please specify)…….....

……

Conclusion
( ) highly probable ( ) probable ( ) possible ( ) unlikely ( ) exclude
Preventability (สามารถเลือกได้ ≥ 1 ข้อ หรือ ระบุเหตุผลอื่นๆ)
( ) no ( ) yes criteria no…… or ( ) other reasons (please specify)…….....

……...

2. Suspected drug (ระบุชื่อยา)…… (ระบุอาการ)……
( ) highly probable ( ) probable ( ) possible ( ) unlikely ( ) exclude (√ หน้าตัวเลือก)
Preventability (สามารถเลือกได้ ≥ 1 ข้อ หรือ ระบุเหตุผลอื่นๆ)
( ) no ( ) yes criteria no…… or ( ) other reasons (please specify)…….....

……...

Conclusion
( ) highly probable ( ) probable ( ) possible ( ) unlikely ( ) exclude
Preventability (สามารถเลือกได้ ≥ 1 ข้อ หรือ ระบุเหตุผลอื่นๆ)
( ) no ( ) yes criteria no…… or ( ) other reasons (please specify)…….....

……...

3. Suspected drug (ระบุชื่อยา)…… (ระบุอาการ)……
( ) highly probable ( ) probable ( ) possible ( ) unlikely ( ) exclude (√ หน้าตัวเลือก)
Preventability (สามารถเลือกได้ ≥ 1 ข้อ หรือ ระบุเหตุผลอื่นๆ)
( ) no ( ) yes criteria no…… or ( ) other reasons (please specify)…….....

……...

Conclusion
( ) highly probable ( ) probable ( ) possible ( ) unlikely ( ) exclude
Preventability (สามารถเลือกได้ ≥ 1 ข้อ หรือ ระบุเหตุผลอื่นๆ)
( ) no ( ) yes criteria no…… or ( ) other reasons (please specify)…….....

……...

……**Pharmacist's assessor**

APPENDIX F

แบบเสนอปัญหาที่คาดว่าจะเกิดจากการใช้ยาและข้อเสนอแนะจากเภสัชกร

Pharmacist's note **Initial……HN……date……visit no….**	
Problem list, Finding	Assessment & Plan

ภญ. สุธาทิพย์ สมจริต

Doctor's opinion
……..
……
……..
……

……**Physician's signature**

Classification and result of pharmacist's intervention

Initial……HN…….....Physician's name…….....
Visit No O 1st O 2nd Date of patient's visit……...

- **Classification of pharmacist's intervention**

A. Addition of drugs
B. Changing dose
C. Clarification or correction of order
D. Cessation of drugs
E. Additional monitoring or other therapy
F. Recommendation of alternative drug therapy
G. Changing amount of drug
H. Changing frequency of administration
I. Changing time of administration

- **Result of pharmacist's intervention**

Accepted intervention

Partially accepted intervention

Rejected intervention

Classification	**Result**
Select 1 out of **A-I**……..	Select **A** or **P** or **R**……
……	…….
……	..……
……	…..……
……	……...……
……	……...……
……	……...……
……	……...……
……	……...……
……	……...……
……	……...……
……	……...……
……	……...……
……	……...……
……	……...……

APPENDIX G

แบบบันทึกเหตุการณ์ไม่พึงประสงค์จากการใช้ยา
(ADVERSE DRUG EVENT RECORD FORM)

Initial……HN……..Date…/……/…..Visit No…….

Date	Suspected symptom	Lab abnormality

Drug&regimen	(S,O,I)*	Start date	Stop date	Duration	Indication	Date of symptom

*** (S = Suspected drug, O = Other drug, I = Interaction drug)**

Organ system involvement

① Urinary system disorders
② Respiratory system disorders
③ Platelet, bleeding & clotting disorders
④ Skin and appendages disorders
⑤ Liver and biliary system disorders
⑥ Gastro-intestinal system disorders
⑦ Cardiovascular disorders
⑧ Other……..

