OUTCOMES ASSESSMENT OF ADVERSE DRUG REACTION MONITORING PROGRAM AT SIRIRAJ HOSPITAL 2006

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A THESIS SUBMITTED IN PARTIAL FULFILLMENT
OF THE REQUIREMENTS FOR
THE DEGREE OF MASTER OF SCIENCE IN PHARMACY
(PHARMACY ADMINISTRATION)
FACULTY OF GRADUATE STUDIES
MAHIDOL UNIVERSITY
2008

Thesis
Entitled

OUTCOMES ASSESSMENT OF ADVERSE DRUG REACTION MONITORING PROGRAM AT SIRIRAJ HOSPITAL 2006

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for the degree of Master of Science in Pharmacy (Pharmacy Administration)
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ACKNOWLEDGEMENTS

I would like to express my sincere gratitude and deep appreciation to my major advisor, Associate Professor Cha-oncin Sooksriwong for his valuable advice guidance, great attention, and assistance with consultant encouragement throughout the study.

I am deeply grateful to Assistant Professor Usa Chaikledkaew, my co-advisor for his helpful guidance, suggestion, comment and recommendation.

I am grateful to Pharmacist Narumon Thana and all staff attending at Siriraj Hospital for their nice co-operation and helpful during the study. They are always nice and friendly.

This thesis could not be as present without consultation and advising on research methodologies by Associate Professor Petcharat Pongcharieansook my thesis proposal examination committee.

I wish to thank Associate Professor Thida Ninsananda for their kindness as the examiner of thesis defense.

Finally, I would like to express the warmest gratefulness to my father, mother, sisters, and friends for their love and full of cares which always cheered me up and assisted me to the success in my life.

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OUTCOMES ASSESSMENT OF ADVERSE DRUG REACTION MONITORING PROGRAM AT SIRIRAJ HOSPITAL 2006

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ABSTRACT

The objective of this study was to determine the outcomes of an ADR Monitoring Program from a benefit to cost ratio and patient's length of stay (LOS) in hospital perspective. A descriptive cross-sectional study was conducted between October 1, 2005, and September 30, 2006. ADR study data were collected for a one-year period with a retrospective review of the electronic database by ADR Monitoring Program, using the classification criteria for preventable ADRs of Schumock and Thornton.(3)

The main measures of this study concerned the benefits and costs of ADR Monitoring Program. The benefits of this program were determined in terms of cost savings and LOS of patient with ADRs during hospitalization. The outcome of ADR Monitoring Program on benefits to costs ratio was 6.65, which indicates that this program is effective. The cost of the ADR Monitoring Program was 432,499.73 baht (Fiscal year 2006) and the subsequent savings were annualized at 2,875,623 baht. The mean cost savings were 6,912.56 baht per patient and the mean savings of LOS were 2.11 hospital days per patient. The age group identified as having the highest percentage of total cost savings (35.51%) was the group ≥ 60 years. A higher percentage of total cost savings was estimated in females than males. On the basis of the Naranjo criteria (2), the possible mean cost savings were classified at 7,136.53 baht per patient, higher than the probable at 6,594.83 baht per patient. The mean cost savings were classified, according to Rawlins and Thompson (21), as type B (7,208.56 baht per patient) which was higher than type A (2,962.48 baht per patient). The highest percentage of total cost savings were for nervous system disorders (17.65%). For drugs, antibiotics represented the highest total cost savings at 1,837,846 baht (63.91%). The outcomes of this study indicate that the ADR Monitoring Program is beneficial in terms of the cost savings and LOS. The benefits to costs ratio of this program ensures that it would provide better financial and administrative outcomes.

KEY WORDS: OUTCOMES ASSESSMENT/ ADVERSE DRUG REACTION/

ADVERSE DRUG REACTION MONITORING PROGRAM

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การประเมินผลลัพธ์ของโครงการเฝ้าระวังอาการไม่พึงประสงค์จากการใช้ยาโรงพยาบาลศิริราช 2549

OUTCOMES ASSESSMENT OF ADVERSE DRUG REACTION MONITORING PROGRAM AT SIRIRAJ HOSPITAL 2006

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บทคัดย่อ

การศึกษานี้มีวัตถุประสงค์เพื่อศึกษาต้นทุน-ผลได้ของโครงการเฝ้าระวังอาการไม่พึงประสงค์จากการใช้ยาโรงพยาบาลศิริราชปี 2549 ของผู้ป่วยที่เกิดอาการไม่พึงประสงค์จากการใช้ยาระหว่างนอนโรงพยาบาล ซึ่งทำการศึกษาในมุมมองของโรงพยาบาล โดยเก็บข้อมูลย้อนหลังเป็นเวลา 1 ปี ตั้งแต่วันที่ 1 ตุลาคม พ.ศ. 2548 – 30 กันยายน พ.ศ. 2549 จากฐานข้อมูลที่บันทึกโดยโครงการเฝ้าระวังอาการไม่พึงประสงค์จากการใช้ยา

ผลการศึกษาพบว่า มีผู้ป่วยที่เกิดอาการไม่พึงประสงค์จากการใช้ยาระหว่างนอนโรงพยาบาลทั้งหมด 416 ราย คิดเป็นมูลค่าของค่าใช้จ่ายที่เพิ่มขึ้นทั้งหมด 2,875,623 บาทต่อปี (ร้อยละ 52.32) หากสามารถป้องกันการเกิดอาการไม่พึงประสงค์จากการใช้ยาของผู้ป่วยกลุ่มนี้ได้โดยโครงการเฝ้าระวังอาการไม่พึงประสงค์จากการใช้ยาจะทำให้ลดต้นทุนค่าใช้จ่ายส่วนนี้ได้ โดยการดำเนินงานของโครงการคิดเป็นมูลค่าของต้นทุนค่าใช้จ่ายทั้งสิ้น 432,499.73 บาทต่อปี ซึ่งสามารถลดต้นทุนค่าใช้จ่ายเฉลี่ยต่อรายเท่ากับ 6,912.56 บาทต่อรายของผู้ป่วยที่เกิดอาการไม่พึงประสงค์จากการใช้ยาระหว่างนอนโรงพยาบาล และลดวันนอนเฉลี่ยที่เพิ่มขึ้นต่อรายเท่ากับ 2.11 วัน เมื่อจำแนกค่าใช้จ่ายตามกลุ่มอายุ พบว่า ผู้ป่วยอายุตั้งแต่ 60 ปีขึ้นไป มีค่าใช้จ่ายรวมของการเกิดอาการไม่พึงประสงค์จากการใช้ยามากที่สุด (ร้อยละ 35.51) ในขณะที่เพศหญิงมีค่าใช้จ่ายรวมสูงกว่าเพศชาย เมื่อใช้เกณฑ์ Naranjo's Algorithm (2) พบว่าค่าใช้จ่ายเฉลี่ยต่อรายของระดับความน่าจะเป็น "อาจจะใช่" มีค่าสูงกว่าระดับ "น่าจะใช่" (7,136.53 เทียบกับ 6,594.83 บาทต่อราย) เมื่อใช้เกณฑ์ของ Rawlins และ Thompson (21) พบว่าอาการไม่พึงประสงค์แบบ type B มีค่าใช้จ่ายเฉลี่ยต่อรายสูงกว่า type A (7,208.56 เทียบกับ 2,962.48 บาทต่อราย) จากผลการศึกษาการประเมินผลลัพธ์ของโครงการเฝ้าระวังอาการไม่พึงประสงค์จากการใช้ยาพบว่าประสิทธิผลที่เกิดขึ้นของโครงการนี้สามารถสร้างความมั่นใจให้กับผู้บริหารในด้านการให้บริการของโครงการว่ามีความคุ้มค่าในเชิงการลดต้นทุนค่าใช้จ่ายที่ไม่จำเป็นจากการเกิดอาการอันไม่พึงประสงค์จากการใช้ยาในมุมมองของโรงพยาบาล

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LIST OF ABBREVIATIONS

%	percentage
ADRs	Adverse drug reactions
ADEs	Adverse drug events
AERS	The Adverse Event Reporting System
ADRMP	Adverse Drug Reaction Monitoring Program
CBA	Cost – benefit analysis
CC	Complications and Comorbidities
CIOMS	The Council for International Organixations of Medical Sciences
CNS	Central Nervous System
DMARDs	Disease-Modifying Anti-Rheumatic Drugs
DoTS	Dose, Time course, Susceptibility
DRG	Diagnosis-Related Group
FDA	Food and Drug Administration
GTN	Glyceryl trinitrate
ICD-10	International Classification of Deisease 10^{th} edition
ICU	Intensive Care Unit
IVIG	Intravenous immunoglobulin
LOS	Length of stay
MDC	Major Diagnostic Category
Misc.	Miscellaneous
NHS	The National Health System
No.	Number
NSAIDs	Nonsteroidal Anti-inflammatory Drugs
PDx	Principle Diagnosis
PEM	Prescription event monitoring systems
PMS	Post-marketing surveillance

LIST OF ABBREVIATIONS (Continued)

RW	Relative Weight
SD	Standard deviation
SJS	Stevens-Johnson Syndrome
SRS	The spontaneous reporting system
sum	summary
TDM	Therapeutic drug monitoring
TEN	Toxic epdermal necrolysis
UK	The United Kingdom
UMC	The Uppsala Monitoring Center
US	The United State
WHO	World Health Organization

CHAPTER I
INTRODUCTION

Adverse drug reactions (ADRs) are common causes of hospitalization and lead to large costs to society.(1) The cost of hospitalization is, however, only a part of the total cost as most adverse reactions never come to clinical attention.

The burden on public health of ADRs remains significant : Pharmacocconomic studies on the costs of adverse reactions suggest that governments pay considerable amounts from health budgets towards covering costs associated with them. In most countries the extent of this expenditure has not been measured.

The main issue of ADRs in health care is to know how to prevent and reduce the costs of ADRs. To be able to make a rational decision about this, all costs and benefits must be taken into account. There are two main costs associated with ADRs : cost of treating illnesses due to ADRs and cost of avoiding them.(1) These two costs are interrelated and increase cost of avoiding ADRs will probably lead to a reduced cost of treating illness due to ADRs. The main issue for health care decision makers is therefore to find the right balance between costs and benefits of drug therapies.

The objective of this study was to determine the outcomes of an ADR Monitoring Program from a benefit to cost ratio and patient's length of stay (LOS) in hospital perspective at Siriraj Hospital in 2006, (focused on patient with ADRs during hospitalization).

This is a descriptive cross-sectional study was conducted between October 1,2005, and September 30, 2006, for one-year period of review at Siriraj hospital focused on all inpatients who were associated with adverse drug reactions (ADRs) during hospitalization. The method used to monitor adverse drug reaction is the spontaneous reporting system. Suspected ADRs leading to hospital admission are specifically noted. The relationship between the reaction and the drug administered (causality) is characterized by the Naranjo algorithm, a validated and frequently used

tool.(2) The data collected retrospectively from each submitted ADRs report are stored in the Adverse Drug Reaction Monitoring Program (ADRMP) database for further review by one drug information pharmacist. This additional review includes identification of any missing data, the need for follow-up with the reporter for additional details or clarification, or identification of immediate system changes to prevent future ADRs. To assess the preventability of each ADR the criteria developed by Schumock et al.(3)

Outcome; The consequence of associated ADRs are severe enough to produce significant changes in clinical or quality of life end points, or lead to significant economic costs.

Adverse drug reactions (ADRs) are regarded as an important public health problem as they may be potentially life-threatening. An ADR is defined by the World Health Organization as a noxious and unintended response to a drug that occurs at a dose normally used in man for the prophylaxis, diagnosis and therapy of disease, or for the modification of physiological function (WHO, 1964).(4, 5) This definition excludes accidental or deliberate excessive dosage or maladministration.

Adverse drug reactions (ADRs) account for 3.2-7% of acute hospital admissions. ADRs cause morbidity, mortality, a longer duration of hospital stay and increased hospital costs, but they are difficult to detect.(6)

During the last decade, several studies, particularly in USA and Europe investigated the frequency, characteristics (e.g. seriousness, avoidance etc.) and cost of adverse drug reactions (ADRs) leading to hospitalization. Adverse drug reactions (ADRs) are a major cause for hospitalizations.(7) Several studies have quantified the rate of ADR-related hospital admissions between 2.4 and 11.3%.(8) Only few data existed concerning hospital readmissions. The proportion of readmissions has been reported variously ranging between 5% after 2 months and 79% after 2 years.(9)

The investigators found that for hospitalized inpatients, antibiotics and opiated were responsible for approximately half of all preventable ADRs.(10) In the UK with its population of 65 million, it has been estimated that more than a quarter of a million patients (up to 6.5% of all admissions) are admitted to hospital each year because of harmful effects after taking drugs.(11) In numerous studies most ADRs are avoidable.

Most ADRs are predictable from the known pharmacology of the drug. Many represent known interactions and are therefore likely to be preventable. Susceptibility varies with ethnicity, age, sex, physiology, exogenous factors and disease states. So given the known epidemiology and based upon findings from these studies, it is incumbent upon prescribers to ensure that a particular drug is necessary for a particular patient and then to use this drug at the lowest possible dose which will benefit the patient. If we wish to prevent ADRs, then the challenge is to recognize the risks of medicines and to extend these standards to healthcare more widely.

Adverse drug reactions are common and cost intensive. The percentage of patients experiencing an adverse drug reaction during hospitalization has been reported to range from 1.5 to 35%.(12) Comorbidity and the number of medications also may influence the incidence of adverse drug reactions and the frequency with which they are detected. Fatal adverse drug reactions are expected in approximately 0.32% of hospitalized patients.(13) Between 1.1 and 8.4% of all hospital admissions are reportedly caused by adverse drug reactions. Apart from the medical impact, adverse drug reactions also have and economic impact. It has been suggested that adverse drug reactions prolong hospitalization and increase healthcare expenditures substantially.(14)

Up to now, spontaneous adverse drug reaction reporting has been the basis of most drug safety evaluation programmes in postmarketing surveillance. However, this method is limited by difficulties in adverse drug reaction recognition, under-reporting, biases, and insufficient report quality. Because of the low costs, most hospitals identify adverse drug reactions by spontaneous or stimulated spontaneous reporting.

Studies of the incidence and cost of ADRs in hospitalized patients have found that between 2.4% and 6.5% of hospitalized patients have an ADR (>770,000 US hospital patients annually), with direct cost between US$1.56 and $4.2 billion annually and an estimated total cost of $12.2 billion in 1996 dollars.(15)

Adverse drug reactions (ADRs) have been reported in nearly 20% of hospitalized patients and account for approximately 17% of hospital admissions.(16) The financial effect of adverse drug events is also considerable.

Pharmacists should actively engage in the identification, reporting, and prevention of ADRs and often coordinate ADR reporting programs in health-system settings. A variety of reporting approaches are used, including spontaneous of voluntary reports, evaluation of tracer or antidote drug use that may indicate the management of an ADR, and medical-record coding of ADRs.(17) Regardless of the method used to identify ADRs, the resultant data must generate meaningful trends and potential opportunities to improve patient care.

In some analyses, ADRs extend hospital stays from two to four days, resulting in an additional treatment cost of $2500 to $5500 per patient.(18-20) Most cost studies have focused on hospitalizations due to ADRs and the literature shows that about 3-7% of all hospitalizations are caused by ADRs.

The important question is whether the balance between the cost of ADRs and the cost of avoiding them is right. If we increase the costs of avoiding ADRs we will reduce the costs of treating them. It is reasonable to assume that we have a diminishing marginal productivity in this work, i.e. the marginal cost of reducing the number of ADRs is increasing. This means that it is more costly to reduce the incidence of ADRs for a specitic drug from 4 to 2% than reducing it from 6 to 4 %. Cost of avoiding ADRs are not only the manufacturers' expenditures for research and testing, they include lost benefit from delayed marketing and reduced rate of innovation as well. The reason for the diminishing marginal productivity can partly be explained by the fact that the benefit per-patient from a therapy is usually reduced when the number of treated patients increases.

Adverse drug reactions are often low-probability events, but when they occur the consequences can be very serious. Where low probabilities are involved, rational decision-making is difficult. Small probabilities are difficult to measure accurately and when they can be measured we have difficulty in incorporating them into our decisions in a rational way. In a situation like this it is important that in situations and mechanisms in the drug area provide patients and their advisors with information that will help them make informed choices of drug.

Therefore, cost-benefit studies of regulatory policy are important tools for helping regulatory hospital make rational decisions and defend the in public. The

problem with ADRs is, from an economic point of view, not a problem of minimization but of optimization, to find the right balance between costs and benefits.

This suggests considerable opportunity for minimizing the risks of ADRs through rational use, monitoring and follow-up. Early detection is important, particularly in hospitals where systems for detecting ADRs will save lives and money. Such systems might be linked to institutional, regional or national pharmacy and therapeutics committees so that information can be use to educate professional staff in safe drug use.

Research in ADRs and pharmacoepidemiology in departments of internal medicine and pharmacology should be encouraged and promoted.

The cost of ADRs or events during hospitalization is possible to estimate by the increased length of hospitalization. Cost estimations can be useful in other ways as well. It could be interesting to compare it with other costs and to study changes over time. The estimates could also give some idea about policy alternatives to improve the balance between costs and benefits. But in isolation, a cost analysis will never come to the heart of the policy problem, the problem statements in this study have a main question as following;

How much benefit is it to have Adverse Drug Reaction Monitoring Program (ADRMP) at Siriraj Hospital, based on hospital perspective?

In hospital, Adverse drug reactions (ADRs) are a threat to patients' health and quality of life, and can generate significant expenses. These kinds of data can be monitored and serve as a useful indicator of the quality of drug prescription in the hospital. This could save hospitals admissions and money.

Objectives

General Objective

To determine the outcomes of an Adverse Drug Reaction Monitoring Program (ADRMP) from a benefit to cost ratio and patient's length of stay (LOS) in

hospital perspective, focused on patient with ADRs during hospitalization at Siriraj Hospital in 2006.

Specific Objectives

1. To determine costs of the ADR Monitoring Program.
2. To determine benefits in terms of monetary value.
3. To calculate the benefits to costs ratio of the ADR Monitoring Program.
4. To study the length of stay of patient with ADRs.

Expectations

This study would result in benefits as follows.

1. The benefits to costs ratio of Adverse Drug Reaction Monitoring Program (ADRMP) ensure that it would provide better financial and administrative outcomes.

2. The development of an economic model for ADR Monitoring Program will facilitate the administrator to consider more rationally in ADR Monitoring Program management.

3. The outcomes of this study may increase the necessarity to prevent and reducing of Adverse Drug Reactions (ADRs) incidence.

CHAPTER II
LITERATURE REVIEW

The literature review is divided into 3 parts as the followings; Part I Adverse Drug Reactions (ADRs), Part II Management of Adverse Drug Reaction Monitoring Program (ADRMP), Part III Costs-benefits determination

PART I Adverse Drug Reactions

1.1 Definition of Adverse Drug Reactions (ADRs)

There are many definitions of Adverse Drug Reactions (ADRs), as follow :

Definition by Food and Drug Administration, Ministry of Public Health, Thailand, an ADR is an unintended reaction which is harmful to the human body, occurring when the drug is used at normal dose for the prophylaxis, diagnosis or treatment of disease or to change the body's physiology, not including any result from unintentional or accidental overdose, use or misuse.

Definition by World Health Organization 2002. An adverse drug reaction is "a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis,diagnosis, or therapy of disease, or for the modification of physiological function". In this description it is of importance that it concerns the response of a patient, in which individual factors may play an important role, and that the phenomenon is noxious (an unexpected therapeutic response, for example, may be a side effect but not an adverse reaction). This would not include intentional or accidental poisioning, or drug abuse. This definition excludes accidental or deliberate excessive dosage or maladministration.

1.2 Classification and mechanisms of adverse drug reactions

There are different type of classification of adverse drug reactions and all are necessary different purposes.

1.2.1 Pharmacological Classification (Rawlins & Thompson et al.(21))

ADRs have traditionally been classified into two broad categories.

Type A ("augmented") reactions ("drug actions")

Type A reactions include normal and augmented , but undesirable, responses to the drug in question. They include an exaggerated therapeutic response at the target site (e.g. hypoglycemia with a sulphonylurea), a desired pharmacological effect at another site (e.g. headache with GTN), and secondary pharmacological effects (e.g. orthostatic hypotension with a phenothiazine). Type A reaction are usually dose dependent and predictable, and are often recognised before a drug is marketed. However, some effects occur after a long latency, such as carcinogenesis or effects on reproduction. An example is vaginal adenocarcinoma in the daughters of women exposed to diethylstilbestrol during pregnancy, Many type A reactions have a pharmacokinetic basis, e.g. impaired hepatic metabolism (due to a genetic polymorphism or the effect of another concurrent medication), leading to increased plasma concentrations.

Type B ("bizarre") reactions ("patient reactions")

Type B reactions are unrelated to the known pharmacological actions of the drugs in question. These reactions are often caused by immunological and pharmacogenetic mechanisms. Type B reactions are generally unrelated to dosage and, although comparatively rare, they are more likely to cause serious illness or death. Immonologic reactions such as anaphylaxis with penicillins fall into this category. Other examples include aplastic anaemia with chloramphenicol, malignant hyperthermia with anaesthetic agents and isoniazid hepatitis. Because of their nature, type B reactions are more likely to result in withdrawal of marketing authorization.

The main differences between type A and B reactions are shown in Table 1.

Although this classification is simple, some adverse reactions do not fit neatly into one type. Additional categories of ADR have subsequently been suggested (22), to include type C (chronic), type D (delayed) and type E (end of use) reactions.

Use of this extended classification does not mitigate all difficulties, however, and a new system has recently been proposed.(23) This takes into account properties of both the reaction and the affected individual, as well as those of the drug itself. The three-dimensional classification system, known as DoTS, is based on dose relatedness, time course and susceptibility. It may have some adventages over previous classifications.

Table 1. Characteristics of type A and type B adverse drug reactions

Type A	**Type B**
Predictable	Unpredictable
Usually dose dependent	Rarely dose dependent
High morbidity	Low morbidity
Low mortality	High mortality
Responds to dose reduction	Responds to drug withdrawal

Adverse drug reaction can be classified into two main types based on mechanism of reaction.

- **Non-immunologic type**

Predictable ADRs: Reactions are dose dependent and affect the majority of individuals who ingest a sufficient amount of the drug. Examples of dose-dependent hepatotoxins are paracetamol (acetaminophen), salicylates, tetracycline and methotrexate.

Unpredictable ADRs or Idiosyncratic: Reactions are generally less frequent, typically occurring in between 1 in every 1000 and 1in every 100000 patients. Examples of drugs involved are chlorpromazine, halothane and isoniazid. Idiosyncratic unrelated to known pharmacologic actions of the drug and not caused by immunologic mechanism: possibly genetically determined.

- **Immunologic type**

These reactions are generally classified into the four types of Coombs and Gell. All of the four Coombs' and Gell immune mechanisms may be involved (See in Table 2).

Table 2. Immunological (hypersensitivity) reactions

Type I reactions are caused by the formation of drug /antigen-specific IgE that cross-links with receptors on mast cells and basophils. This leads to immediate release of chemical mediators, including histamine and leukotrienes. Clinical features include pruritus, urticaria, angio-oedema and, less commonly, bronchoconstriction and auaphylaxis. The drugs most commonly responsible for type I hypersensitivity are aspirin, opioids, penicillins and some vaccines. **Type II or cytotoxic reactions** are based on IgG or IgM-mediated mechanisms. These involve binding of antibody to cells with subsequent binding of complement and cell rupture. This mechanism accounts for blood cell dyscrasia such as haemolytic anaemia and thrombocytopenia. **Type III reactions** are mediated by intravascular immune complexes. These arise when drug antigen and antibodies, usually of IgG or IgM class, are both present in the circulation, with the antigen present in excess. Slow removal of immune complexes by phagocytes leads to their deposition in the skin and the microcirculation of the kidneys, joints and gastrointestinal system. Serum sickness and vasculitis are examples of type III reactions. **Type IV reactions** are mediated by T cells causing "delayed" hypersensitivity reactions. Typical examples include contact dermatitis or delayed skin tests to tuberculin. Drug-related delayed-type hypersensitivity reactions include Stevens-Johnson syndrome and toxic epidermal necrolysis (TEN). Recent work has proposed that type IV reactions be divided into four subtypes based on the T-lymphocyte subset and cytokine expression profile involved.
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1.2.2 Causality classification

The causality categories described by WHO-UMC are as follows:

Certain : a clinical event , including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.

Probable/Likely: a clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfil this definition.

Possible: a clinical event, including loboratory test abnormality, with a reasonable time sequence to administrations of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.

Unlikely: a clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausilde explanations.

Conditional/Unclassified: a clinical event, including laboratory test abnormality, reported as an adverse reaction, about which more data is essential for a proper assessment, or the additional data is under examination.

Unassessable/Unclassifiable: a report suggesting an adverse reaction which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified.

As a step towards harmonization in drug regulation in the countries of the European Union, the EU pharmacovigilance working parties proposed the following three causality categories:

- **Category A:** “Reports including good reasons and sufficient documentation to assume a causal relationship, in the sense of plausible, conceivable, likely, but not necessarity highly probable”.
- **Category B:** “Reports containing sufficient information to accept the possibility of a causal relationship, in the sense of not impossible and not unlikely, although the connection is uncertain and may be even doubtful, e.g. because of missing data, insufficient evidence or the possibility of another explanation”.
- **Category O:** “Reports where causality is, for one or another reason, not acssessable, e.g. because of missing or conflicting data.

1.2.3 Seriousness Classification

Non-serious: means any adverse drug reactions that is not classified as serious.

Serious: means any adverse drug reactions of the following kinds:

- **Death (givedate / month / year):** means any death that is suspected to be the result of an adverse drug reactions caused by using the suspected health product. Indicate date, month and year of death (if known). This does not include death with a certain link with the product use, or fetal death or abortion attributed to congenital anomaly or miscarriage.
- **Life-threatening:** means there is high risk of loss of the patient’s life during the occurrence of the adverse drug reactions or that continued use of the product may result in death, for example anaphylactic shock.
- **Hospitalization-initial/prolonged:** means the adverse drug reactions is the cause of the patient’s hospitalization or prolonged hospitalization. (If the patient needs only observation in the emergency room, without admission, tick other choices such as life-threatening, required intervention to prevent permanent impairment or damage, etc.)
- **Disability:** means the adverse drug reactions resulted in the patient being unable to maintain their normal life. This applies if the adverse drug reactions results in temporary or permanent change or damage or destruction of the

functional structure of the patient's body or the patient's ability or quality of life, for example blindness, renal failure, etc.

- **Congenital anomaly:** means the health product that the patient used before or during pregnancy resulted in fetal congenital anomaly.

1.2.4 Severity Classification

- **Mild / Minor:** Uncomplicated primary disease, no treatment required, and drug discontinuation not necessary.
- **Moderate:** Some but not all of the "mild" criteria and none of the "severe" criteria.
- **Severe:** more than one month in duration and / or life-threatening, associated organ system dysfunction, reduced life expectancy, or death.

1.2.5 Intervention Classification

- **Preventable ADRs;** Detected ADRs
  Undetected ADRs
- **Unpreventable ADRs**

1.3 The importance of adverse drug reactions

Adverse drug reactions continue to be an important public health issue, causing considerable patient harm and creating a burden on limited healthcare resources. Healthcare professionals have a responsibility to their patients, who themselves are becoming more aware of problems associated with drug therapy. It is essential that all involved have some knowledge of the potential adverse effects of medicines. The main challenge is to prevent the occurrence of ADRs; to do this effectively requires an assessment of the balance between benefit and harms, taking into account the strength or quality of the evidence. It is also important to be aware of the patient groups that are predisposed to drug toxicity. The key to appropriate management of ADRs is prompt recognition that the patient's new symptoms and sings may be drug related.

Adverse drug reactions (ADRs) have been known to cause significant morbidity and mortality for centuries. ADRs are common cause of hospitalization and lead to large costs to society. The cost of hospitalization is, however, only a part of the total costs as most adverse reactions never come to clinical attention.

The cost of ADRs or events during hospitalization is possible to estimate by the increased length of hospitalization. Studies have also showed that ADRs during hospitalization lead to delayed time to discharge. Studies investigated 190 ADEs from 4108 hospital admissions at medical and surgical departments. On average, each event caused 2.2 days longer hospitalization time.(14) Two other similar studies found ADRs to cause 1.91 and 3.5 extra days of hospitalization.(15) Therefore, cost-benefit studies of regulatory policy are important tools for helping regulatory to make rational decisions and defend them in public.

Several studies have investigated incidence and costs of ADRs in hospitals and have found that hospitalizations due to adverse reactions are responsible for substantial costs.

From an economic point of view the problem of ADRs is not a problem of minimizing but of optimizing, to find the right balance between the costs and benefits. ADRs also have a significant impact on healthcare costs.

In the last decades we have become more aware of the fact that, at the margin, the costs of reducing ADRs may exceed benefits and we have seen support for a policy aimed at deregulating healthcare system. However, we have also seen that increased information and education at the pharmacy (pharmaceutical care) could produce large cost savings due to reduced incidence of drug-related problems, which indicates that we instead should increase our expenditures of avoiding ADRs.

Because of these potential hazards, The World Health Organization established the WHO Program for International Drug Monitoring in the late 1960s. This, with cooperation from more than eighty countries (2005), aims to collect, monitor and analyse data about adverse events in order to detect early signals which indicate risk or harzard. Believing this program to be great importance, the Thai Ministry of Public Health set up its spontaneous adverse drug reaction reporting system in 1983, and was the twenty-sixth member of the WHO Program.(45)

1.4 Incidence of adverse drug reaction

Many investigators have studied the incidence of ADRs in a variety of settings. The estimates of incidence in these studies vary widely, and this reflects differences in the methodologies used to detect suspected reactions, including differences in the definition of an ADR.(24-28)

The Harvard Medical Practice study showed that 3.7% of 30195 patients admitted to acute hospitals in 1984 experienced adverse events.(29) Further data from this group suggested a 6% incidence of adverse drug events (ADEs) and a 5% incidence of potential ADEs among 4031 medical and surgical admissions over a 6-month period.(30) (Note that these investigators studied ADEs , a classification that included overdose and medication error). Of all events observed 1% were fatal, 12% life-threatening, 30% serious and 57% significant. Twenty-eight percent of observed ADEs, were considered preventable, with a greater proportion of the life-threatening and serious reactions in that category.

The drug classes most frequently implicated were analgesics, antibiotics, sedatives, cytotoxics, cardiovascular drug, anticoagulants, antipsychotics, antidiabetic and electrolytes. Another US study in hospital inpatients in 1992 found a similar frequency and type of adverse events to those observed in the Harvard study.(31) Data on nearly 15,000 patients discharged from 28 hospitals in two US states identified adverse events (not necessarily drug related) associated with 2.9% of hospitalizations. ADRs were the second most common type of adverse event, accounting for 19% of those identified. Antibiotics, cardiovascular agents, analgesics and anticoagulants were the drugs most commonly implicated. More than a third of these ADRs were considered avoidable, and nearly 1 in 10 caused irreversible harm. UK data from the mid 1990s suggested that 7% of over 20,000 medical inpatients experienced an ADR during their hospital stay.(32)

ADRs are responsible for a significant number of hospital admissions, with reported rates ranging from 0.3% to 11%.(33, 34) Data from meta-analyses and systematic reviews suggest that the rate of admissions directly due to ADRs is 5%. (22, 35, 36) Recent work has suggested that many of these reactions are predictable and preventable.(37) Patients were categorized as having having an ADR if the cause of admission was consistent with the known adverse-effect profile of the drug; if there

was a temporal relationship with the start of drug therapy; and if, after appropriate investigations, other causes were excluded. Causality assessment was carried out for all cases using two published methods. The avoidability of ADRs was assessed using the definitions developed by Hallas et al.(38) (Box 1). The main outcome measures were the prevalence of admissions due to an ADR, length of stay, avoidability and patient outcome.

The incidence of all ADRs is as we have seen difficult to estimate and has not been widely studied. The incidence in hospitalized patients and the number of ADRs leading to hospital admissions has, however, been investigated in several previous studies. Table 3 shows an overview of findings in some of these studies.

Box 1. Avoidability of adverse drug reactions. (38)

Definitely avoidable - the ADR was due to a drug treatment procedure inconsistent with current knowledge of good medical practice.

Possibly avoidable - the ADR could have been avoided by an effort exceeding the obligatory demands of current knowledge of good medical-practice.

Unavoidable - the ADR could not have been avoided by any reasonable means.

Source: Hallas I, Harvald B, Gram LF et al. Drug related hospital Admissions: the role of definitions and intensity of data collection, and the possibility of prevention. J Intern Med. 1990 ; 228 : 83-90.

Table 3. Incidence and prevalence of adverse drug reactions (ADRs) reported in the literature. (1)

Study	Incidence / prevalence	outcome
		ADR-related hospital admissions
Einarson	4.2%	Drug - related hospital admissions
Dartnell et al.	5.7%	Drug - related admissions to an emergency department
Easton et al.	3.4%	Hospital admissions associated with drug - related problems among children
Pouyanne et al.	3.2%	Hospital admission caused by ADRs
Cooper	15.7%	ADR - related hospitalization of the residents at a nursing facility (during 4 years)
Lagnaoui et al.	7.2%	Patients with ADRs as reason for hospital admission
		ADRs in hospitalized patients
Lazarou et al.	6.7%	Serious ADRs in hospitalized patients
Lapeyere - Mestre et al.	5%	ADRs during hospitalization in a cancer institute
Lagnaoui et al.	10.1 cases	Number of ADRs per 1000 patient-days in a medical ward
Moore et al.	5.6 cases	Number of ADRs per 1000 patient-days in a internal medicine department

1.5 Costs of adverse drug reactions

ADRs are a threat to patients' health and quality of life, and they can cause significant costs to the health care system. Hospital marginal costs were used to evaluate the economic impact of ADRs.

ADRs continue to be a major cause of morbidity and mortality. Several studies have investigated incidence and costs of ADRs in hospitals and have found that hospitalizations due to adverse reactions are responsible for substantial costs.

The cost of ADRs or events during hospitalization is possible to estimate by the increased length of hospitalization. The direct and indirect costs resulting from ADRs are difficult to estimate as description of the consequences. Of most adverse reactions is very limited. It is possible to identify and measure the costs of those cases where ADRs are probable causes of death or lead to hospitalization. It is also possible from the description of the nature of adverse reactions to get some information about the severity of the effects and make cost estimations. However, it is not possible to identify, for example, the medical expenditures or number of days lost from work due to all kinds of ADRs.

There are two main costs associated with ADRs: cost of treating illnesses due to ADRs and cost of avoiding ADRs. These two costs are interrelated and increased cost of avoiding ADRs will probably lead to a reduced cost of treating illnesses due to ADRs. The main issue for health care decision makers is therefore to find the right balance between costs and benefits of drug therapies.

From literature reviewed and summarized studies investigating cost and occurrence of ADRs. Three different approaches to assess the costs of ADR are distinguished. The first is cost studies, as following three steps must be done to estimate the costs: define ADR, estimated the incidence of ADRs and measure the costs of ADRs. Most cost studies have focused on hospitalization due to ADRs and the literature shows that about 3-7% of all hospitalizations are caused by ADRs.(36, 39, 41, 42) The second approach concerns costs and benefits of safety: the decision to prescribe, use distribute or produce a drug involves both costs and benefits and decisions makers must weigh costs of ADRs against costs of avoiding ADRs. The third approach discusses regulations and mechanisms for achieving an optimal balance between costs and benefits of drug therapies.

The real cost, time, skills and human resources necessary to communicate drug safety issues pro-actively to the media, the public and health professionals need to be carefully considered. Such planning and resources need to be given a higher priority than in the past. Local issues such as culture, literacy and the socio-economic status of the population at risk may have bearing on the way the message is presented. Communication of information must ensure that participants' rights to confidentiality are protected.

The costs to society of drug-related problems. When considering the cost of disease to society, ADRs and what is spent on detecting, preventing and managing them need to be included in the analysis. As pharmaceuticals become an increasingly prominent item in health budgets, and reliance is increasingly placed on physicians for controlling costs and curtailing their prescribing practices, ADRs have growing importance in addressing health costs.

Table 4. Studies about cost of adverse drug reaction (focused on hospitalization). (43)

Reference, Service	Study design and Sample Size	Major Selected Outcomes Reported	Results
Leape at,18 Medical ICU	Pre-post (N = 275) Pre (I = 75, C = 50) Post (I = 75, C = 75)	Intervention Group	
		ADEs, pre vs post, No.	33.0-11.6 per 1000 patient-days, *P*< .001
		Preventable ADEs, pre vs post No.	10.4-3.5 per 1000 patient-days, *P*< .001
		Control Group	
		ADEs, pre vs post, No.	34.7 vs 46.6 per 1000 patient-days, *P*< .76
		Preventable ADEs, pre vs post No.	10.9 vs 12.4 per 1000 patient-days, *P*< .001

Table 4. Studies about cost of adverse drug reaction (focused on hospitalization), (continued).

Reference, Service	Study design and Sample Size	Major Selected Outcomes Reported	Results
Bjornson et al,	Quasi-experimental	ADRs documented, %	1.7 (I) vs 0.5 (C); *P*=NR
General Medicine	(N = 3081)	ICU transfer, %	5.8 (I) vs 8.5 (C); *P*=.02
and Surgery	I = 1201	Readmission at 30 d, %	10 (I) vs 11.1 (C); *P*=NS
	C = 1880	In-hospital mortality rate, %	1.75 (I) vs 2.45 (C); *P*=.20
		Length of stay, log-d	7.6 (I) vs 8.2 (C); *P*=.03
Clapham et al,	Pre-post	Length of stay, d	10.02 (I) vs 11.53 (C); *P*=NS
General Medicine	(N = 1155)	Hospital cost per patient,$	5997 (I) vs 7290 (C); *P*<.05
and Surgery	I = 496	Drug cost per patient, $	494 (I) vs 649 (C); *P*=NS
	C = 659		

Table 4. Studies about cost of adverse drug reaction (focused on hospitalization), (continued).

Reference, Service	Study design and Sample Size	Major Selected Outcomes Reported	Results
Haig and Kiser, General Medicine	Randomized (N = 619) I = 332 C = 287	Length of stay, d	5.9 (I) vs 7.2 (C); *P*=.004
		Hospital charge per patient,$	6122 (I) vs 8187 (C); *P*=.001
		Pharmacy cost per patient,$	173 (I) vs 287 (C); *P*=.01
		Pharmacy charges per patient,$	652 (I) vs 1020 (C); *P*=.001
Boyko et al, General Medicine	Randomized (N = 867) I = 414 C = 453	Length of stay, d	4.2 (I) vs 5.5 (C); *P*<*.001*
		Hospital cost per patient,$	4501 (I) vs 6155 (C); *P*<.001
		Pharmacy cost per patient,$	481 (I) vs 782 (C); *P*<.001

Table 4. Studies about cost of adverse drug reaction (focused on hospitalization), (continued).

Reference, Service	Study design and Sample Size	Major Selected Outcomes Reported	Results
Kucukarslan et al, General Medicine	Nonrandomized, single-blind (N = 165) I = 86 C = 79	Preventable ADEs per 1000 patient-days,No.	5.7 (I) vs 26.5 (C); *P*=NR
		ADEs, No.	2 (I) vs 9 (C); *P*=.02
		Length of stay, d	0.3 d shorter, I vs C; *P*=NS
Nester and Hale, Admission	Randomized, (N = 100) I = 50 C = 50	Herbal and nonprescription medications per patient, No.	5.1 (I) vs 1.5 (C); *P<.001*
		Patient with incorrect allergy information identified, No.	4/50 (I) vs 0/50 (C); *P<.001*
		Time from admission to entry of allergy information, min	68 (I) vs 156 (C); *P<.005*
		Medication histories clarified by community pharmacies, %	24 (I) vs 4 (C); *P<.001*

Table 4. Studies about cost of adverse drug reaction (focused on hospitalization), (continued).