Probability of ADEs

① Highly probable ② Probable ③ Possible ④ Unlikely ⑤ Exclude
Assessed by ……(Pharmacist), Date……

Probability of ADEs

① Highly probable ② Probable ③ Possible ④ Unlikely ⑤ Exclude
Assessed by ……(Physician), Date……

Conclusion

① Highly probable ② Probable ③ Possible ④ Unlikely ⑤ Exclude

เกณฑ์การประเมิน preventable ADE

ที่	เกณฑ์การประเมิน **preventable ADE**	แพทย์ ผู้ประเมิน	เภสัชกร ผู้ประเมิน
1	ยาที่สงสัยว่าเป็นสาเหตุของเหตุการณ์อันไม่พึงประสงค์นั้น ผู้ป่วยได้รับอย่างไม่เหมาะสมกับโรคหรือภาวะทางคลินิกของผู้ป่วย		
2	ขนาดยา วิถีการบริหารยา ความถี่ ของการบริหารยาไม่เหมาะสม กับอายุ น้ำหนัก และสภาวะของโรคของผู้ป่วย		
3	ไม่ได้ทำการตรวจวัดระดับยาหรือค่าทางห้องปฏิบัติการที่จำเป็นในการประเมินการรักษา		
4	ผู้ป่วยเคยมีประวัติการแพ้หรือเกิดอาการจากยาดังกล่าวมาก่อน		
5	เกิดปฏิกิริยาระหว่างยาที่เกี่ยวข้องกับ ADEs ที่เกิดขึ้น		
6	มีการบันทึกค่าระดับยาหรือค่าการทดสอบทางห้องปฏิบัติการที่บ่งบอกถึงความเป็นพิษของยา		
7	มีการใช้ยาที่ไม่เป็นไปตามที่แพทย์สั่ง (poor compliance)		
ประเมิน preventable ADEs หรือไม่		O ใช่ O ไม่ใช่	O ใช่ O ไม่ใช่
สรุปผลการประเมิน		O ใช่ O ไม่ใช่	

ระดับความรุนแรงของ ADEs

ระดับความรุนแรง	รายละเอียด	เภสัชกร ผู้ประเมิน
1	อาการที่เกิดขึ้นไม่ทำให้ต้องเปลี่ยนแปลงการใช้ยานั้นๆ	
2	อาการที่เกิดขึ้นทำให้ต้องมีการหยุดยา เปลี่ยนแปลงการใช้ยานั้นๆ แต่ไม่ต้องการยาต้านฤทธิ์หรือการรักษาอาการไม่พึงประสงค์ และไม่ต้องนอนรักษาตัวในโรงพยาบาลนานขึ้น	
2a	อาการที่เกิดขึ้นทำให้ต้องมีการ**เปลี่ยนขนาดของยา**นั้นๆ	
2b	อาการที่เกิดขึ้นทำให้ต้องมีการ**เปลี่ยนการใช้ยานั้นๆ เป็นยาตัวอื่นๆ แทน**	
2c	อาการที่เกิดขึ้นทำให้ต้องมีการ**หยุดการใช้ยานั้นๆ**	
3	อาการที่เกิดขึ้นทำให้ต้องมีการหยุดยา เปลี่ยนแปลงการใช้ยานั้น ๆ และ/หรือต้องการยาต้านฤทธิ์หรือการรักษาอาการ แต่ไม่ต้องนอนรักษาตัวในโรงพยาบาล	
4	- อาการไม่พึงประสงค์ในระดับ 3 ซึ่งผู้ป่วยต้องนอนรักษาตัวในโรงพยาบาล - อาการไม่พึงประสงค์ที่เกิดขึ้นเป็นสาเหตุให้เข้าพักรักษาตัวในโรงพยาบาล หรือ**ต้องเข้ารับการรักษาเร่งด่วนที่ห้องฉุกเฉินของโรงพยาบาล**	
5	อาการไม่พึงประสงค์ในระดับ 4 ซึ่งผู้ป่วยต้องอยู่ในความดูแลใกล้ชิด	
6	อาการไม่พึงประสงค์ที่เกิดขึ้นเป็นอันตรายต่อผู้ป่วยถาวร	
7	อาการไม่พึงประสงค์ที่เกิดขึ้นเป็นสาเหตุของการเสียชีวิตของผู้ป่วยทั้งทางตรงและทางอ้อม	

Management of ADEs

O require medical treatment O not require medical treatment

① Change dose or interval of suspected drug……

② No changes

③ Discontinuation of suspected drug

④ Discontinuation of suspected drug & take as an alternative drug

.....