Reference, Service	Study design and Sample Size	Major Selected Outcomes Reported	Results
Stowasser et al,	Randomized,	Readmissions per subject at 30 d, No.	0.12 (I) vs 0.46 (C); *P=.06*
Admission and	(N = 240)	Health care professional visits at 30 d, No.	7.54 (I) vs 9.94 (C); *P<.05*
discharge	I = 113	Patient with > 1 pharmacist intervention, %	68 (I) vs 44 (C); *P<.05*
	C = 127	Patient with > 1 medication change, %	97 (I) vs 90 (C); *P<.05*
		Health status, SF-36	No charge; P>.05
Bolas et al,	Randomized,	Mismatch between discharge and home drug list	1.5 (I) vs 7 (C); *P<.005*
Discharge	(N = 162)	Drug name, %	10 (I) vs 17 (C); *P<.07*
			11 (I) vs 18 (C); *P<.004*
	I = 81	Drug dose, %	
	C = 81	Drug frequency, %	

Table 4. Studies about cost of adverse drug reaction (focused on hospitalization), (continued).

Reference, Service	Study design and Sample Size	Major Selected Outcomes Reported	Results
		Error in drug therapy knowledge	15 (I) vs 43 (C); *P*<.001
		Drug name, %	14 (I) vs 39 (C); *P*<.001
		Drug dose, %	15 (I) vs 39 (C); *P*<.001
		Drug frequency, %	
		Readmission at 30 d	*P* >.05 (NS)
Lipton and Bird, Discharge and telephone follow-up	Randomized (N = 706) I = 350 C = 356	Medical care use (charge and hospital), d	*P* = NS
		Medication compliance score	94.4 (I) vs 91.4 (C); *P*=.04
		Assessment 1	94.4 (I) vs 92.3 (C); *P*<.001
		Assessment 2	92.7 (I) vs 84.6 (C); *P*=.02
		Patient knowledge of purpose of medications, %	

Table 4. Studies about cost of adverse drug reaction (focused on hospitalization), (continued).

Reference, Service	Study design and Sample Size	Major Selected Outcomes Reported	Results
		Assessment 1	95.7 (I) vs 84.9 (C);
		Assessment 2	*P*<.001
		Polypharmacy at assessment 2 (12-14 wk), No.	5.16 (I) vs 6.75 (C); *P<.001*
		Long-term medications	8.30 (I) vs 12.04 (C);
		Total daily doses of medications	*P*<.001
		Length of stay, d	7.2 (I) vs 8.2, d (C); *P=.06*
Schnipper et al, Discharge and telephone follow-up	Randomized (N = 176) I = 92 C = 84	ADEs, %	18 (I) vs 16 (C); *P=.99*
		Preventable ADEs, %	1 (I) vs11(C); *P=.01*
		Readmission or emergency department visit at 30 d, %	30 (I) vs 30 (C); *P=.99*
		Medication compliance score	88.9 (I) vs 87.5 (C); *P=.91*

Table 4. Studies about cost of adverse drug reaction (focused on hospitalization), (continued).

Reference, Service	Study design and Sample Size	Major Selected Outcomes Reported	Results
Fraser et al, Antibiotics	Randomized (N = 225) I = 127 C = 98	Antibiotic charges per patient, $	1287 (I) vs 1673 (C); *P=.05*
		Daily doses of IV antibiotic per patient, n	10.16 (I) vs 13.59 (C); *P=.09*
		Clinical response, %	79.5 (I) vs 80.6 (C); *P=NS*
		Length of stay, d	20.0 (I) vs 24.7 (C); *P=NS*
		Readmission at 30 d, %	15.0 (I) vs 10.2 (C); *P=NS*
		In-hospital mortality, %	13.4 (I) vs 11.2 (C); *P=NS*
		Readministration of antibiotics within 7 d, %	4.7 (I) vs 13.3 (C); *P=.01*
Gentry et al, Antibiotics	Pre-post (N = 7219) I = 3570 C = 3649	In-hospital mortality, %	6.61 (I) vs 8.28 (C); *P=.01*
		Readmission because of infection, %	10.42 (I) vs 10.96 (C); *P=.46*
		Length of stay, d	10.8 (I)vs 13.2 (C); *P<.001*

Table 4. Studies about cost of adverse drug reaction (focused on hospitalization), (continued).

Reference, Service	Study design and Sample Size	Major Selected Outcomes Reported	Results
Bailey et al,	Randomized	Intravenous antibiotic, d	
Antibiotics	(N = 102)	Hospital A	1.2 (I) vs 1.9 (C) 0.4 (I) vs
	Hospital A	Hospital B	2.4 (C);P=.01, ANOVA
	I = 41	Antibiotic cost	
	C = 38	Hospital A, $	21.38 (I) vs 29.36 (C)
	Hospital B	Hospital B, $	13.40 (I) vs 54.79 (C);
	I = 10		P = .03, ANOVA
	C = 13	Length of stay, d	
		Hospital A	4.9(I)vs 4.4 (C)
		Hospital B	4.8(I)vs4.8(C)
			P = .95, ANOVA

Table 4. Studies about cost of adverse drug reaction (focused on hospitalization), (continued).

Reference, Service	Study design and Sample Size	Major Selected Outcomes Reported	Results
		Readmission at 30 d, %	
		Hospital A	34 (I) vs 10 (C)
		Hospital B	10 (I) vs 7.7 (C); P = .02, ANOVA
		In-hospital mortality, %	
		Hospital A	4.9 (I) vs 5.3 (C)
		Hospital B	10 (I) vs 7.7 (C); P = .96, ANOVA
Gums et al, Antibiotics	Randomized (N = 252) I = 127	In-hospital mortality, %	6.3 (I) vs 12.0 (C); *P=.17*
		Length of stay from randomization, d	5.7 (I) vs 9.0 (C); *P=.001*

Table 4. Studies about cost of adverse drug reaction (focused on hospitalization), (continued).

Reference, Service	Study design and Sample Size	Major Selected Outcomes Reported	Results
	C = 125	Overall length of stay, d	10.1 (I) vs 14.5 (C); *P=.001*
Destache et al, TDM: aminoglycosides	Randomized (N = 145) I = 75 C = 70	Nephrotoxicity, %	8 (I) vs 14.4 (C); *P=.08*
		Febrile period, d	2.09 (I) vs 3.84 (C); *P<.05*
		In-hospital mortality, %	18.7 (I) vs 10.0 (C); *P>.05*
		Length of stay, d	13.4 (I) vs 18.4 (C); *P=.08*
		Hospital cost per patient, $	7102 (I) vs 13758 (C); *P<.05*
Destache et al, TDM: aminoglycosides	Retrospective (N = 46) I = 23 C =23	Duration of aminoglycoside therapy, d	6.27 (I) vs 7.65 (C); *P=NS*
		Dosage changes, No.	1.5 (I) vs 1.1 (C); *P=NS*
		Temperature return to normal, d	1.76 (I) vs 3.18, d (C); *P<.05*

Table 4. Studies about cost of adverse drug reaction (focused on hospitalization), (continued).

Reference, Service	Study design and Sample Size	Major Selected Outcomes Reported	Results
		Heart rate return to normal, d	1.0 (I) vs 3.75 (C); *P=.005*
		Respiratory rate return to normal, d	1.63 (I) vs 3.95 (C); *P=.05*
		Maximum peak, µg/mL	6.31 (I) vs 5.82 (C); *P=NS*
		Length of stay, d	13.09 (I) vs 19.08 (C); *P<.05*

Abbreviations: ADE, adverse drug event; ADR , adverse drug reaction; ANOVA, analysis of variance; C, control group; I, intervention group; ICU,intensive care unit; IV, intravenous; NR, not reported; NS, not significant; Pre-post, before or after intervention; SF-36, 36-Item Short-Form Health Survey; TDM, therapeutic drug monitoring;

1.6 Preventability of adverse drug reactions

An ongoing program should be in place for preventing, monitoring, and reporting adverse drug reaction. The program should include timely communication about the occurrence of adverse drug reactions to affected patients, their caregivers and other providers. The pharmacist participates in reporting ADEs to institutional committees and to the Food and Drug Administration (FDA) Medwatch program. The pharmacist identifies and assists in the management and prevention of ADRs; the pharmacist develops process improvements to reduce medication errors and preventable ADRs.

A landmark study(44) involving critical care pharmacists confirmed that pharmacist rounding in the ICU with the multidisciplinary team reduces preventable ADRs and associated costs caused primarily by prescribing errors. Pharmacist intervention during prescribing decreased the rate of preventable ADRs by 66% from 10.4 to 3.5 per 1000 patient-days ($p < .001$). Pharmacist recommendations were categorized as medication order clarification (45%), provision of drug information (25%), and recommendation of alternative therapy (12%). Based on an estimated cost of $4,685 per preventable ADR, the annualized financial impact in the unit studied would be $270,000 (in 1995 dollars).

Other studies that have specifically evaluated this possibility reported that 28% of adverse events caused by drugs could have been prevented.

Many of the adverse drug reactions (ADRs) could be avoided and that if, as some studies seem to indicate, the avoidance values were similar in those patients hospitalized in Healthcare, the estabalishment of a program designed to decrease ADRs and to improve the patient’s quality of care could have a favorable cost / benefit relationship.

Preventable Adverse Drug Reaction Criteria (9)

- Drug inappropriate for the clinical condition.
- Drug dose, route, or frequency wrong for age, weight, or disease state of patient.
- Required therapeutic drug monitoring or laboratory tests not performed.
- Patient had a history of allergy or previous ADR to the drug

- Drug interaction.
- Toxic drug concentration or laboratory test.
- Patent had a known poor adherence with the suspected drug.

Current ADRs reporting systems and need to be reviewed and developed further in the face of these important future challenges. The following summarize some of the priority areas that need to be addressed either at a national or international level:

Detection of ADRs (17)

- Improve detection and accurate diagnosis of ADRs by healthcare providers and patients.
- Improve signal detection systems by facilitating the rapid availability of ADR data that may have international relevance.
- Develop and implement ADR detection systems that could benefit populations with restricted access to healthcare.
- Further development of automated signal detection systems used in spontaneous monitoring programmes.
- Improve access to reliable and unbiased drug information at all levels of healthcare.
- Improve access to safer and more effective medicines for neglected diseases prevalent in developing communities.
- Encourage awareness of drug safety and rational drug use among health professionals and the public.
- Integrate Adverse drug reactions activities into national drug policies and the activities arising from these. (e.g. standard treatment guidelines, essential drugs lists etc.)
- Develop systems which assess the impact of preventive actions taken in response to drug safety problems.

- Develop a better understanding of patients, their expectations of drugs and their perception of risk associated with the use of drugs in order to facilitate programmes that will better inform the public on the benefit and harm associated with drugs.

- Consider the sensitivity and specificity of current signal detection and assessment methods and the extent to which Contemporary Adverse drug reaction reporting systems have been successful in detecting and preventing potential disasters while avoiding the premature withdrawal of safe and useful medicines from the healthcare systems.

- Taking drug histories, and prescribing them, are among the commonest of activities of people who are unwell and of those who care for them. It makes sense that those medicines should be monitored to equally demanding standards as those evident in the development and evaluation of drugs, and that prescribing habits and the extent of rational and cost-effective use should be reviewed.

- Difficulties in communication between patients and healthcare providers represent an important and preventable potential source of harm. The following elements are likely to reduce significantly the risks of adverse effects and their severity :

  . an adequate drug history of the patient
  . rational prescribing and dispensing
  . proper counseling
  . the provision of clear and understandable drug information.

- Medication error and ADRs are well documented in hospitalized and non-hospitalized patients, and they contribute substantially to morbidity and mortality. They also contribute to the number of hospital admissions and are known to occur in the community setting. Many are predictable and preventable.(48)

- This suggests considerable opportunity for minimizing the risks of ADRs through rational use, monitoring and follow-up. Early detection is important, particularly in hospitals where systems for detecting ADRs and medication errors will save lives and money. Such systems might be linked to institutional, regional or national pharmacy and therapeutics committees so that information can be used to educate professional staff in safe drug use.

- The healthcare professionals, drug developers, requlators, public policy makers, patients and the general public all have their own complementary roles in achieving what is envisaged. Among the important issues are information, information sharing and broader communication. What we need is a continuing and dynamic development of modern professional practice. We must recognize that solutions to the challenges will come from those inspired and committed individuals and institutions round the world with a vision of improved public health and patient safety. Most important in this venture, is the need for a new spirit of sharing of information and intelligence in line with the vision and aspirations of the Erice Declaration.

1.7 Post-marketing surveillance (PMS) of adverse drug reactions

Post-marketing is the stage when a drug is generally available on the market. Post-marketing surveillance of medicines is mainly co-ordinated by The National Pharmacovigilance Centers.(12) In collaboration with the Uppsala Monitoring Centers (UMC) the Nation Centers have achieved a great deal in:

. Collecting and analysing case report of ADRs

. distinguishing signals from background “noise”

. making regulatory decisions based on strengthened signals

. alerting prescribers, manufacturers and the public to new risks of adverse reactions.

The number of National Centers participating in the WHO International Drug Monitoring Program has increased from 10 in 1968 when the Program started to 67 in 2002.(45) The centers vary considerably in size, resources, support structure, and scope of activities. Collecting spontaneous reports of suspected ADRs remains their core activity.

National centers have played a significant role in increasing public awareness of drug safety. As a result, pharmacovigilance is increasingly seen as more than a regulatory activity, having also a major part to play in clinical practice and the development of public health policy. This development is partly attributable to the fact that many national and regional centers are housed within medical hospitals, or poison and drug information centers, rather than within the confines of a drug regulatory authority.

The scope of activities of National Centers has expended to include communication of information about benefit, harm, effectiveness and risk to practitioners, patients and the public. Major centers in developed countries have established active surveillance program using record linkage and prescription event monitoring systems (PEM) to collect epidemiological information on adverse reactions to specific drug. Such systems have already been implemented in New Zealand, the United Kingdom, Sweden and the United States of America. The source and extent of funding of different National Centers also varies significantly, Most ministries of health fund their National Center, at least in part. The entire cost of a pharmacovigilance system, compared with the national expenditure on medicines or the cost of ADRs to the nation is very small indeed.

It is now generally accepted that part of the process of evaluation drug safety needs to happen in the post-marketing (approval) phase, if important innovations are not to be lost in an unduly restrictive regulatory net. Judgement as to whether and how this might happen lies with the regulators.

The stronger the national system of pharmacovigilance and ADR reporting, the more likely it is that reasonable regulatory decisions will be made for the early release of new drugs with the promise of therapeutic advances. Legislation governing the regulatory process in most countries allows for conditions to be placed on approvals, such as a requirement that three should be detailed pharmacovigilance in the early years after a drug’s release. However, to new drug or to significant therapeutic advances. It has an important role to play in the introduction of generic medicines, and in review of the safety profile of older medicines already available, where new safety issues may have arisen. In a developing country, these latter considerations are likely to be more important than the benefits a novel therapeutic entity might bring to an already pressed health service.

While spontaneous reporting remains a cornerstone of pharmacovigilance in the regulatory environment, and is indispensable for signal detection, the need for more active surveillance has also become increasingly clear. Without information on utilization and on the extent of consumption, spontaneous reports do not make it possible to determine the frequency of an ADR attributable to a product, or its safety in relation to a comparator. More systematic and robust

epidemiological methods that take into account the limitations of spontaneous reporting are required to address these important safety questions. They need to be incorporated into post-marketing surveillance programmes.

There are other aspects of drug safety that have been rather neglected until now, which should be included in monitoring latent and long-term effects of medicines.

These include :

. detection of drug interactions

. measuring the environmental burden of medicines used in large populations

. assessing the contribution of “inactive” ingredients (excipients) to the safety profile

. systems for comparing safety profiles of similar medicines

. surveillance of the adverse effects on human health of drug residues in animals, e.g. antibiotics and hormones.

A more difficult question is whether pharmacovigilance has resulted in inappropriate removal from the market of potentially useful medicines as a result of misplaced fears or false signals.

The Council for International Organizations of Medical Sciences (CIOMS) report on benefit-risk assessment of medicines after marketing has contributed to a more systematic approach to determining the merit of available medicines.(46) Systematic medical and prescription record linkage, with drug utilization studies, would contribute to greater accuracy. This is a responsibility that falls outside the strict traditional terms of reference of national pharmacovigilance centers.

In Thailand there is a structured system for linking each level of the hospital network. Each hospital has an active role in the surveillance and monitoring of adverse drug reaction caused by health products and is responsible for reporting events to one of the 22 nationwide regional hospitals. Each regional hospital acts as a center for technical support and assistance to other hospitals in their region. Regional hospitals communicate with the national center at the FDA and send on reports

received from other hospitals. The national center is responsible for communicating with other centers outside the country.

The PMS of ADR may be classified into three types, according to the circumstances of the report:

. Spontaneous Reporting System: when the report is made by an individual healthcare professional reporting an adverse event suffered by a patient or health product consumer.

. Intensive Reporting System: when the report is made for intensive monitoring in the early stages of the use of a health product.

. Clinical Trial : when the report results from clinical research.

1.8 The spontaneous reporting system (SRS)

System whereby case reports of adverse drug events are voluntarily submitted from health professionals and pharmaceutical manufacturers to the national regulatory.(12)

It was not until the disaster caused by thalidomide in 1961 that the first systematic international efforts were initiated to address drug safety issues . At that time many thousands of congenitally deformed infants were born as the result of exposure in utero to an unsafe medicine promoted for use by pregnant mothers. The Sixteenth World Health Assembly (1963) adopted a resolution that reaffirmed the need for early action in regard to rapid dissemination of information on adverse drug reactions led, later, to creation of the WHO Pilot Research Project for International Drug Monitoring in 1968.(45) The purpose of this was to develop a system, applicable internationally, for detecting previously unknown or poorly understood adverse effects of medicines. A WHO technical report followed based on a consultation meeting held in 1971.

From these beginning emerged the practice and science of pharmacovigilance. Systems were developed in Member States for the collection of individual case histories of ADRs and evaluation of them. The collection of international ADR reports in a central database, would serve the important function of contributing to the work of national drug regulatory, improve the safety profile of medicines, and help avoid further disasters.(20)

Careful study of adverse drug events may identify diagnostic features, syndromes or pathogenic mechanisms. Moreover, clinical, pathological and epidemiological information relating to adverse reactions is necessary for a full understanding of the nature of an adverse reaction and for identifying paients at risk.

Although spontaneous reporting is the mainstay of passive surveillance, the information obtained is inherently limited and likely to be insufficient for regulatory and clinical decisions. Active or intensive surveillance programmes for addressing serious safety concerns have had success in identifying and quantifying drug safety issues, using:

. case control networks
. hospital - based intensive monitoring systems
. record linkage systems
. epidemiological studies

ADRs have the potential to provide insights into structure-activity relationships, pharmacokinetic, pharmacodynamic and genetic factors affecting the action of medicines. They may provide leads for other novel, indications. This is why it is important for the negative connotation of an ADR to be removed and for systems to be developed that enable medical, pharmaceutical and chemical information to be applied constructively to a better understanding of how drugs work.

The success or failure of any spontaneous reporting system depends on the active participation of reporters. Although limited schemes for reporting by patients have been initiated recently, health professionals have been the major providers of case reports of suspected ADRs throughout the history of pharmacovigilance.

Originally physicians were the only professionals invited to report as judging whether disease or medicine causes a certain symptom by exercising the skill of differential diagnosis. It was argued that accepting ADR reports from physicians only, would ensure high quality information and minimize the reporting of unrelated, random associations. Studies have shown, however, that different categories of health professionals will observe different kinds of drug related problems.

Only by inviting reports from all professionals involved in the care of patients will it be possible to detect the full spectrum of complications related to pharmaceutical treatment. If, for example, only healthcare practitioners (including doctors, nurses and pharmacists) contribute to the pool of information, medicines used primarily by specialists will not be covered. To get a representative picture of the reality, all sectors of the healthcare system would need to be involved, such as public and private hospitals, healthcare practitioners, nursing homes, retail dispensaries, and clinics for traditional medicine. Wherever medicines are being used there should be a readiness to observe and report unwanted and unexpected adverse reactions.

Only a patient knows the actual benefit and harm of a medicine taken. Observations and reports made by a health professional will be an interpretation of a description originally provided by the patient, together with objective measurements. Some believe strongly that direct patient participation in the reporting of drug related problems will increase the efficiency of the pharmacovigilance system and compensate for some of the shortcomings of systems based on reports from health professionals only.

Patients who suspect they have been affected by an ADR are normally recommended to report to their doctor to enable the doctor to report it to the pharmacovigilance center.(39) However, since only 5% of doctors are estimated to participate in any pharmacovigilance system, this process is not efficient in ensuring that the patient’s concerns are being recorded. There are studies indicating that systems for recording patient concerns might identify new drug safety signals earlier than the professional reporting systems alone.

Limiting factor during research, such as study group selection, population type, age and gender, may be the cause of unexpected problems later. There have been such cases over the years, and they still occur:

. Thalidomide, an anti-emetic drug used for pregnant woman, was later found to be teratogenic

. Cerivastation, an antihyperlipidemia, caused rhabdomyosis

. A dietary supplement made from the herb Kara Kara caused liver injury.

Such examples highlight the importance of reporting adverse events suspected of being caused by health products. Subsequent investigation confirming such suspicions may save lives.

Because of these potential hazards, The World Health Organization astablished the WHO Program for International Drug Monitoring in the late 1960s. This, with cooperation from more than eighty countries (2005), aims to collect, monitor and analyse data about adverse events in order to detect early signals which indicate risk or hazard. Believing this program to be of great importance**,** the Thai Ministry of Public Health set up its spontaneous adverse drug reaction reporting system in 1983, and was the twenty-sixth member of the WHO Program.(45)

In 2001 the boundaries of the task were extended to cover all health products, under the responsibility of the FDA. In 2004, the monitoring system was renamed the Adverse Event Reporting System (AERS).

In the past, data needed for evaluating the risk of health products and detecting signals of potential hazards frequently came from reports and good systematic data collection in western countries. However, due to social and physical variations between Thais and western people-for example genetics, body mass, health patterns, consumer behaviour and epidemiologic factors-adverse reactions to some pharmaceutical products were not the same for Thai as for western people. (The only exception was for some drug used in the treatment of some tropical diseases.) This is why the establishment of the Thai national adverse event monitoring system was so essential.

The objective of the system are as follows:

. To detect new signals of unexpected adverse events, especially rare events.

. To publish statistics of the frequency of adverse events, both known and previously unreported.

. To detect risk factors or predisposing factors for adverse events.

. To produce risk assessment and analysis of the data collected on products; this enables medical personnel to prescribe drugs more accurately, safety and rationally, leading to better quality of patient welfare and public health.

. To gain new knowledge, leading to further study and research by medical and public health personnel.

. To establish the nation’s product safety database, allowing overall risk assessment and generating further regulatory or administrative measures such as label changes or product with drawals. It is also helpful in the communication of prompt and timely information to all interested parties, leading to the spread of greater confidence in health product usage.

The department of pharmacy, an Adverse Drug Reaction Monitoring Program (ADRMP) at Siriraj Hospital formed a team consisting of 4 pharmacists and one staff. ADRMP focused on a strategy for decreasing adverse drug reactions (ADRs) and preventable ADRs at Siriraj Hospital. This program aims to collect, monitor and analyse data about ADRs in order to detect early signals which indicate risk or hazard. ADRMP set up its spontaneous ADR reporting system. The report will then be sent to the FDA, The Thai Ministry of Public Health.

The cause-effect relationship of the ADRs to the suspected drug was evaluated according to the method of Naranjo et al.(2) This method consists of a series of ten questions that can be scored. The questions cover the following aspects: previous bibliographic information regarding the ADR, temporal sequence of drug administration and appearance of ADR, effect of drug concentrations and dose dependence, and a personal history of this type of ADR. To assess the preventability of each ADR the criteria developed by Schumock et al.(3)

1.9 The burden of adverse drug reactions (ADRs)

Table 5. The burden of adverse drug reactions (ADRs)

Hospital admissions	5% of all hospital admissions (Einarson, 1993)
ADRs while in hospital	6.7% of hospitalized patients (Lazarou et al., 1998)
Prolongation of hospital stay	Increased length of stay by 2 days (Bates et al., 1995)
Cost	Increases cost by approximately $2500 per patient (Bates et al., 1997)
Drug withdrawals	4% of drugs introduced in the UK between 1974 and 1994 (Jefferys et al., 1998)

Adapted from Toxicology 192 (2003)

Burden of ADRs on bed occupancy and cost

Patients with an ADR stayed a median of eight days.(47) Extrapolating this to the whole NHS bed base in England for patients aged > 16 years suggests that at any one time the equivalent of up to seven 800 bed hospitals may be occupied by patients admitted with ADRs. This is higher than the estimate in a recent systematic review (four to six 400 bed hospitals) (48), which was based on shorter hospital stays derived from smaller studies. However, it is important to exercise caution in interpreting this estimate of bed use as it is based on extrapolation from two hospitals to the whole NHS bed base, we were not able to determine the causative fractions for all the implicated drugs, and the estimate does not take into account the bed days saved through the beneficial effects of the drugs.

Data suggest that admissions related to ADRs cost the NHS up to £466m annually. Although estimates of costs in the literature vary (49), on a per capita basis our figure is comparable with the lower estimates from the United State and also with a total costs estimated in a recent UK systematic review.(48) Further detailed analysis, however, is required to provide more accurate figures.

PART II Management of the Adverse Drug Reaction Monitoring Program.

WHO International Programme for Adverse Reaction Monitoring (45)

National surveillance centers send information regarding ADRs to the WHO Collaborating Center for International Drug Monitoring (the Uppsala Monitoring Center) for analysis. The rational for setting up the WHO International Program for Adverse Reaction Monitoring, over 30 years ago, was to make it possible to identify rare ADRs that could not be identified through clinical trial program.

The Swedish government provides the only regular budgetary contribution to the centre. In each country participating (currently 58 full members and six associate members) in the WHO program, there is a national centre which is responsible for collecting spontaneously reported suspicions of ADRs originating from health professionals.

At the Uppsala monitoring center, reports are checked for technical accuracy and are then entered into the WHO database. The center has also set up an international panel of approximately 30 expert consultants who assist it in identifying new and clinically important adverse reaction signals within their own specific areas of expertise.

Difficulties associated with the database include: incompleteness of the data; delays in reporting of ADRs; the vast numbers of potential signals, many of which may be spurious; a lack of patient details, which makes causality assessment difficult; and limited resources for medical assessment of potential signals.

The role of the international system is to concentrate on rare but clinically significant reactions where pooling of international data is most likely to increase the chance of detection. An other important new approach in the signal analysis process is the combination of ADR reporting rates with information on drug utilization and demographic data on an international level. This provides a quantitative measure of the strength of association of a drug-reaction combination in the database.

Drug safety issues frequently differ between countries, so there is a need for each country to monitor its own profile of adverse drug reactions, rather than rely solely on data made available from elsewhere, or on decisions made in other countries. Efforts to improve the reporting of ADRs by health care professionals will also increase the detection of such reactions.

Future challenges in the reporting of adverse drug reactions include a need to improve reporting to the Uppsala Monitoring Center, a need to increase the openness and trust between parties involved in drug-safety assessment and communication, and a need to attract more resources for signal analysis and follow-up.

Healthcare systems rely mainly on the detection and reporting of suspected ADRs to identify new reactions, record the frequency with which they are reported, evaluate factors that may increase risk and provide information to prescribers with a view to preventing future ADRs.

2.1 Methods and Systems to Detect ADRs in hospitals

Detection of adverse drug reactions (ADRs) in hospitals offers the change to detect serious ADRs resulting in hospitalization and ADRs occurring in hospitalized patients, i.e. patients with high comorbidity and receiving drugs that are administered only in hospitals.(17)

The most commonly applied methods involve stimulated spontaneous reporting of doctors and nurses, comprehensive collection by trained specialists, more recently, computer-assisted approaches using routine data from hospital information systems. The different methods of ADR detection used result in different rates and types of ADRs and, consequently, in different drug classes being responsible for these ADRs. Another factor influencing the results of surveys is the interpretation of the term ADR.

Depending on the method used for screening of patients, a high number of possible ADRs and only few definite ADRs are found. These variations have to be taken into account when comparing the results of further analyses performed with these data. ADR rates and incidences in relation to the number of drugs prescribed or patients exposed have been calculated in only a few surveys and program, and this interesting pharmacoepidemiological approach deserve further study.

In addition, the pharmacoeconomic impact of ADRs, either resulting in hospitalization or prolonging hospital stay, has estimated using different approaches. Although detection of ADRs in hospitals offers the opportunity to detect severe ADRs of newly approved drugs, these ADRs are still discovered by spontaneous reporting systems. The prospects offered by electronic hospital information systems as well as implementation of pharmacoepidemiological approaches increases the possibilities and the value of ADR detection in hospitals.

2.1.1 Usefulness of ADRs detection in hospitals

- ADRs can be the reason for hospital admission or they can occur during hospital stay. Both ‘types’ of ADR can be assessed with different goals.
- Moderate to severe ADRs lead to hospital admission, these ADRs can be used to generate signals for serious risks, especially of newly approved drugs.
- A comprehensive collection of all ADR-related hospitalizations to one hospital or department enables the ADR-associated morbidity as well as the economic impact of ADRs to be calculated.(18, 19)
- Using prescription data of the region (record linkage), incidences of serious ADRs for frequently administered drugs can be estimated and compared.
- Collecting ADRs in the hospital setting provides, particularly, data on safety of drug use in special patient populations (e.g. patients with haemodynamic instability) and data on safety of drugs used exclusively in hospitals, such as most of the intravenous antibacterials, cytokines and anaesthetics, consequences (e.g. prolongation of hospital stay) and associated cost can be calculated.(14, 15)

2.1.2 Methods applied for detection of ADRs in hospitals

- The shortcomings of spontaneous reporting systems in hospitals, even after special training of doctors and nurses, are similar to the problem of under-reporting known for the ambulatory sector.
- Stimulated reporting or intensified collection of ADRs, as a result of increased awareness of physicians, nurses and pharmacists, may yield higher reporting rates, but is not yet sufficient for calculation of prevalence and incidence of ADRs.
- A comprehensive collection of ADRs is time consuming and can be performed only in the framework of well defined program.
- ADR collection under predefined conditions (e.g. only ADRs occurring on an intensive care unit or detected by means of computer signals, such as pathological laboratory values) may be implemented into the daily routine of hospitals as a means of quality control.(50)

2.1.3 Comprehensive collection of ADRs in hospitals

- Comprehensive collection of ADRs can be used to detect ADRs occurring during hospitalization and ADRs leading to hospital admission. This method can be applied either retrospectively or prospectively.
- Retrospective analyses rely on chart review.(20, 29, 51) However, according to Lau and co-workers(52), 25% of prescription drugs used were not recorded in the medical charts, but their use was indicated in the hospital pharmacy record. 61% of patients in general internal medicine wards took at least one drug that was not documented in the charts.
- Prospective collection of ADRs (and adverse drug events; ADEs) is performed by frequent, usually daily, visits by a trained health professional (e.g. clinical pharmacologist, pharmacist or nurse) on selected wards or departments over a restricted time period to record all patients and all events.(44, 53)

2.1.3.1 ADRs occurring during hospitalization

- During daily ward rounds, Leape and colleagues(44), identified 33 ADEs (including prescribing errors) per 1000 patient-days on an intensive care unit.

- Moore and colleagues(54), 6.6% of patients in medical departments experienced an ADR.
- In a study by the French network of regional pharmacovigilance centers, the prevalence of ADRs in hospitalized patients (all specialities) was calculated to be 10.3% (of which 33% were serious) with an incidence rate of 1.8%.(55)
- A meta-analysis pooled data from publications with different methodological approaches and estimated an average rate of 10.9% of patients experiencing an ADR during their hospital stay (serious 2.1%, fatal 0.19%).(34) Because of economic pressures, duration of hospitalization decreases steadily in most hospitals.
- Thus, it may be more helpful in future to calculate incidence of ADRs per patient-day rather than per patient to compare data between hospitals and over time. It would be interesting to know whether shorter duration of hospitalization results in more or fewer ADRs.

2.1.3.2 ADRs leading to hospital admission

- In the aforementioned study by Moore and colleagues(54), in medical departments, 3% of admissions were caused by ADRs.
- Hallas et al.(56) reported that 8.4% of hospital admissions to medical wards were caused by ADRs and a further 3.0% by therapeutic failures.
- In a French cross-sectional study, comprehensive surveillance of all patients admitted to 62 departments of internal medicine at 33 hospitals during an observation period of 14 days was conducted.(39) From a total of 3137 admissions, 3.19% were due to an ADR.
- Slightly lower incidence rates of ADR-related admissions were reported from Australian studies (2.4 to 3.6%)(57), and US studies (4.7%).(34)

- Interestingly, Muehlberger and colleagues(18) reported a frequency of ADR-related admissions of 1.6% for studies using spontaneous of intensified ADR reporting, whereas the ADR frequency in studies with comprehensive collection came to 5.7%, emphasizing the influence of the type of data collection on the estimated incidence rates of ADRs.

2.1.4 Detection of ADRs using computer-assisted approaches

- Computerised hospital information systems represent an elegant tool to detect ADRs.
- A similar procedure has been reported from Switzerland for two medical departments in two different hospitals.(58) All available routine data, such as demographic data and laboratory values, in addition to drug prescriptions and predefined ‘clinical events’, were entered into a relational database. Causality assessment was performed after patients’ discharge, and in 11% of all hospitalized patients at least one clinically relevant ADR was recorded.
- In a pilot study(20) retrospectively analyzing 153 admissions to a gastroenterological ward, 40 ADRs were detected by chart review. 65% of these ADRs could have been identified by abnormal laboratory values.
- A comparison with stimulated reporting was published by Dormann et al.(59), 34 ADRs were detected by the automated system and only 17 reported by physicians. Even when compared with retrospective chart review, monitoring of abnormal values reveals slightly more than half of all ADRs occurring on medical wards. In addition, depending on the speciality of the department/ward, different sensitivities and specificities for pathological parameters are calculated because of the prevailing underlying diseases.
- The use of this method for pharmacoepidemioloty and pharmacovigilance, however, remains to be proven, especially with more hospitals having electronic patient charts.

2.1.5 Economic considerations

- Program to detect ADRs were used to calculate attributable excess length of stay, cost of hospitalizations due to ADRs and additional use of healthcare resources.

- A meta-analysis on studies detecting ADR-related hospital admissions, the cost of admissions to medical departments has been calculated.(19) These ADR-related admissions resulted in an average length of hospital stay (LOS) of 8.7 days, allowing for country-specific calculations of the impact on the healthcare system.

- The situation becomes more complex when the prolongation of LOS due to ADRs occurring during hospitalization is calculated. By just comparing the crude LOS data of patients with and without ADR, Moore et al.(54) estimated an increase of the LOS of about 8.5 days. When adjusting for the above-mentioned risk factors age, sex and number of drug classes, the difference decreased to 7 days.

- Interesingly, according to the judgement of the responsible physician, the ADRs prolonged LOS only by 3 days. When the LOS is even further corrected for admission diagnoses, the ADR-attributable additional LOS comes to 3.5 days.(59)

- Implementation of a comorbidity index and a severity of disease scale into the estimations further reduces the excess LOS caused by ADRs to 2.2 days.(14)

- These examples emphasise the relevance of adjustment for underlying diagnoses and ADR risk factors to provide for meaningful economic calculations.

- All instances, where the ADR was not preventable or where there were no treatment alternatives, the risk and cost of nontreatment has to be taken into consideration.

- Most studies took LOS as an indicator for economic impact of ADRs, this may not be suitable for the perspective of the hospital, depending on the national health system and reimbursement scheme.

- Although health insurance in some countries may pay per hospital day, the additional cost of ADRs may not be covered adequately in the Diagnoses-Related Group (DRG) system.
- At present, no standards for the estimation of ADR-related cost for hospitals and the healthcare systems have been established. It has often been claimed that prevention of ADRs could result in cost saving.(19) Prerequisites are preventability of ADRs (roughly 30%) (19, 50) and implementation of prevention programmes.(44, 60)
- The preventability of ADRs has so far been judged only retrospectively, i.e. after occurrence of the ADR. It has not yet been demonstrated if indeed 30% of ADRs can be prevented.
- Intervention programmes including evening symposia for general practitioners and leaflets on ADRs showed a reduction of preventable ADR-related hospital admissions by 83%.(60)
- Unfortunately, only very few of the studies published on ADR detection in hospitals were followed by intervention programmes, demonstrating the potential economic impact of ADR prevention.
- Computer-assisted methods and record linkage with ambulatory healthcare data represent a feasible way for the future, and widespread use may be implemented especially as a means of quality management. The methods and systems used have to be further evaluated, and more standardization (e.g. with regard to definition of ADR terms, causality assessment and pharmacoeconomic analyses) is required.

2.2 Adverse Drug Reaction Monitoring Program (ADRMP) at Siriraj Hospital

Siriraj Hospital is a medical university hospital under the Faculty of Medicine Siriraj Hospital, Mahidol University, the Ministry of education. There are 2,500 beds. In fiscal year 2006, there were 1,448,896 out-patients and 387,523 in-patients, approximately. The average length of stay was 8 days per patient. The number of in-patient classified by department was shown in table 6. There were 110 pharmacists of pharmacy department in Siriraj Hospital.

Table 6. The number of in-patient were classified by department at Siriraj Hospital 2006.

Department	Number of in-patient
Medicine	25,678
Surgery	25,712
Obstetrics & Gynecology	36,333
Pediatrics	17,483
Oto - rhino - laryngology	4,315
Ophthalmology	10,183
Orthopedic Surgery	8,161
Rehabilitation Medicine	182
Radiology	2,361
Psychiatry	421
Total	**130,829**

In the ADR Monitoring Program, normal practice is that all new ADR card reports for drug substances. The main purpose of the ADR card scheme is to provide early warnings' of previously unsuspected ADRs (signals). An action plan for preventable ADRs, the clinical importance of the ADR and its potential for prevention.

2.2.1 Management of ADR Monitoring Program

- Multi-disciplinary system; ADR committee formed a team consisting of a physicians, pharmacists, and nurses.
- This program aims to collect, monitor and analyse data about ADRs in order to detect early signals which indicate risk or hazard, focused on a strategy for decreasing ADRs and preventable ADRs.
- ADRMP set up its spontaneous ADR reporting system.

- The report will be sent to the FDA, The Thai Ministry of Public Health.
- To assess the preventability of each ADR the criteria developed by Schumock et al.(3)
- The suspected drug was evaluated according to the method of Naranjo et al.(2)

2.2.2 Pharmacists activities and responsibilities focused on inpatients

- Patient interview
- Medication profile and medical record review
- Presentation of drug regimen recommendations to care team or physician
- Participating on rounds with inpatient care team
- Drug monitoring and recommendation follow-up
- Drug therapy dosing or management
- Documentation of clinical interventions or recommendations
- Patient counseling before discharge
- Telephone follow-up after discharge

2.2.3 Pharmacists assessed avoidability of the ADRs using the definitions developed by Hallas et al. (38)**,** as follows:

- **Definitely avoidable**- the ADR was due to a drug treatment procedure inconsistent with present day knowledge of good medical practice.
- **Possible avoidable**- the ADR could have been avoided by an effort exceeding the obligatory demands of present day knowledge of good medical practice.
- **Unavoidable**- the ADR could not have been avoided by any reasonable means.