Outcome after ADEs

① Complete recovered with treatment or drug changes

② Complete recovered without treatment or drug change

③ Recovered with sequelae

④ Not yet recovered

⑤ Death due to ADEs

⑥ Death due to other causes

⑦ Other……

APPENDIX H

The list of system-organ classes according to

WHO Collaborating Centre for international drug monitoring

No	System-organ classes
1	Skin and appendages disorders
2	Musculo-skeletal system disorders
3	Collagen disorders
4	Central & peripheral nervous system disorders
5	Autonomic nervous system disorders
6	Vision disorders
7	Hearing and vestibular disorders
8	Special senses other, disorders
9	Psychiatric disorders
10	Gastro-intestinal system disorders
11	Liver and biliary system disorders
12	Metabolic and nutritional disorders
13	Endocrine disorders
14	Cardiovascular disorders, general
15	Myo-, endo-pericardial & valve disorders
16	Heart rate and rhythm disorders
17	Vascular (extracardiac) disorders
18	Respiratory system disorders
19	Red blood cell disorders
20	White cell and RES disorders
21	Platelet, bleeding & clotting disorders
22	Urinary system disorders
23	Reproductive disorders, male
24	Reproductive disorders, female
25	Foetal disorders
26	Neonatal and infancy disorders
27	Neoplasms
28	Body as a whole-general disorders
29	Application site disorders
30	Resistance mechanism disorders

RES = Reticuloendothelial system

APPENDIX I

Details of pharmacist's interventions

Case	Problem	Pharmacist's intervention	Physician acceptance
1 A 47 years old female	Systems error : Dispensing error At 1st visit, indomethacin long-acting dosage form was not dispensed because this formulation was not available in Thailand and the physician was not informed about this problem, therefore the patient had no medicine for pain relief. Patient complained that she occasionally had pain.	Recommendation of alternative drug therapy Indomethacin short-acting dosage form should be prescribed.	Accepted
	Systems error : Prescribing error At 2nd visit, MTX was not prescribed because of computer error resulted in incomplete list of re-medication.	Clarification or correction of order MTX should be prescribed.	Accepted .
2 A 64 years old female	potADEs requiring additional monitoring At 1st visit, She took HCQ for 3 years but she had never been consulted an ophthalmologist.	Additional monitoring Patient required annual check-up with ophthalmologist to early detection of retinal toxic effects	Accepted
	Non compliance : Delay of follow up At 1st visit, she had postponed the appointment date for 10 days and had experienced joint pain because of run out of her medication.	Changing amount of drugs Amount of drugs were prescribed more than the expected next visit date in case of postpone the appointment.	Accepted

Details of pharmacist's interventions (cont.)

Case	Problem	Pharmacist's intervention	Physician acceptance
3 A 63 years old female	Systems error : Prescribing error MTX was not prescribed from computer error of re-medication.	Clarification or correction of order MTX should be prescribed.	Accepted
4 A 40 years old male	Systems error : Dispensing error At 1st visit, short-acting indomethacin was dispensed instead of long-acting dosage form which was not available in Thailand and the physician was not informed about this problem. Patient complained that the short-acting dosage form inadequately controlled her pain during the night time.	Recommendation of alternative drug therapy Long-acting NSAIDs should be prescribed.	Accepted
5 A 52 years old female	Adverse event required additional monitoring. During 1st visit to 2nd visit, patient had palpitation that required stopping of all the medications, but the symptom remained until 2nd visit.	Additional monitoring Additional monitoring was required and physician was reminded about this problem.	Partially accepted Patient was appointed to the cardiologist at the next visit.
6 A 48 years old female	Non compliance : Incorrect administration At 1st visit, she took CQ after breakfast but the order was prescribed at bed time.	Changing time of administration The time of drug taking should be changed for better compliance.	Accepted

Details of pharmacist's interventions (cont.)

Case	Problem	Pharmacist's intervention	Physician acceptance
6 A 48 years old female	potADEs required additional drug treatment She had menopause about 5 years and received prednisolone 5 mg OD. She usually supplemented with calcium approximately 600 mg from 2 glasses of milk/ day.	Addition of drug Calcium 1,000 mg should be prescribed for total calcium 1,500 mg/day.	Partially accepted Physician prescribed calcium 600 mg for total calcium supplement 1,200 mg/ day.
7 A 38 years old female	Adverse drug event Patient experienced vomiting from SSZ 2 tablets twice a day after meals.	Addition of drug Domperidone should be prescribed but still continued SSZ	Partially accepted Physician prescribed domperidone, another DMARD was prescribed instead of SSZ.
	Dosage too low Physician prescribed etoricoxib (60) 1tablet/ day p.r.n. which was not enough for pain control.	Changing dose Etoricoxib (60) 1 tablet/ day should be prescribed.	Partially accepted Physician prescribed Etoricoxib (90) 1 tablet/ day.
8 A 71 years old female	Adverse drug event At 1st visit, patient suffered from abdominal pain associated with etoricoxib.	Addition of drug PPI should be prescribed.	Accepted

Details of pharmacist's interventions (cont.)