2.2.4 Monitoring adverse drug reactions: implications for practice

- Wherever medications are prescribed, adverse drug reactions (ADRs) are an important cause of morbidity.
- Strategies to systematically detect and action ADRs are not always incorporated into practice. Therefore, the burden of treatment is higer than it needs to be.
- The numerous omissions, imprecise nature, and practical difficulties of some instruments, together with any lack of resources to action problems identified, may detract from the usefulness of this approach.
- Further work is needed to explore the clinical effectiveness of the ADR profile in a range of settings.

2.2.5 Outcome measures

- Mortality
- Adverse drug reactions/adverse drug events
  - Identification of frequency and severity of events
  - Prevention of events
  - Events requiring further treatment
- Health services use
  - Admission and readmission rates because of complications
  - Transfer to more intensive care
  - Emergency department/urgent care use after discharge
  - Length of stay
- Changes in medication regimen
  - No. of medications
  - Medication appropriateness
  - Nonindicated medications

2.2.6 Expected outcomes and benefits of ADR Monitoring Program

- Patient safety
- Prevention of ADRs could result in cost savings of drug therapy
- Decreased length of hospitalization
- Encourage health care professionals to reporting of ADRs in Siriraj hospital
- Implementation of prevention program
- Ultimately improve safety through early detection and treatment of serious ADRs
- Collection of ADRs in the hospital setting provides, particulary, data on safety of drug use in patient populations
- To improve the detection of previously unknown serious ADRs and knowledge about the regulatory actions taken in response to ADR reports.

PART III Costs-benefits determination.

3.1 Costs

Pharmacoeconomic studies on the costs of adverse reactions suggest that healthcare providers pay considerable amounts from health budgets towards covering cost associated with them. In most countries the extent of this expenditure has not been measured.

Cost associated with Adverse Drug Reactions were direct medical costs, direct non-medical costs and indirect costs. Direct medical costs are those directly associated with patient care, including laboratory tests, medications, and other supplies. These costs are built for the entire hospital, are reported on the procedure level, and are accumulated at the department level. Procedure level costs represent an average for the time period covered. Direct costs for non-medical services that are the result of illness or diseases but do not involve purchasing medical services, such as specical food services, transportation for health care, family care during treatment.

Indirect costs are those which cannot be directly identified with patient care or a particular unit within the hospital. Indirect costs are attributed to departments that provide support to the patient care areas and include costs of morbidity and mortality resulting from illness or disease, such as loss productivity. This Cost Analysis, the most important costs are direct medical costs in assessing costs of alternative medical treatment.

Cost of the intervention were divided into:

1. **Tangible costs:**

- **Capital cost:** these cost include opportunity costs of land and depreciation costs of building and depreciation costs of durable goods. The total costs were spread over their useful lifetime by straight-line depreciation method.

- **Operating costs: includes labor cost and material cost**

. **labor costs** are defined as incentives of work, such as salaries, wages, overtime, health benefits and other benefits income supplements, bonus, housing and travel allowances.

. **Material costs** are costs of consumed materials in an organizational operation. They are drug and medical supplies, utility such as electricity, telephone, mailing, office materials, and other materials such as household material, fuel, kitchen goods.

2. **Intangible costs:**

Costs of pain suffering, grief, and other non-financial outcomes of disease and medical care.

Note that these analyses are limited to the hospital perspective thus any costs related to professional fess are not considered.

A cost analysis of ADRs raises two key issues. The first is that of the perspective of the analysis, which is important as certain costs or benefits may not be relevant for all parties. The social perspective is often preferred in pharmacoeconomic evaluations and is supposed to include all relevant costs. An analysis of the costs of ADRs from a social perspective is, however, difficult to perform as most ADRs are mild and do not lead to contact with medical care. However, these mild problems are

important to include in a cost analysis as they are common and probably cause substantial costs.

The second issue is to define what should be considered an ADR. It is not easy to define ADRs or separate them from other symptoms or complaints. The pharmacological effects of drug are often complex and there are also psychological or placebo effects, which must be considered. Consumption of drugs will have several effects on the patient, but all of these effects are not to be considered adverse reactions. It is also difficult to know if the symptoms are caused by the drug itself, by non-compliance with the drug or by other, nondrug-related factors. Sofar is that we do not have a reliable estimate of the social direct and indirect cost of ADRs. We do not have the necessary epidemiological information to establish causal link between drug consumption, ADRs and the cost of ADR-related illnesses.

The direct and indirect costs resulting from ADRs are difficult to estimate as description of the consequences of most adverse reactions is very limited. It is possible to identify and measure the costs of those cases where ADRs are probable causes of death or lead to hospitalization. It is also possible from the description of the nature of adverse reactions to get some information about the severity of the effects and make cost estimations. However, it is not possible to identify, for example, the medical expenditures or number of days lost from work due to all kinds of ADRs.

The cost of ADRs or events during hospitalization is possible to estimate by the increased length of hospitalization. The literature on ADR-related costs other than those caused by hospitalization is very small. Johnson and Bootman calculated the cost of all drug-related morbidity and mortality by estimates from practicing pharmacists.(61) The resulting cost varied from a conservative estimate of $30 billon to a worst-case estimate of $130 billon annually in the US.(61) The result must, however, be approached with caution as it was based on uncertain assumptions and included problems like untreated indications, inappropriate drug choices, over dosages and noncompliance.

There have been some attempts to estimate the costs of ADRs but the possibilities of performing empirical studies of the total cost of ADRs are limited and it is therefore interesting to analyse the problem from a theoretical point of view as well.

3.2 Benefits

From an economic point of view the problem of ADRs is not a problem of minimizing but of optimizing, to find the right balance between the costs and benefits. The costs of reducing ADRs may exceed benefits and we have seen support for a rational decision making policy in healthcare provider.(1)

The Benefits to cost of avoiding ADRs can be classified by Intervention are as follows: direct benefits, indirect benefits, and intangible benefits of health.

Direct benefits: are incremental reduction in the direct costs due to the intervention. That are calculated based on a significant change occurring between the before and after intervention periods of the experimental hospital. Direct benefits were identified as the savings in drug expenditures, calculate the direct benefit as costs averted of the monitoring service, based on information.

The outcomes measured for benefit (or costs) calculation were medication cost, length of stay (during hospitalization or treatment), mortality rate.

Indirect benefits: were patient productivity gains attributed to estimate by the decreased length of hospitalization (length of stay; LOS) and decreased mortality rate calculated by morbidity savings and mortality savings.

Intangible benefits: of health resulting from ADRs are difficult to estimate as description of the consequences of most adverse reactions is very limited. These include the psychological benefits of health, such as satisfaction with life or health.

3.3 Cost-benefit analysis (CBA)

Cost benefit analysis is methodology to compare the costs and benefits of a program; cost and benefits expressed in monetary terms.

A cost-benefit analysis from a societal perspective in the ordinary way, with monetary values of the benefits, is difficult to make as the benefits of drug therapy is not easily quantified. Instead, researchers will identify the relevant decision

makers in the drug area and discuss the costs and benefits from their point of view.(1) ADRs are a cost for patient, physician, pharmacist, nurse and healthcare provider. Investments in research and development, and also resources used to inform doctors and patients about known adverse reactions can partly be seen as costs to avoid ADRs.

Merely identifying the costs and benefits of drug consumption is not enough to decide whether more resources should be spent on reducing ADRs or not. The important question is whether the balance between the cost of ADRs and the cost of avoiding ADRs is right. If we increase the costs of avoiding ADRs we will reduce the cost of treating them. It is reasonable to assume that we have a diminishing marginal productivity in this program, i.e. the marginal cost of reducing the number of ADRs is increasing.

The reason for the diminishing marginal productivity can partly be explained by the fact that the benefit per patient from a therapy is usually reduced when the number of treated patients increases.

CHAPTER III
METHODOLOGY

1. Study design

This study was designed as descriptive cross-sectional study, data of ADRs conduceted in Adverse Drug Reaction Monitoring Program(ADRMP) of Siriraj Hospital during 1-year of review, focused on patients with ADRs during hospitalization.

Data source; ADR Monitoring Program to improve the detection of ADRs at Siriraj Hospital. The Naranjo method uses a standardized set of questions to classify the ADR in relation to the suspect drug or relationship to a drug as either definite, probable, possible, or negative. Information on each ADR were stored in a relational database; data elements included patient demographics (patient age, sex), medical record number (admission number), the causative drug or suspected medication, ADR type, severity of ADR, symptoms, clinical services, date of ADR occurrence, admission date.

2. Study location

A medical university Siriraj Hospital, the Ministry of education, in Thailand.

3. Periods of study

The data of patient with ADRs during hospitalization between October 1, 2005, and September 30, 2006.

4. Study population

Subjects were recruited according to the following criteria:

4.1. Inclusion criteria

4.1.1. All inpatients who were associated with ADRs duringhospitalization at Siriraj Hospital between October 1, 2005, and September 30, 2006.

4.2. Exclusion criteria

4.2.1. Patients who were admitted due to adverse drug reaction at Siriraj Hospital.

5. Study procedure

5.1. Steps in determining costs of the Adverse Drug Reaction Monitoring Program (ADRMP)

In this study, costs of ADR Monitoring Program was determined from operating costs (administration costs) including labor costs and material costs. The steps of calculation costs of ADR Monitoring Program are shown in Figure 2. Data required in calculating costs of ADR Monitoring Program were as follow:

5.1.2. Operating costs (Administration costs)

5.1.2.1. Labor costs

Labor costs of ADR Monitoring Program could be estimated in terms of time used by staff activities multiply by the salary of staff responsibility for this program during the study period. Time used of staff activities in the ADR Monitoring Program were estimated in proportion of total work hour per day, total work-hour per month, and salary of staff responsibility for this program. (The data collection forms see in Appendix A)

For example, time used for a staff activities was estimated about two hours per work-day could be calculated from 2 hours per work-day x 22 work-days per month / 8 hours per work-day = 5.5 work-day per month.Salary of this staff was 20,500 baht/month or 20,500 baht per month / 22 work-days per month = 931.82 baht per work-day. The labor costs for this staff would be 931.82 baht per work-day x 5.5 work-day per month x 12 month = 61,500 baht per year.

5.1.2.2. Material costs

Material costs of the ADR Monitoring Program was the total costs of material used in this program, such as office materials, telephone, mailing.

Fiscal year 2006, at Siriraj Hospital, there were annualized buggets supported for this program activities cost 80,000 baht.

5.2. Steps in determining benefits of the Adverse Drug Reaction Monitoring Program (ADRMP)

The benefits of the ADR Monitoring Program was determined in terms of the cost savings and length of stay (LOS) of patient with ADRs during hospitalization.

The cost saved by ADRMP, it was the difference costs between costs of treatment for detected ADRs (Costs B) and costs of treatment if this ADR is prevented (Costs A). The steps of calculation benefits of this program are shown in Figure 1.

This study consisted of all inpatients who were associated with ADRs during hospitalization between October 1,2005,and September 30, 2006, at Siriraj Hospital, focusing on ADR reports to the Thai Food and

Drug Administration (FDA). Data collection available from electronic data recorded by ADR Monitoring Program, focusing on ADRs during during hospitalization.

5.2.1 Costs of treatment if this ADR is prevented (Costs A)

Costs of treatment if this ADR is prevented, these costs are those directly associated with patient care, including medications, laboratory tests, medical supplies, and hospital charges. In this study costs of treatment if this ADR is prevented would be determined from costs of treatment of Principle Diagnosis (PDx) with complications and/or comorbidity for each patient, depending on

Diagnosis-Related Groups;DRGs (Thai DRG version 3.0). The DRG codes were assigned by Siriraj Hospital employed coders by examining individual patients discharge diagnoses in their medical records. DRGs with complications and/or comorbidity were used when appropriate, within any particular DRG, a patient reaches outlier status.

5.2.2 Costs of treatment for detected ADRs (Costs B)

Costs of treatment for detected ADRs, these costs are those directly associated with patient care such as medications, laboratory tests, medical supplies, and hospital charges.

In this study costs of treatment for detected ADRs by ADR Monitoring Program, would be determined from costs of treating ADRs consequences during hospitalization plus costs of treatment of Principle

Diagnosis (PDx) with complications and/or comorbidity for each patient is assigned a DRG based on their combination of discharge diagnoses, depending on Diagnosis-Related Groups;DRGs (Thai DRG version 3.0).

Siriraj Hospital was defined using the Relative weight (RW) value unit; 1 unit of RW = 13,000 baht, based on estimated resources utilized.

- Relative weight (RW) was the proportion of costs associated with patients who were classified as DRG outlier status as compared with all DRGs.

- Principle Diagnosis (PDx) was diagnosis-related hospital admissions of the individual patients.

In this study, leading to the benefits of the ADR Monitoring Program were determined from the cost saved by this program according to the following formula:

Benefits of the ADRMP = Costs B – Costs A

5.2.3 The savings of length of stay (LOS)

The costs of ADRs occurred during hospitalization is possible to estimate by the increased length of hospitalization.

The savings of length of stay (LOS) of ADRs consequences, it was the difference between date of treating ADRs stop and date of ADRs occurrence.

In this study, the savings of length of stay (LOS) were determined by the increased length of stay of ADRs consequences. Hospitalization (long-term and day-hospital) was quantified by means of DRGs (Thai-DRG version 3.0).

The outcomes measure for benefits of the ADR Monitoring Program were calculated in terms of cost-savings and length of stay of

ADRs consequences, focused on hospitalization for one-year period. (The data collection forms as shown in Appendix A)

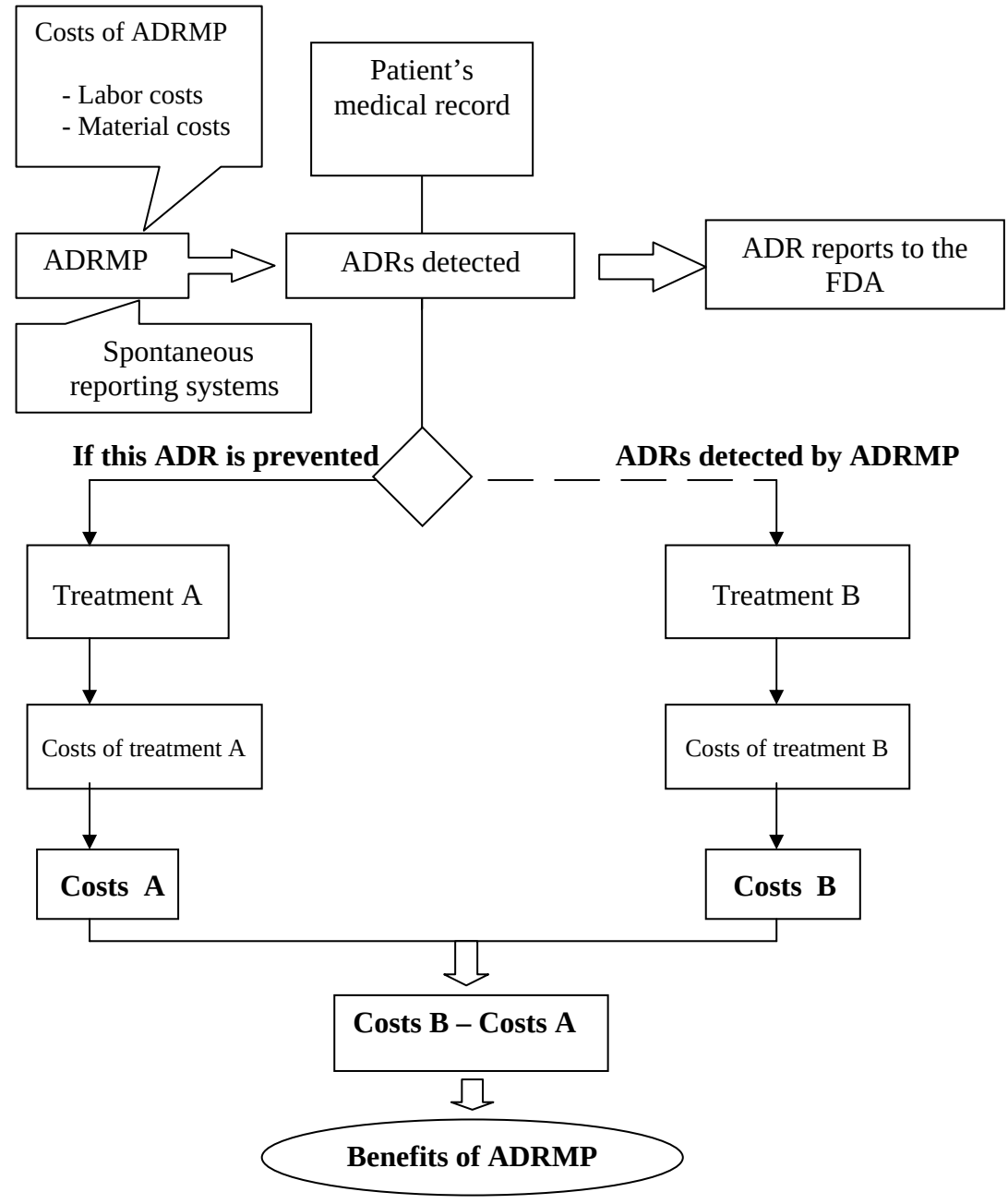
5.3 Steps in determining benefits to costs ratio of the Adverse Drug Reaction Monitoring Program (ADRMP)

The calculation of costs and benefits of the ADR Monitoring Program could be determined the benefits to costs ratio of this program and the conceptual framework of the outcomes of an ADR Monitoring

Program on benefits to costs ratio, based on hospital perspective were shown in Figure 1.

The benefits to costs ratio of the ADR Monitoring Program was calculated, according to the following formula:

$$\text{Ratio of benefits to costs} = \frac{\text{Benefits of the ADR Monitoring Program}}{\text{Costs of the ADR Monitoring Program}}$$



Benefits of ADRMP = Costs B – Costs A

Ratio of benefits to costs = $\frac{\text{Benefits of ADRMP}}{\text{Costs of ADRMP}}$

Figure 1. Conceptual framework; The outcomes of an ADR Monitoring Program on benefits to costs ratio, based on hospital perspective.

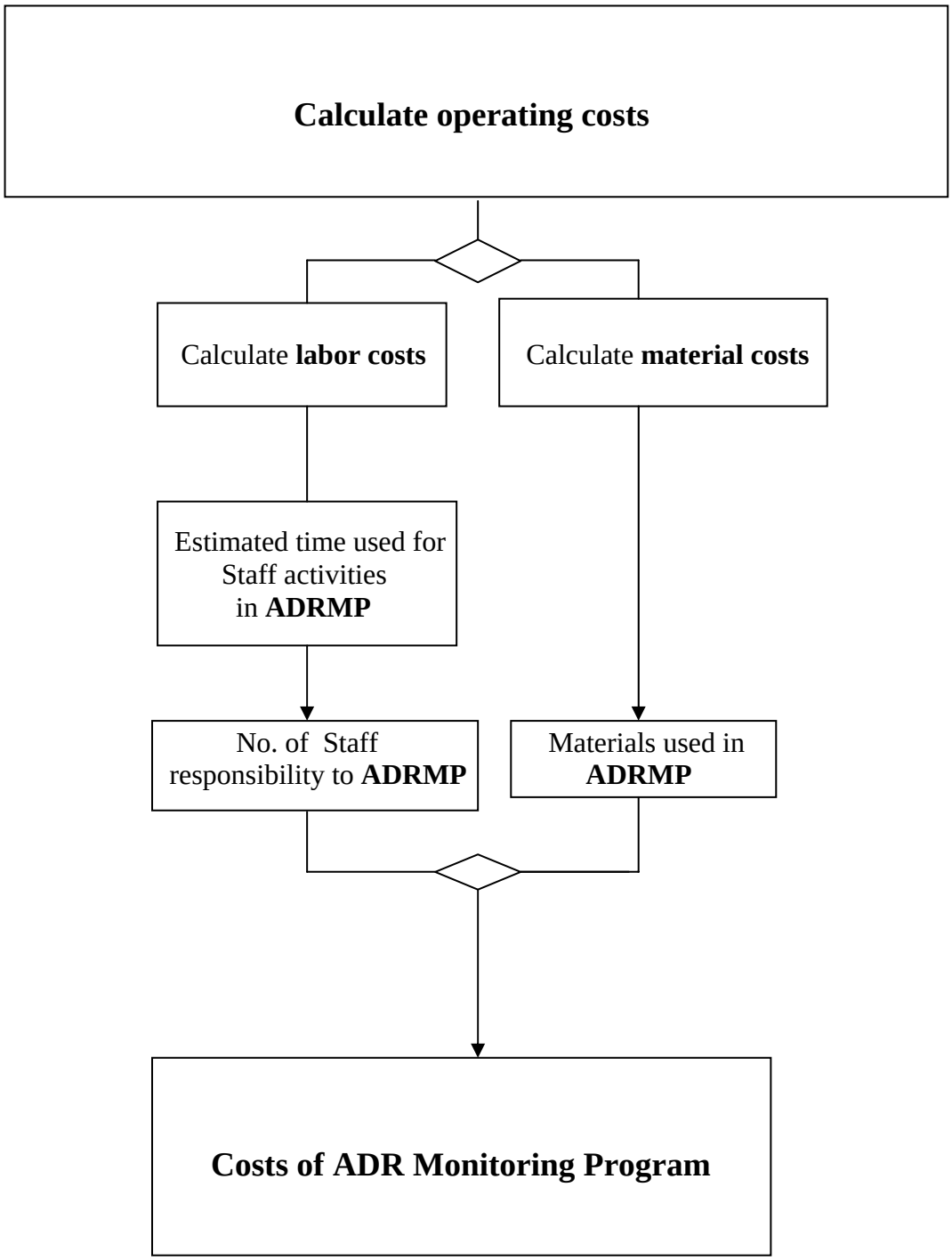


Figure 2. Steps in determining cost of the ADR Monitoring Program

6. Data collection

The following data were collected and recorded in the data collecting form (See-in Appendix A).

In this study, data collection available from electronic data recorded by Adverse Drug Reaction Monitoring Program (ADRMP).

The initial data for adverse drug reactions (ADRs) consisted of adverse drug reaction (ADR) reports to the Thai Food and Drug Administration (FDA), maintained by the Adverse Drug Reaction Monitoring Program (ADRMP).

The data collected from ADR Monitoring Program database included baseline;

- Demographic data: gender, age, medical record number, clinical service, date of ADRs occurrence, length of hospital stay, admit diagnoses.
- Characteristics of ADRs detected by ADR Monitoring Program during hospitalization: severity of the ADR (such as serious or non-serious), type of reaction (such as pharmacologic; type A, idiosyncratic; type B) cause/effect relationship (such as probable, possible), suspected medication or causative drug.

The data collecting forms of the ADR Monitoring Program;

- Costs of the ADR Monitoring Program: administration costs (labor costs and material costs), (See in Appendix A).

Variable;

- The dependent variable was defined as the presence or absence of an ADR as identified by an ADR report.
- Independent variables included patient age, gender, admission diagnoses, length of hospital stay, International Classification of Disease, 10^{th} Revision (ICD-10) codes, and all diagnostic groupings, medication names, major disease category (MDC).

7. Data analysis

Data analyses were performed using descriptive statistic. The value of this data is that it does demonstrate that the benefits to costs ratio of the ADR Monitoring Program from hospital point of view.

Descriptive statistic (e.g. mean, standard deviation, median, percentage and frequency) was used to report the data. The following analysis was carried out.

The reporting of ADR is to identify trends in occurrences and develop strategies to prevent ADRs from occurring by using the classification criteria for preventable ADRs of Schumock and Thornton criteria (3), (See in Appendix A).

Outcomes of interest were costs and benefits of the ADR Monitoring Program.

Costs of the ADR Monitoring Program were calculated from the sum of administration costs: labor costs and material costs.

The benefits of the ADR Monitoring Program were calculated in terms of cost savings and length of stay (LOS) of patients with ADRs occurred during hospitalization at Siriraj Hospital from hospital point of views, to estimated the annualized cost savings and the savings of length of stay (LOS) by this program.

The benefits to costs ratio of the ADR Monitoring Program was calculated using the follow equation, (based on hospital point of view, under the assumption of the benefits and costs occurred in the same time period)**.**

$$\textbf{Ratio of benefits to costs} = \frac{\textbf{Sum of the benefits of the ADRMP}}{\textbf{Sum of the costs of the ADRMP}}$$

Results of the benefits to costs ratio indicated, if a ratio of benefits to costs was more than one that the benefits are worth the costs.

8. Sensitivity analysis

In this study, sensitivity analysis for cost data was performed over a 10-100% range for labor costs and costs of treatment ADRs based on available information. There were two assumptions made for the ADR Monitoring Program.

8.1. Costs of the ADR Monitoring Program

The labor costs of the ADR Monitoring Program depend on in terms of time used by staff activities multiply by the salary of staff responsibility for this program. Thus the labor costs are considered these costs of the ADR Monitoring Program, the benefits to costs ratio of this program should be changed.

8.2 Benefits of the ADR Monitoring Program

Costs of treatment if this ADR is prevented, these costs are those directly associated with patient care, depend on medications (drugs), laboratory tests, medical supplies, hospital charges. Then the costs of treatment if this ADR is prevented would be considered these costs of the ADR Monitoring Program, these would result in changing in the benefits to costs ratio of this program.

CHAPTER IV
RESULTS

In this study is a descriptive cross-sectional study from retrospective data of ADRs in a medical university Siriraj Hospital between October 1, 2005, to September 30, 2006, focused on patient with ADRs during hospitalization. Adverse Drug Reaction Monitoring Program (ADRMP) to improve the detection of ADRs at Siriraj Hospital.

The results were presented, as follows:

1. Patient's data
    - 1.1 Demographic data: age groups, gender
    - 1.2 Characteristics of ADRs:
        - 1.2.1 Severity of ADRs: classified as serious, non-serious
        - 1.2.2 Cause/effect relationship (Naranjo criteria (2))
        - 1.2.3 Type of reaction: classified as pharmacologic; type A, idiosyncratic; type B, according to Rawlins and Thompson (21)
    - 1.3 The diagnostic groupings of patients with ADRs, classified by Diagnostic-Related Groups (DRGs)
    - 1.4 Types of ADRs
    - 1.5 Causative drug groups (suspected medication)
2. Cost of the ADR Monitoring Program data
3. Benefits of the ADR Monitoring Program data
4. Benefits to costs ratio of the ADR Monitoring Program data
5. Classification of the cost savings and length of stay (LOS) of patients with ADRs during hospitalization

1. Patient's data

1.1 Demographic data

From 416 inpatients who were associated with ADRs occurred duringhospitalization at Siriraj Hospital. Their demographic data were reported in Table 7. The highest numbers of patients with ADRs were reported in the patient's age groups who were ≥ 60 years, than in other groups. No difference in the number of patients with ADRs between male and female was showed in this study.

Table 7. Demographic data.

Demographic data	No. of patients (%)
1.**Age (year)**	
< 1	1 (0.24)
1-15	58 (13.94)
16-33	67 (16.11)
34-46	78 (18.75)
47-59	69 (16.59)
≥ 60	143 (34.37)
2.Gender	
Male	208 (50)
Female	208 (50)
Total	**416 (100)**

1.2 Characteristics of ADRs

The general characteristics of ADRs were presented in Table 8 and 9. The severity of ADRs was categorized as non-serious, or serious. In ninety-two cases (22.12% of cases) were rated as serious. The numbers of patients with ADRs were classified by the method of Naranjo et al.(2), for an ADR to be classified as possible and probable were 244 cases (58.65%) and 172 cases (41.35%), respectively. The percentage numbers of patients with ADRs were classified, according to Rawlins and Thompson (21), as type B (93.03%) which was higher than type A (6.97%).

Table 8. Characteristics of ADRs.

Characteristics of ADRs	No. of patients (%)
1. Severity of ADRs	
Non-serious	324 (77.88)
Serious	92 (22.12)
2. Cause/effect relationship (Naranjo et al.(2))	
Probable	172 (41.35)
Possible	244 (58.65)
3. Type of reaction (Rawlins and Thompson (21))	
Pharmacologic (Type A)	29 (6.97)
Idiosyncratic (Type B)	387 (93.03)
Total	**416 (100)**

Table 9. Severity of ADRs and type of reaction.

Characteristics of ADRs	No. of ADRs (%)		Total
	Non-serious	Serious	(%)
Pharmacologic (Type A)	18 (5.56)	11 (11.96)	29 (6.97)
Idiosyncratic (Type B)	306 (94.44)	81 (88.04)	387 (93.03)
Total	**324 (100)**	**92 (100)**	**416 (100)**

1.3 The diagnostic groupings of patients with ADRs, classified by Diagnosis-Related Groups (DRGs)

The diagnostic groupings of patients with ADRs during hospitalization at Siriraj Hospital is provided in Table 10. The highest percentage numbers of patients with ADRs were for nervous system disorders (16.35%), followed by musculoskeletal system and connective tissue disorders (12.02%).

1.4 Types of ADRs

For types of ADRs, maculopapular represented the highest numbers ofpatients at 180 cases (43.27%), followed by rash (50 cases; 12.02%) and urticaria (38 cases; 9.14%). Types of ADRs in this study were described in Table 11.

Table 10. The diagnostic groupings of patients with ADRs were classified by Diagnosis-Related Groups (DRGs).

DRGs	No. of ADRs (%)
Nervous system	68 (16.35)
Musculoskeletal system	50 (12.02)
Myeloproliferative	45 (10.82)
Circulatory system	31 (7.45)
Respiratory system	30 (7.21)
Skin, subcutaneous	28 (6.73)
Injuries, toxic drug effect	24 (5.77)
Kidney & urinary tract	19 (4.57)
Hepatobiliary system	17 (4.09)
Ear, mouth & throat	16 (3.85)
HIV infections	15 (3.61)
Infectious & parasitic	14 (3.37)
Pregnancy, childbirth	12 (2.88)
Digestive system	11 (2.64)
Female reproductive	8 (1.92)
Blood & immunological	8 (1.92)
Endocrine & metabolic	7 (1.68)
Eye	4 (0.96)
Male reproductive	3 (0.72)
Newborns & neonates	2 (0.48)
Mental disorders	2 (0.48)
Burns	1 (0.24)
Multiple significant trauma	1 (0.24)
Total	**416 (100)**

Table 11. Types of ADRs.

Types of ADRs	No. of patients (%)
Maculopapular	180 (43.27)
Rash	50 (12.02)
Urticaria	38 (9.14)
Angio-edema	19 (4.57)
Anaphylactic	17 (4.09)
Stevens-Johnson syndrome	13 (3.13)
Erythema multiforme	10 (2.41)
Hypersensitivity drug	10 (2.41)
Erythematous	7 (1.68)
Agranulocytosis	6 (1.44)
Nausea-Vomiting, Constipation	6 (1.44)

Table 11. Types of ADRs (continued).

Types of ADRs	No. of patients (%)
Eczema	5 (1.20)
Myopathy drug induced	5 (1.20)
Therapeutic injection	5 (1.20)
Acidosis, Hyponatremia, Hyperkalemia	4 (0.96)
Convulsion, Epilepsy	3 (0.72)
Edema eyelid, Conjunctiva	3 (0.72)
Eruption drug localized	3 (0.72)
Exfoliative dermatitis	3 (0.72)
Pruritus	3 (0.72)
Renal failure, Acute tubular-necrosis	3 (0.72)
Bronchospasm	2 (0.48)
Extrapyramidal	2 (0.48)
Toxic epidermal necrolysis	2 (0.48)
Toxic liver due to drug	2 (0.48)
Vasculitis allergic	2 (0.48)
Aplastic anemia	1 (0.24)
Dyspnea	1 (0.24)
Dyshidrosis	1 (0.24)
Edema localized	1 (0.24)
Flushing	1 (0.24)
Nephritis-interstitial acute	1 (0.24)
Nephropathy drug-induced	1 (0.24)
Palpitations	1 (0.24)
Peripheral vascular	1 (0.24)
Polyneuropathy drug-induced	1 (0.24)
Respiratory failure	1 (0.24)
Thrombocytopenia	1 (0.24)
Thrombosis deep vein	1 (0.24)
Total	**416 (100)**

1.5 Causative drug groups (suspected medication)

For drugs, the most common causative drug groups were antibiotics groups (61.78% of cases) followed by central nervous system drug groups (12.74%). The causative drug groups were presented in Table 12.

Table 12. Causative drug groups

Causative drug groups	No. of patients (%)
Anti-biotics	257 (61.78)
CNS-Psychiatric	53 (12.74)
Unclassified therapeutic agent	23 (5.53)
Musculoskeletal:NSAIDs	17 (4.10)
Hematologic-oncologic	14 (3.37)
Gastro-intestinal	9 (2.16)
Musculoskeletal:misc	9 (2.16)
Cardiovascular	7 (1.68)
Endocrine	7 (1.68)
Musculoskeletal:Gout, DMARDs	7 (1.68)
Anti-fungals	6 (1.44)
Anti-virals	5 (1.20)
Anti-tuberculous	2 (0.48)
Total	**416 (100)**

2. Costs of the ADR Monitoring Program data.

The department of pharmacy, an Adverse Drug Reaction Monitoring Program (ADRMP) at Siriraj Hospital formed a team consisting of 4 pharmacists and one staff. ADR Monitoring Program focused on a strategy for decreasing adverse drug reactions (ADRs) and preventable ADRs. (as shown in Table 13)

Table 13. Cost of an Adverse Drug Reaction Monitoring Program (ADRMP) at Siriraj Hospital 2006.

Descriptions	Annual Costs (baht)	Percent (%)
Labor costs	352,499.73	81.50
Material costs	80,000.00	18.50
Total	**432,499.73**	**100.00**

Costs of the ADR Monitoring Program was determined from operating costs (administration costs) including labor costs and material costs.

2.1 Labor Costs

Labor costs of the ADR Monitoring Program could be estimated in terms of time used by staff activities multiply by the salary of staff responsibility for this program during one year period. Time used of staff activities in the ADR Monitoring Program were estimated in proportion of total work-hour per day, total work-hour per month, and salary of staff responsibility for this program. (as shown in Table 14, 15)

2.2 Material costs

Material costs of the ADR Monitoring Program was the total costs of material used in this program, such as office materials, telephone, mailing. Fiscal year 2006, at Siriraj Hospital, there were annualized buggets supported for this program activities cost 80,000 baht.

Table 14. Staff activities and time used in the ADR Monitoring Program (ADRMP) at Siriraj Hospital 2006.

Activities	Staff responsibility to ADRMP	Time used (hour/work-day)
Medical record delivery	Staff 1	1.5
Patient interview	Pharmacist 1,2,3,4	0.5
Medical record review	Pharmacist 1,2,3,4	0.5
Care team rounds	Pharmacist 1,2,3,4	0.5
ADRs monitoring and follow-up	Pharmacist 1,2,3,4	0.5
ADRs information	Pharmacist 2,3,4	0.5,1,1
	Staff 1	1
Physician's consult	Pharmacist 2	0.5
ADRs report and ADRs card	Pharmacist 3,4	1
ADRs record	Staff 1	1.5

Table 15. Analysis labor costs of the ADR Monitoring Program (ADRMP) at Siriraj Hospital 2006.

Staff responsibility to ADRMP	Time used in ADRMP		Salary (baht/month)	Labor costs (baht/year)
	Hour per work-day	Work-day/month		
Pharmacist 1	2	5.50	22,000.00	66,000.00
Pharmacist 2	3	8.25	21,000.00	94,500.45
Pharmacist 3	4	11.00	12,000.00	71,999.40
Pharmacist 4	4	11.00	12,000.00	71,999.40
Staff 1	4	11.00	8,000.00	48,000.48
Total	17	46.75	75,000.00	352,499.73

3. Benefits of the ADR Monitoring Program data.

In this study data on ADRs were collected for one year period of review. From416 inpatients who were associated with ADRs during hospitalization, using the classification criteria for preventable ADRs of Schumock and Thornton. (3)

The excess in healthcare costs as a result of ADRs has been estimated to reachalmost 2,875,623 baht in 416 inpatients (Fiscal year 2006).

Overall, mean additional cost per case associated with an ADR was estimated to exceed 6,912.56 baht per patient and increased length of stay 2.11 hospital days per patient. (as shown in Table 16)

Table 16. The benefits of the Adverse Drug Reaction Monitoring Program (ADRMP) at Siriraj Hospital 2006.

Benefits of the ADRMP	Mean	Total
Cost savings (baht)	6,912.56 (baht per patient)	2,875,623 (baht per year)
Savings of LOS (day)	2.11 (days per patient)	876 (days per year)

The benefits of the ADR Monitoring Program was determined in terms of the cost savings and length of stay (LOS) of patient with ADRs during hospitalization.

The cost saved by ADR Monitoring Program, it was the difference costs between costs of treatment for detected ADRs (Costs B) with a 5,496,500 baht (as shown in Table 11) and costs of treatment if this ADR is prevented (Costs A) with a 2,620,877 baht. The ADR Monitoring Program is subsequent savings were annualized at 2,875,623 baht to hospital, costs may be considered from an overall hospital perspective.

Overall, mean costs of treatment if this ADR is prevented (Costs A) were 6,300.18 baht per patient and mean costs of treatment for detected ADRs (Costs B) were 13,212.74 baht per patient. That this ADRs was associated with 6,912.56 baht, higher costs per patient. Using the 6,912.56 baht in costs attributable to ADRs, the 416 ADRs-patients identified resulted in 2,875,623 baht in additional cost to Siriraj hospital during the one-year study period. ADRs was associated with a 52.32% increase in costs. Table 17 shows a summary of results for costs of treatment.

Table 17. The benefits of the ADR Monitoring Program based on costs of treatment at Siriraj Hospital 2006. (n = 416)

Costs of treatment	Mean costs (baht per patient)	Total costs (%) (baht per year)
Costs A	6,300.18	2,620,877 (47.68)
Costs B	13,212.74	5,496,500 (100)
Annual cost savings	6,912.56	2,875,623 (52.32)

4. Benefits to costs ratio of the ADR Monitoring Program data

As a result, the annual costs of ADR Monitoring Program were 432499.73 baht in the study period at Siriraj Hospital 2006. (as shown in Table 13)

The benefits of the ADR Monitoring Program, this program is subsequent cost-savings were annualized at 2,875,623 baht, during the study period.

The benefits to costs ratio of the ADR Monitoring Program was 6.65, which indicates that this program is effective in the present study. (as shown in Table 18)

Table 18. The benefits to costs ratio of the Adverse Drug Reaction Monitoring Program (ADRMP) at Siriraj Hospital 2006. (n = 416)

Benefits of the ADRMP (Annual cost savings)	Costs of the ADRMP (Annual costs)	Benefits to costs ratio of the ADRMP
2,875,623 (baht per year)	432,499.73 (baht per year)	6.65

5. Classification of the cost savings and length of stay (LOS) of patients with ADRs during hospitalization.

5.1 Demographic data: cost savings and length of stay (LOS)

The highest percentages of cost-savings (35.51%) were reported in the patient's age groups who were ≥ 60 years, than in other groups (see in Figure 4) because many patients (34.37%) in the present study. (as shown in Table 19) In this age groups (≥ 60 years), the mean cost-savings per patient were 7,139.77 baht and increased length of stay 2.28 hospital days per patient.

The mean cost-savings per patient and the percentage of cost-savings in relation to age groups of patients are shown in Figure 3, 4.

In the patients who were < 1year of age, the cost-savings per patient in this age group found only one case were highest (8,639.80 baht per patient), when comparing for all other groups and increased length of stay 1 hospital day per patient.