Case	Problem	Pharmacist's intervention	Physician acceptance
9 A 64 years old male	Systems error : Prescribing error At 1st visit, MTX was prescribed in medication order with dose of 5 tablets per week but the printed order was 4 tablets/ week.	Clarification or correction of order Computer order should be changed to dose of 5 tablets/ week.	Accepted
10 A 46 years old female	Adverse drug event At 1st visit, patient experienced nausea from SSZ 1 tablet twice a day.	Addition of drug Domperidone should be prescribed but still continued the same SSZ dose.	Accepted Physician prescribed domperidone but titrated SSZ dose until 2 tablets twice a day without nausea symptom.
11 A 44 years old female	Adverse drug event At 2nd visit, patient experienced steroid acne from prednisolone.	Changing dose Prednisolone should be tapered to low dose because of ADEs occurring and patient had stable RA (ESR = 8).	Partially accepted Prednisolone would be tapered to low dose at the 3rd visit.
	Untreated indication She experienced leucorrhea for 3 months and receiving also oral antifungal and vaginal tablet from drugstore but the symptom still remained.	Additional monitoring Patient should be investigated the cause.	Accepted
	PotADEs from unnecessary drug use Stable RA and no pain	Cessation of drug Naproxen should be discontinued.	Accepted

Details of pharmacist's interventions (cont.)

Case	Problem	Pharmacist's intervention	Physician acceptance
12 A 53 years old male	Adverse drug event At 2nd visit, increasing SGPT associated with MTX.	Cessation of drug Hold MTX and Nimesulide.	Partially accepted Physician stopped MTX order but increased naproxen dose.
	potADEs from duplication of drug therapy Patient received nimusulide from drug store and physician prescribed ibuprofen for pain relief.	Cessation of drug Ibuprofen should not be prescribed**.**	Accepted
13 A 62 years old female	potADEs from duplication of drug therapy : Prescribing error At 1st visit, patient with hypertension received manidipine from rheumatology clinic while she received felodipine from hypertension clinic. Both calcium channel blockers were prescribed to control blood pressure.	Cessation of drug Only one calcium channel blocker should be prescribed.	Rejected Physician gave the reason that the problem should be resolved at hypertension clinic.
14 A 64 years old female	Systems error : Prescribing error HCQ was recorded in medication order sheet but was not prescribed in the prescription.	Clarification or correction of order HCQ should be prescribed in the prescription.	Accepted
	potADE from non compliance : Incorrect administration At 1st visit, she took MTX 3 tablets/ week but the prescribed	Changing dose The drug should be reduced 3 tablets/ week according to the	Accepted

Details of pharmacist's interventions (cont.)

Case	Problem	Pharmacist's intervention	Physician acceptance
	order was 5 tablets/ week.	patient because of controlled disease.	
15 A 43 years old female	Untreated indication She experienced alopecia since 5 month ago and drug cause was not suspected.	Additional monitoring Patient should be investigated the cause.	Accepted Patient was sent to the dermatologist.
16 A 69 years old female	Untreated indication At 1st visit, patient suffered from abdominal pain.	Addition of drug PPI should be prescribed.	Accepted
17 A 60 years old female	Systems error : Prescribing error At 1st visit, Glucosamine was prescribed in prescription but was not recorded in medication order sheet.	Clarification or correction of order Glucosamine was prescribed in the medication order sheet.	Accepted
18 A 25 years old female	Untreated indication At 1st visit, she experienced leucorrhea 2 day ago and numerous bacteria were found in urine.	Addition of drug Antibacterial drug should be prescribed.	Accepted
19 A 51 years old female	potADEs from systems error : Prescribing error Physician stopped methylcobal at 1st visit and re-prescribed at 2nd visit because it was still present in medication order sheet.	Clarification or correction of order Methylcobal should be stopped in prescription and medication order sheet.	Accepted

Details of pharmacist's interventions (cont.)

Case	Problem	Pharmacist's intervention	Physician acceptance
20 A 58 years old female	Untreated indication At 1st visit, patient suffered from dyspepsia for many months.	Addition of drug PPI and antiemetic should be prescribed.	Partially accepted PPI and antiemetic were prescribed when ADE was estimated.
	ADEs from dosage too high At 1st visit, anorexia occurred that involve with too high MTX 5 tablets/ week.	Changing dose MTX may be reduced (ESR =16, no morning stiffness)	Accepted MTX were prescribed 3 tablets/ week.
21 A 36 years old female	ADEs from non compliance : Incorrect administration At 1st visit, she took MTX 10 tablets/ week but the order was prescribed 5 tablets/ week. Anorexia was presented.	Changing dose MTX dosage should be continued and the correct dosage was explained to the patient.	Rejected Physician stopped MTX because patient had skin infection.
22 A 69 years old female	Dosage too low At 1st visit, physician prescribed SSZ 1 tablet once a day (ESR =23, no swelling joint). But 2nd visit ESR rose to 49 with swelling joint symptom.	Changing dose SSZ dose should be increased.	Accepted
23 A 40 years old male	potADE from dosage too high At 1st visit, patient with renal impairment (ClCr 47 ml/ min).	Cessation of drug Gold injection should not prescribed when ClCr < 50 ml/ min.	Accepted
	Untreated indication At 2nd visit, patient experienced hypokalemia (K^+ = 2.7 mmol/ L	Addition of drug Oral KCl should be prescribed until K^+ was normal level.	Accepted Physician prescribed KCl elixir 30 ml bid

Details of pharmacist's interventions (cont.)

Case	Problem	Pharmacist's intervention	Physician acceptance
			for 3 days.
24 A 44 years old female	Dosage too low At 1st visit, prednisolone was reduced 2.5 mg each other day but uncontrolled symptom.	Changing dose Prednisolone should be increased to dose of 5 mg once a day.	Accepted
25 A 77 years old female	Dosage too low Amlodipine, atovastatin and aspirin gr I; medications for co-morbidity were not enough. Patient lacked of these drugs for 10 days thus her blood pressure was high. (BP 140/100)	Changing amount of drugs At least amlodipine should be added in order for control blood pressure.	Rejected The physician gave the reason that patient have appointment time at cardiologist at the next 3 day.
26 A 71 years old female	PotADE from systems error : Prescribing error At 2nd visit, SSZ was prescribed in medication order sheet with dose of 2 tablets in the morning and 3 tablets in the evening but was prescribed in the prescription 2 tablets three time a day.	Clarification or correction of order SSZ should be prescribed according to prescription.	Accepted
27 A 54 years old female	Adverse drug event At 2nd visit, hyperpigmentation increased as a result of HCQ	Changing dose HCQ should be reduced to 2 tablets/ week.	Accepted HCQ was reduced from 1 tablet OD, 5 days/ week to 1 OD Monday and Wednesday.

Details of pharmacist's interventions (cont.)

Case	Problem	Pharmacist's intervention	Physician acceptance
27 A 54 years old female (continued)	Adverse drug event At 2nd visit, patient suffered from dyspepsia associated with SSZ and naproxen.	Addition of drug PPI should be prescribed and continued 2 suspected drugs.	Accepted
28 A 61 years old female	Adverse drug event At 1st visit, hyperpigmentation increased as a result of HCQ	Changing dose HCQ dose should be reduced.	Accepted
	Dosage too low Before 1st visit, physician changed the frequency of omeprazole from 1 capsule in the morning to 2 capsules at bedtime. Patient complained that one time a day could not control her abdominal pain during day time.	Changing frequency of administration PPI should be prescribed 1 capsule twice a day before meals.	Accepted
	Untreated indication Patient suffered from insomnia.	Addition of drug Anti-anxiety drug and PPI should be prescribed p.r.n.	Accepted Lorazepam (0.5) was prescribed 1 tablet at bedtime p.r.n.
	Non compliance At 2nd visit, patient received prednisolone 2.5 mg once a day p.r.n but she took 2.5 mg every day thus the amount of drug was not enough until the next visit.	Changing frequency of administration Prednisolone should be prescribed 2.5 mg every day.	Rejected Physician gave the reason that this problem was steroid dependence.

BIOGRAPHY

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