Table 19. The cost savings and LOS were classified by age groups of patients at Siriraj Hospital 2006. (n = 416)

Age groups (years)	No. of patients (%)	Mean Cost (baht per patient)			Mean Savings of LOS
		Cost B	Cost A	Cost savings	(day per patient)
< 1	1 (0.24)	4479.8	-4160	8639.8	1
1-15	58 (13.94)	14404.27	8171.4	6232.87	1.33
16-33	67 (16.11)	14816.49	7946.38	6870.11	1.42
34-46	78 (18.75)	12193.42	5165.77	7027.65	2.46
47-59	69 (16.59)	15028.18	8159.12	6899.06	2.68
≥ 60	143 (34.37)	11704.66	4564.89	7139.77	2.28
Mean (±SD)	-	13212.74 (±7337.95)	6300.18 (±8148.40)	6912.56 (±2840.39)	2.11 (±4.25)
Total	**416 (100)**	**5496500**	**2620877**	**2875623**	**876**

Table 20. The cost savings and LOS were classified by gender at Siriraj Hospital 2006. (n = 416)

Gender	No. of patients (%)	Mean Cost (baht per patient)			Mean Savings of LOS
		Cost B	Cost A	Cost savings	(day per patient)
Male	208 (50)	13314.18	6472.76	6841.41	2.14
Female	208 (50)	13111.31	6127.61	6983.70	2.07
Mean (±SD)	-	13212.74 (±7337.95)	6300.18 (±8148.40)	6912.56 (±2840.39)	2.11 (±4.25)
Total	**416 (100)**	**5496500**	**2620877**	**2875623**	**876**

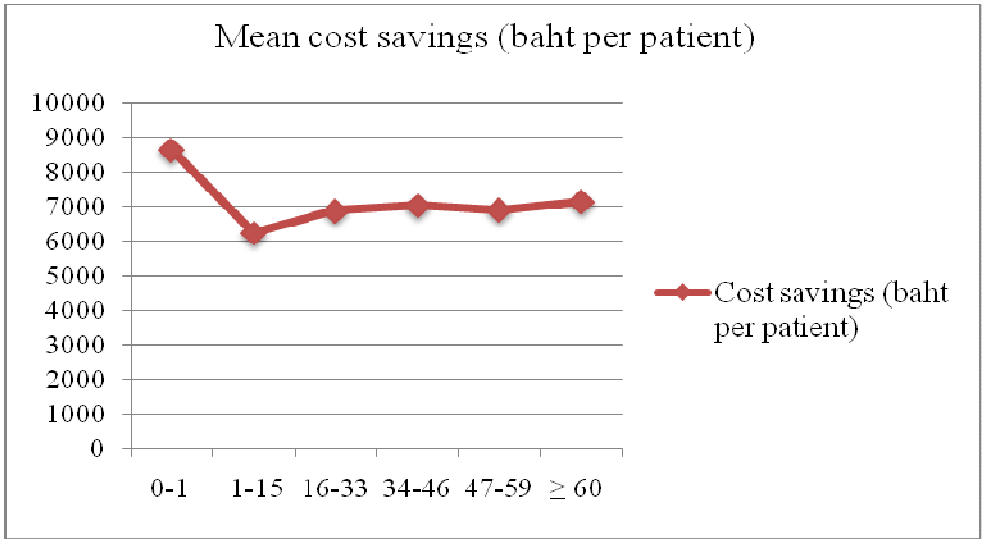


Figure 3. The mean cost savings per patient among different age groups.

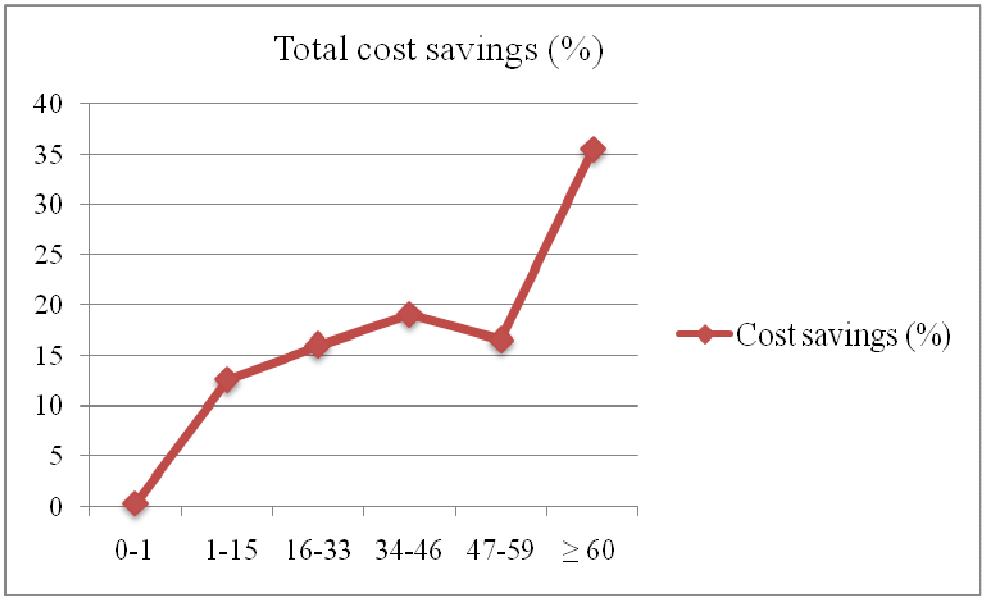


Figure 4. The percentage of total cost savings among different age groups.

Overall, the number of patients who were associated with ADRs during hospitalization at Siriraj Hospital for one year period, the ratio of male to female was 50:50. A higher percentage of cost-saving were reported in females than males. (as shown in Table 20)

5.2 Characteristics of ADRs: cost savings and length of stay (LOS)

The general characteristics of the ADRs detected can be seen in Table 21. The severity of ADRs was categorized as non-serious, or serious. In 92 cases (22.12% of cases) were rated as serious. The total cost-savings of serious ADRs were 509,740.40 baht (17.73% of total cost-savings), (See in Appendix B) and increasing length of stay by 2.77 hospital days per patient. The non-serious ADRs mean cost-savings were classified at 7,302.11 baht per patient, higher than the serious ADRs at 5,540.66 baht per patient.

Table 21. The cost savings and LOS were classified by characteristics of ADRs at Siriraj Hospital 2006. (n = 416)

Characteristics Of ADRs	No. of ADRs (%)	Mean Cost (baht per patient)			Mean Savings of LOS
		Cost B	Cost A	Cost savings	(day/patient)
1.Severity of ADRs					
Non-serious	324 (77.88)	13348.70	6046.59	7302.11	1.92
Serious	92 (22.12)	12733.94	7193.28	5540.66	2.77
2.Naranjo Algorithm					
Probable	172 (41.35)	13259.71	6664.88	6594.83	2.32
Possible	244 (58.65)	13179.63	6043.10	7136.53	1.96
3.Rawlins&Thompson					
Pharmacologic (Type A)	29 (6.97)	15762.05	12799.58	2962.48	4.76
Idiosyncratic (Type B)	387 (93.03)	13021.71	5813.15	7208.56	1.91
Mean (±SD)	-	13212.74 (±7337.95)	6300.18 (±8148.40)	6912.56 (±2840.39)	2.11 (±4.25)
Total	**416 (100)**	**5496500**	**2620877**	**2875623**	**876**

The total cost-savings of ADRs were classified by the method of Naranjo et al. (2), for an ADR to be classified as possible and probable were 1,741,312.30 baht

(60.55%) and 1,134,311.10 baht (39.45%), respectively. (as shown in Table 21) The possible mean cost-savings were classified at 7,136.53 baht per patient, higher than the probable at 6,594.83 baht per patient.

In this study, the total cost-savings were classified, according to Rawlins and Thompson (21) as type A (85,911.80 baht or 2.99% of total cost-savings) and type B reactions (2,789,711.60 baht or 97.01% of total cost-savings), respectively. When considering, the type B mean cost-savings were classified at 7,208.56 baht per patient, higher than the type A at 2,962.48 baht per patient, becaused of type B (bizarre, idiosyncratic) reactions could not be explained by the drug's pharmacological action.

5.3 Diagnosis-Related Groups (DRGs) of Principle Diagnosis (PDx) ofpatients with ADRs during hospitalization: cost savings and length of stay (LOS)

Classification of Diagnosis-Related Groups (DRGs) of Principle Diagnosis (PDx) of patients with ADRs during hospitalization at Siriraj Hospital is provided in Table 22. Twenty-three of the diagnostic groupings evaluated were different between the cost savings and length of stay of ADRs-consequences in study period.

The diagnostic of nervous system occurred ADRs during hospitalization in a higher percentage of total cost-savings were 17.65%, followed by musculoskeletal system and connective tissue (12.57%) than in other diagnoses groups. While the diagnostic of multiple significant trauma showed a lower percentage of total cost-savings of ADRs (0.22%).

In this study, the diagnostic of burns occurred in a higher mean cost-savings were 8,187.40 baht per patient, than in other diagnoses groups and increased length of stay 1 hospital day per patient, followed by the diagnostic of skin, subcutaneous tissue and breast (8,014.73 baht per patient) and increased length of stay 1.43 hospital days per patient, and the diagnostic of endocrine, nutritional and metabolic (7,978.84 baht per patient) and increased length of stay 3 hospital days per patient, respectively.

As a result, data suggest that prolongation of length of stay due to ADRs occurring during hospitalization is estimated an increase of the length of stay of mental disorders to be as high as 4.5 hospital days per patient, followed by the diagnostic of pregnancy, childbirth and puerperium (3.25 hospital days per patient) and the diagnostic of Human Immunodeficiency Virus (HIV) infections (3.13 hospital days per patient), respectively, when comparing for all other diagnoses groups.

Table 22. The cost savings and LOS were classified by DRGs of PDx of patients with ADRs during hospitalization at Siriraj Hospital 2006. (n = 416)

DRGs of PDx	No. of ADRs (%)	Mean Cost (baht per patient)			Mean Savings of LOS
		Cost B	Cost A	Cost savings	(day/patient)
Nervous system	68 (16.35)	15367.05	7904.25	7462.80	1.85
Musculoskeletal system	50 (12.02)	11857.79	4628.31	7229.48	2.59
Myeloproliferative	45 (10.82)	29318.61	23132	6186.61	2.82
Circulatory system	31 (7.45)	11505.46	5530.62	5974.84	2.87
Respiratory system	30 (7.21)	9895.77	3059.85	6835.92	1.17
Skin, subcutaneous	28 (6.73)	8244.55	229.82	8014.73	1.43
Injuries, toxic drug effect	24 (5.77)	7320.79	396.99	6923.80	1.29
Kidney & urinary tract	19 (4.57)	9351.72	3074.50	6277.22	2.63
Hepatobiliary system	17 (4.09)	12086.71	5250.93	6835.78	1.82
Ear, mouth & throat	16 (3.85)	11210.06	3769.19	7440.87	1.25
HIV infections	15 (3.61)	11302.20	4546.36	6755.84	3.13
Infectious & parasitic	14 (3.37)	10178.07	3280.09	6897.99	2.5
Pregnancy, childbirth	12 (2.88)	8446.42	1518.94	6927.48	3.25
Digestive system	11 (2.64)	7561.51	99.39	7462.12	0.91
Female reproductive	8 (1.92)	10257.33	4719.65	5537.68	0.75
Blood & immunological	8 (1.92)	9015.83	2684.34	6331.49	1.63
Endocrine & metabolic	7 (1.68)	11837.99	3859.14	7978.84	3
Eye	4 (0.96)	10034.05	2690.68	7343.37	1.75
Male reproductive	3 (0.72)	17851.60	13058.07	4793.53	1
Newborns & neonates	2 (0.48)	12455.30	6145.10	6310.20	2.5
Mental disorders	2 (0.48)	10593.70	6500	4093.70	4.5

Table 22. The cost savings and LOS of were classified by DRGs of PDx of patients with ADRs during hospitalization at Siriraj Hospital 2006 (n = 416), (continued).

DRGs of PDx	No. of ADRs (%)	Mean Cost (baht per patient)			Mean Savings of LOS
		Cost B	Cost A	Cost savings	(day/patient)
Burns	1 (0.24)	26782.60	18595.20	8187.40	1
Multiple trauma	1 (0.24)	16524.30	10331.10	6193.20	2
Mean (±SD)	-	13212.74 (±7337.95)	6300.18 (±8148.40)	6912.56 (±2840.39)	2.11 (±4.25)
Total	**416 (100)**	**5496500**	**2620877**	**2875623**	**876**

Our data of the diagnostic groupings showed a higher percentage of patients who were associated with an ADR for nervous system disorders (16.35% of cases). Consequent to our findings, that the highest overall percentage of types of ADRs were for maculopapular events (55.88% of cases), followed by rash (19.12%) and urticaria (4.41%) and anaphylactic (4.41%), respectively. (as shown in Table 23)

Table 23. Types of ADRs of the nervous system disorders in 68 patients.

Types of ADRs	No. of patients (%)
Maculopapular	38 (55.88)
Rash	13 (19.12)
Urticaria, Anaphylactic (each event = 3 cases)	6 (8.82)
Agranulocytosis	2 (2.94)
Angio-edema, Bronchospasm, Erythematous, Exfoliative dermatitis, Flushing, Hypersensitivity drug, Myopathy drug induced, Pruritus, Thrombocytopenia (each event = 1 case)	9 (13.24)
Total	**68 (100)**

For drugs, central nervous system drugs class were the most commonly involved in ADRs of nervous system disorders (44.12% of cases) followed by antibiotics drugs (42.65% of cases) and hematologic-oncologic drugs (4.41% of cases) and gastro-intestinal drugs (4.41% of cases), respectively. (as shown in Table 24)

Table 24. Drugs causing ADRs of the nervous system disorders in 68 patients.

Causative drug groups	No. of patients (%)	Causative drugs	Types of ADRs (events)
CNS-Psychiatric	30 (44.12)	Phenytoin(26), Sodium valproate(3), Carbamazepine(1)	Maculopapular(22), Rash(3), Agranulocytosis(1), Angio-edema(1), Anaphylactic(1), Drug hypersensitivity syndrome(1), Thrombocytopenia(1)
Anti-biotics	29 (42.65)	Cefotaxime(6), Ceftriaxone(4), Vancomycin(4), Amoxycillin(3), Piperacillin(3), Ciprofloxacin(2), Imipenem plus cilastatin(2), Cefazolin(1), Cefepime(1), Cloxacillin(1), Dicloxacillin(1), Meropenem(1)	Maculopapular(14), Rash(7), Anaphylactic(2), Urticaria(2), Agranulocytosis(1), Bronchospasm(1), Erythematous(1), Exfoliative dermatitis(1)
Hematologic-oncologic	3 (4.41)	Cytarabine(2), Paclitaxel(1)	Rash(2), Maculopapular(1)
Gastro-intestinal	3 (4.41)	Omeprazole(2), Rabeprazole(1)	Urticaria(1), Maculopapular(2)
Endocrine	2 (2.94)	Methylprednisolone(1), Simvastatin(1)	Pruritus(1), Myopathy drug induced(1)
Unclassified therapeutic agent	1 (1.47)	Almitrine plus raubasine(1)	Flushing(1)
Total	**68 (100)**	**68**	**68**

The influence of the underlying diseases and their complication or comorbidity in patients who were associated with ADRs during hospitalization by the diseases expressed in distribution of Diagnosis-Related Groups (DRGs) and complication index presented in Appendix B. The mean savings of length of hospitalization was 2.11 hospital days per patient (SD ± 4.25, range 0-39, n = 416) predominantly influenced by the diseases expressed in DRG and by ADRs. Comparing patients who were associated with ADRs, the highest mean savings of length of stay (LOS) in severity ill patients, mostly with hepatobiliary system and pancreas disorders (11 hospital days per patient) followed by infectious and parasitic disorders (8 hospital days per patient) and mental disorders (6 hospital days per patient) and Human Immunodeficiency Virus (HIV) infections disorders (5 hospital days per patient), respectively.

Table 25. Drug causing and types of ADRs of catastrophic complications and comorbidities level in 121 patients.

Causative drugs	Types of ADRs
Ceftriaxone(11)	Urticaria(2), Maculopapular(9)
Vancomycin(9)	Maculopapular(3), Erythema multiforme(3), Angio-edema(1), Urticaria(1), Vasculitis allergic(1)
Imipenem plus cilastatin(8)	Toxic epidermal necrolysis(1), Nausea-vomitting(1), Maculopapular(6)
Piperacillin(7)	Maculopapular(2), Urticaria(3), Anaphylactic(1), Erythema multiforme(1)
Ceftazidime(6)	Anaphylactic(2), Urticaria(1), Maculopapular(2), Erythema multiforme(1)
Phenytoin(6)	Drug hypersensitivity syndrome(1), Maculopapular(4), Rash(1)
Cefepime(5)	Maculopapular(2), Erythema multiforme(2), Rash(1)
Clindamycin(4)	Dyshidrosis(1), Maculopapular(3)
Co-trimoxazole(4)	Maculopapular(3), Nephritis-interstitial acute(1)
Teicoplanin(4)	Maculopapular(3), Urticaria(1)
Carbamazepine(3)	Maculopapular(2), Stevens-Johnson syndrome(1)
Cefazolin(3)	Urticaria(1), Maculopapular(2)
Cefoperazone(3)	Maculopapular(1), Anaphylactic(1), Urticaria(1)
Allopurinol(2)	Stevens-Johnson syndrome(1), Eczema(1)
Amikacin(2)	Renal failure(2)
Amoxycillin(2)	Maculopapular(1), Rash(1)
Ciprofloxacin(2)	Rash(2)
Cloxacillin(2)	Bronchospasm(1), Urticaria(1)

Table 25. Drug causing and types of ADRs of catastrophic complications and comorbidities level in 121 patients (continued).

Causative drugs	Types of ADRs
Cytarabine(2)	Maculopapular(2)
Dexamethasone(2)	Myopathy drug induced(2)
Fluconazole(2)	Toxic epidermal necrolysis(1), Toxic liver due to drug(1)
Levofloxacin(2)	Eczema(2)
Meropenem(2)	Maculopapular(2)
Omeprazole(2)	Erythema multiforme(1), Maculopapular(1)
Vrincristine(2)	Constipation(1), Rash(1)
Ampicillin(1)	Urticaria(1)
Celecoxib(1)	Urticaria(1)
Etoricoxib(1)	Acute tubular-necrosis(1)
Ibuprofen(1)	Stevens-Johnson syndrome(1)
Indapamide(1)	Nephropathy drug-induced(1)
Itraconazole(1)	Maculopapular(1)
L-Asparaginase(1)	Rash(1)
Mesna(1)	Rash(1)
Metformin(1)	Acidosis(1)
Metronidazole(1)	Maculopapular(1)
Naproxen(1)	Maculopapular(1)
Nifedipine(1)	Erythema multiforme(1)
Oseltamivir(1)	Nausea-vomitting(1)
Paclitaxel(1)	Maculopapular(1)
Pethidine(1)	Epilepsy(1)
Primaquine(1)	Angio-edema(1)
Phenobarbital(1)	Drug hypersensitivity syndrome(1)
Simvastatin(1)	Myopathy drug induced(1)
Sodium valproate(1)	Maculopapular(1)
Sulfasalazine(1)	Vasculitis allergic(1)
Vitamin K 1(1)	Convulsion(1)
Voluven(1)	Anaphylactic(1)
Voriconazole(1)	Toxic liver due to drug(1)

Table 26. Drug causing and types of ADRs of severe complications and comorbidities level in 66 patients.

Causative drugs	Types of ADRs
Phenytoin(9)	Maculopapular(5), Drug hypersensitivity syndrome(3), Stevens-Johnson syndrome(1)
Ceftriaxone(6)	Urticaria(2), Maculopapular(4)
Clindamycin(5)	Maculopapular(4), Rash(1)
Imipenem plus cilastatin(4)	Maculopapular(3), Rash(1)
Cefotaxime(3)	Maculopapular(3)
Vancomycin(3)	Maculopapular(1), Agranulocytosis(2)
Allopurinol(2)	Stevens-Johnson syndrome(2)
Cytarabine(2)	Rash(2)
Ibuprofen(2)	Anaphylactic(1), Angio-edema(1)
Omeprazole(2)	Maculopapular(2)
Prednisolone(2)	Eruption drug localized(2)
Penicillin G sodium(2)	Agranulocytosis(1), Maculopapular(1)
Piperacillin(2)	Rash(1), Anaphylactic(1)
Rifampicin(2)	Maculopapular(2)
Sodium valproate(2)	Agranulocytosis(1), Thrombocytopenia(1)
Almitrine plus raubasine(1)	Flushing(1)
Azithromycin(1)	Therapeutic injection(1)
Cefepime(1)	Bronchospasm(1)
Cefminox(1)	Urticaria(1)
Cefpirome(1)	Maculopapular(1)
Ceftazidime(1)	Erythema multiforme(1)
Co-trimoxazole(1)	Stevens-Johnson syndrome(1)
Ertapenem(1)	Polyneuropathy drug-induced(1)
Furosemide(1)	Maculopapular(1)
Ibuprofen(1)	Angio-edema(1)
Levofloxacin(1)	Therapeutic injection(1)
Lomefloxacin(1)	Maculopapular(1)
Metoclopramide(1)	Rash(1)
Nevirapine(1)	Stevens-Johnson syndrome(1)
Oxcarbamazepine(1)	Hyponatremia(1)
Risperidone(1)	Thrombosis deep vein(1)
Sulfasalazine(1)	Maculopapular(1)

5.4 Types of ADRs: cost savings and length of stay (LOS)

The cost-savings were classified by types of ADRs, the highest percentage of cost as a result of maculopapular accounting for 50.68% of the total cost-saving, followed by rash (14.12%) and urticaria (7.72%). (see in Appendix B)

While, erythema multiforme and toxic epidermal necrolysis had the higher mean cost-savings were 8,639.80 baht per patient (as shown in Table 27), and increased length of stay 1.40 and 2 hospital days per patient, respectively followed by Stevens-Johnson syndrome (8,605 baht per patient) and increased length of stay 2.08 hospital days per patient, when comparing for all other types.

Table 27. The cost savings and LOS were classified by types of ADRs at Siriraj Hospital 2006. (n = 416)

Types of ADRs	No. of events (%)	Mean Cost (baht per patient)			Mean Savings of LOS
		Cost B	Cost A	Cost savings	(day/patient)
Maculopapular	180 (43.27)	13779.10	5682.67	8096.43	2.07
Rash	50 (12.02)	13742.17	5620.76	8121.41	1.76
Urticaria	38 (9.14)	11599.42	5755.58	5843.84	1.21
Angio-edema	19 (4.57)	7139.26	1646.01	5493.25	0.42
Anaphylactic	17 (4.09)	15341.38	10059.25	5282.13	0.59

Table 27. The cost savings and LOS were classified by types of ADRs at Siriraj Hospital 2006 (n = 416), (continued).

Types of ADRs	No. of events (%)	Mean Cost (baht per patient)			Mean Savings of LOS
		Cost B	Cost A	Cost-savings	(day/patient)
Stevens-Johnson syndrome	13 (3.13)	9267.10	662.10	8605	2.08
Erythema multiforme	10 (2.41)	12341.42	3701.62	8639.80	1.40
Hypersensitivity drug	10 (2.41)	8990.28	1569.88	7420.40	3.40
Erythematous	7 (1.68)	9409.21	2508.81	6900.4	1.14
Agranulocytosis	6 (1.44)	15788.07	9236.93	6551.13	7.83
Nausea-Vomiting, Constipation	6 (1.44)	16371.12	10651.12	5720	9.67
Eczema	5 (1.20)	18554.90	11654.50	6900.40	3.40
Myopathy drug induced	5 (1.20)	19912.62	19912.62	0	4.20
Therapeutic injection	5 (1.20)	10655.32	8018.14	2637.18	0.40
Acidosis, Hyponatremia, Hyperkalemia	4 (0.96)	10191.35	7053.80	3137.55	2.75
Convulsion, Epilepsy	3 (0.72)	27261.43	22599.63	4661.80	0
Edema eyelid, Conjunctiva	3 (0.72)	11901.93	8883.33	3018.60	0
Eruption drug localized	3 (0.72)	17549.13	17549.13	0	0
Exfoliative dermatitis	3 (0.72)	21095.53	21095.53	0	3
Pruritus	3 (0.72)	11426.13	9126	2300.13	0.33
Renal failure, Acute tubular-necrosis	3 (0.72)	19005.13	19005.13	0	2.67
Bronchospasm	2 (0.48)	15984.80	15984.80	0	0
Extrapyramidal	2 (0.48)	11823.50	5324.15	6499.35	1
Toxic epidermal necrolysis	2 (0.48)	10293.40	1653.60	8639.80	2
Toxic liver due to drug	2 (0.48)	24375	24375	0	20
Vasculitis allergic	2 (0.48)	9517.95	9517.95	0	2.50
Aplastic anemia	1 (0.24)	9284.60	2701.40	6583.20	2

Table 27. The cost savings and LOS were classified by types of ADRs at Siriraj Hospital 2006 (n = 416), (continued).

Types of ADRs	No. of events (%)	Mean Cost (baht per patient)			Mean Savings of LOS
		Cost B	Cost A	Cost-savings	(day/patient)
Dyspnea	1 (0.24)	13759.20	7510.10	6249.10	0
Dyshidrosis	1 (0.24)	9753.90	2853.50	6900.40	1
Edema localized	1 (0.24)	11753.30	11753.30	0	1
Flushing	1 (0.24)	13755.30	13755.30	0	0
Nephritis-interstitial acute	1 (0.24)	11302.20	11302.20	0	9
Nephropathy drug-induced	1 (0.24)	16555.50	16555.50	0	4
Palpitations	1 (0.24)	8170.50	-3770	11940.50	0
Peripheral vascular	1 (0.24)	14036.10	14036.10	0	14
Polyneuropathy drug-induced	1 (0.24)	10908.30	-1948.70	12857	1
Respiratory failure	1 (0.24)	6193.20	-6990.10	13183.30	1
Thrombocytopenia	1 (0.24)	6992.70	-16400.80	23393.50	4
Thrombosis deep vein	1 (0.24)	11766.30	11766.30	0	6
Mean (±SD)	-	13212.74 (±7337.95)	6300.18 (±8148.40)	6912.56 (±2840.39)	2.11 (±4.25)
Total	**416 (100)**	**5496500**	**2620877**	**2875623**	**876**

5.5 Causative drug groups: cost savings and length of stay (LOS)

For drugs, when the estimate from the study by causative drug groups is considered (as shown in Appendix B), the cost of ADRs of antibiotics groups allowed a saving of total cost were higher (1,837,846 baht or 63.91% of total cost-savings) and the mean savings of length of stay (LOS) by 1.90 hospital days per patient.

According to CNS-psychiatric, the obtainable savings were 411,099 baht in total cost-savings, these costs accounted for 14.30% and the mean savings of length of stay by 2.92 hospital days per patient.

This suggests that, the mean cost-savings for drugs, anti-tuberculous to be as high as 8,187.40 baht per patient (as shown in Table 28), than in other causative drug groups, followed by hematologic-oncologic (8,034.28 baht per patient) and the mean savings of length of stay by 1.17 hospital days per patient, and anti-virals drugs (7,874.88 baht per patient) and the mean savings length of stay 5 hospital days per patient, respectively.

Consequently, data suggest that prolongation of length of stay due to ADRs occurring during hospitalization is estimated an increase of the length of stay of anti-fungals to be as high as 10 hospital days per patient when comparing for all other causative drug groups, followed by anti-virals (5 hospital days per patient) and cardiovascular groups (3.43 hospital days per patient).

Interesingly, the most common causative drug groups were antibiotics groups (61.78% of cases) presented in Table 29. The three most common antibiotics drugs were cephalosporins groups (35.41% of cases) followed by penicillins groups (19.45%) and carbapenems (10.51%).

Table 28. The cost savings and LOS were classified by causative drug groups at Siriraj Hospital 2006. (n = 416)

Therapeutic drug class (Causative drug groups)	No. of ADRs (%)	Mean Cost (baht per patient)			Mean Savings of LOS
		Cost B	Cost A	Cost savings	(day/patient)
Anti-biotics	257 (61.78)	12752.63	5601.48	7151.15	1.90
CNS-Psychiatric	53 (12.74)	12890.97	5134.39	7756.59	2.92
Unclassified therapeutic agent	23 (5.53)	13778.13	8782.40	4995.73	0.52
Musculoskeletal:NSAIDs	17 (4.10)	9423.55	2334.88	7088.67	1.12
Hematologic-oncologic	14 (3.37)	26977.79	18943.51	8034.28	1.71
Gastro-intestinal	9 (2.16)	12268.10	5111.46	7156.64	2.11
Musculoskeletal:misc	9 (2.16)	8600.08	3068.14	5531.93	1
Cardiovascular	7 (1.68)	9839.89	3186.30	6653.59	3.43

Table 28. The cost savings and LOS were classified by causative drug groups at Siriraj Hospital 2006 (n = 416), (continued).

Therapeutic drug class (Causative drug groups)	No. of ADRs (%)	Mean Cost (baht per patient)			Mean Savings of LOS
		Cost B	Cost A	Cost-savings	(day/patient)
Endocrine	7 (1.68)	19631.11	19631.11	0	2.86
Musculoskeletal:Gout, DMARDs	7 (1.68)	9269.74	3346.94	5922.80	2.86
Anti-fungals	6 (1.44)	23841.35	20373.38	3467.97	10
Anti-virals	5 (1.20)	9704.76	1829.88	7874.88	5
Anti-tuberculous	2 (0.48)	15247.70	7060.30	8187.40	0
Mean (±SD)	**-**	13212.74 (±7337.95)	6300.18 (±8148.40)	6912.56 (±2840.39)	2.11 (±4.25)
Total	**416 (100)**	**5496500**	**2620877**	**2875623**	**876**

Table 29. Causative antibiotics groups of ADRs at Siriraj Hospital 2006. (n = 257)

Antibiotics groups	No. of ADRs (events)	Percent (%)
Beta- lactam; Cephalosporins	91	35.41
Beta- lactam; Penicillins	50	19.45
Beta- lactam; Carbapenems	27	10.51
Aminoglycosides	26	10.12
Lincosamides	22	8.56
Quinolones	17	6.61
Sulfonamides	16	6.22
Oxazolidinediones	3	1.17
Misc.	3	1.17
Macrolides	2	0.78
Total	**257**	**100**

Summary of major findings

In this study is a descriptive cross-sectional study was conducted between October 1, 2005, and September 30, 2006. ADR study data were collected for a one -year period with a retrospective review of the electronic database by ADR Monitoring Program, using the classification criteria for preventable ADRs of Schumock and Thornton.(3) The main measure of this study concerned the benefits and costs of ADR Monitoring Program. The benefits of this program were determined in terms of cost savings and length of stay (LOS) of patient with ADRs during hospitalization in hospital perspective. The outcome of ADR Monitoring Program on benefits to costs ratio was 6.65, which indicates that this program is effective. The cost of the ADR Monitoring Program was 432,499.73 baht (Fiscal year 2006) and the subsequent savings were annualized at 2,875,623 baht. The cost saved by this program, it was the difference costs between costs of treatment for detected ADRs (Costs B) with a 5,496500 baht (or 13,212.74 baht per patient) and costs of treatment if this ADR is prevented (Costs A) with a 2,620,877 baht (or 6,300.18 baht per patient). The mean cost savings were 6,912.56 baht per patient and the mean savings of length of stay (LOS) were 2.11 hospital days per patient.

The results of this study were presented, as follows:

1. **Patient's data: cost savings and length of stay (LOS)**

1.1 Demographic data

From 416 inpatients who were associated with ADRs occurred during hospitalization. The highest numbers of patients with ADRs were reported in the patient's age groups who were ≥ 60 years, than in other groups. The age group identified as having the highest percentage of total cost savings (35.51%) was the group ≥ 60 years.

No difference in the number of patients with ADRs between male and female was showed in this study. A higher percentage of total cost savings was estimated in females than males.

1.2 Characteristics of ADRs

The severity of ADRs was categorized as non-serious, or serious. In ninety-two cases (22.12% of cases) were rated as serious. The total cost savings of serious ADRs were 509,740.40 baht (17.73 % of total cost savings) and the mean savings of length of stay (LOS) by 2.77 hospital days per patient.

The numbers of patients with ADRs were classified by the method of Naranjo et al.(2), for an ADR to be classified as possible and probable were 244 cases (58.65%) and 172 cases (41.35%), respectively. The possible mean cost savings were classified at 7,136.53 baht per patient, higher than the probable at 6,594.83 baht per patient.

The percentage numbers of patients with ADRs were classified, according to Rawlins and Thompson (21), as type B (93.03%) which was higher than type A (6.97%). When considering, the type B mean cost savings were classified at 7,208.56 baht per patient, higher than type A at 2,962.48 baht per patient.

1.3 The diagnostic groupings of patients with ADRs

The highest percentage numbers of patients with ADRs were for nervoussystem disorders (16.35%), followed by musculoskeletal system and connective tissue disorders (12.02%). The diagnostic of nervous system occurred ADRs during hospitalization in a higher percentage of total cost savings were 17.65%, that the highest percentage of types of ADRs were for maculopapular events (55.88% of cases), followed by rash (19.12%) and urticaria (4.41%) and anaphylactic (4.41%), respectively. For drugs, central nervous system drugs class were the most commonly involved in ADRs of nervous system disorders (44.12% of cases) followed by anti-biotics drugs (42.65%) and hematologic-oncologic drugs (4.41%) and gastro-intestinal drugs (4.41%), respectively.

The highest mean savings of length of stay (LOS) in severity ill patients, mostly with hepatobiliary system and pancreas disorders were 11 hospital days per patient, followed by infectious and parasitic disorders (8 hospital days per patient) and mental disorders (6 hospital days per patient) and Human Immunodeficiency Virus (HIV) infections disorders (5 hospital days per patient), respectively.

1.4 Types of ADRs

For types of ADRs, maculopapular represented the highest numbers ofpatients at 180 cases (43.27%), followed by rash (50 cases; 12.02%) and urticaria (38 cases; 9.14%). While, erythema multiforme and toxic epidermal necrolysis had the higher mean cost savings were 8,639.80 baht per patient followed by Stevens-Johnson syndrome (8,605 baht per patient), in level of severity

1.5 Causative drug groups

The most common causative drug groups were anti-biotics groups (61.78% of cases) followed by central nervous system drug groups (12.74%). For drugs, anti-biotics represented the highest total cost savings at 1,837,846 baht (63.91%) and the mean savings of length of stay (LOS) by 1.90 hospital days per patient, followed by central nervous system (14.30% of total cost savings) and the mean savings of length of stay (LOS) by 2.92 hospital days per patient.

The three most common anti-biotics drugs were cephalosporins groups (35.41% of cases) followed by penicillins groups (19.45%) and carbapenems (10.51%).

CHAPTER V
DISCUSSION

The main measures of this study is the determinations of benefits to costs ratio of the Adverse Drug Reaction Monitoring Program (ADRMP), focused on patients with ADRs during hospitalization at Siriraj Hospital in fiscal year 2006, based on hospital perspective.

The important finding of this study will be discussed as follows;

1. **Benefits to costs ratio of the ADR Monitoring Program.**
2. **Benefits and costs of the ADR Monitoring Program.**

1. Benefits to costs ratio of the ADR Monitoring Program.

In hospital point of views, the result were determined the benefits to costs ratioof the ADR Monitoring Program, focused on patient with ADRs during hospitalization at Siriraj Hospital in fiscal year 2006. As a result, suggest that admission related to ADRs costs the hospital up to 2,875,623 baht, annually. The cost of the ADR Monitoring Program was annualized at 432,499.73 baht. The outcomes of ADR Monitoring Program on benefits to costs ratio was 6.65. (as shown in Table 18)

The main measures of this study concerned the costs and benefits of ADR Monitoring Program. The benefits to costs ratio of the ADR Monitoring Program was 6.65, which indicates that this program is effective. The outcomes of this study indicate that the ADR Monitoring Program is beneficial in terms of the cost savings and length of stay (LOS) of patient with ADRs occurred during hospitalization in a medical university Siriraj Hospital for one-year period of review. In addition, the benefits to costs ratio of this program ensures that the success of the ADR Monitoring Program, it is necessary to maintain early detect and preventable of ADRs during hospitalization from hospital point of views.

2. Benefits and costs of the ADR Monitoring Program (ADRMP)

This study is a descriptive cross-sectional during one-year period of review at Siriraj Hospital focused on patients with ADRs during hospitalization. From results of this study concerned the benefits and costs of the ADR Monitoring Program. ADR Monitoring Program to detect ADRs were used to calculate the ADR-attributable additional length of stay (LOS) and costs of treating patients who were associated with ADRs during hospitalization. Consequently, the ADR Monitoring Program is beneficial in terms of cost savings and length of stay (LOS) of patient with ADRs occurred during hospitalization at Siriraj Hospital.

The results of the present study indicated that the Adverse Drug Reaction Monitoring Program (ADRMP) is effective, for early detecting and prevention of 416 patients with ADRs during hospitalization, using the classification criteria for preventable ADRs of Schumock and Thornton. (3) (see in Appendix A) The costs of the ADR Monitoring Program was annualized at 432,499.73 baht. (as shown in Table 13) From hospital point of views, this program is subsequent savings were annualized at 2,875,623 baht. (as shown in Table 16) The mean cost-savings were 6,912.56 baht per patient and the mean savings of length of stay (LOS) were 2.11 hospital days per patient.

The cost saved by ADR Monitoring Program, it was the difference costs between costs of treatment for detected ADRs (Costs B) with a 5,496,500 baht in total hospital costs (or 13,212.74 baht per patient) and costs of treatment if this ADR is prevented (Costs A) with a 2,620,877 baht in total hospital costs (or 6,300.18 baht per patient).

In Thailand, the study of Lumpoon Hospital concluded that the mean excess cost of hospitalization for an ADR was almost 1,482.47 baht per patient (as shown in Table 19), and the mean savings of length of stay (LOS) were 1.25 hospital days per patient focused on patient with ADRs during hospitalization.(100) Our study shows that the mean cost-savings were higher compared with that the Lumpoon Hospital (6,912.56 baht per patient compared with 1,482.17 baht, respectively). Because the limited of study of Lumpoon Hospital had a small sample size for patient with ADRs data in 68 events of patients admission to female-medical ward and the change in values of relative weight (RW) may be affects hospital reimbursement,

depending on DRG (1 unit of RW = 5,000 baht of Lumpoon Hospital but Siriraj Hospital, 1 unit of RW = 13,000 baht), which may have resulted in lower cost savings when comparing for a medical university Siriraj Hospital.

In Thailand, other studies that have specifically evaluated this possibility reported that 31.40% of ADRs caused by drugs could have been prevented and the percentage of admission that were classified as preventable 71.05%, the median length of stay was four days (range, 0-34 days).(90)

In Global, H. Dormann et al. estimated that the mean length of hospitalization was 10.80 days predominantly influenced by the diseases expressed in DRG and by ADR.(7) The national costs of the preventable ADRs in hospitalized patients have been estimated to be 2 million USdollars in the US.(14) Bordet et al. concluded that the mean excess cost of hospitalization for an ADR was almost 3800 USdollars.(63) Evans et al. estimated that each ADR increased per-patient costs by 2000 USdollars.(80)

However, this finding was confirmed in 416 cases study for one-year period of review, in which patients with adverse drug reactions had longer hospitalization periods (2.11 hospital days per patient) and higher per-patient costs of 6,912.56 baht in this study.

Considering, the age group identified as having the highest percentage of cost-savings (35.51% of total cost-savings) who were ≥ 60 years-old patients than in other groups, a relatively high percentage number of patients with ADRs in this age group (see in Table 13). As a result, this study show that the patients ≥ 60 years-old were related to both increased length of stay and costs per case associated with an ADR was estimated to exceed 7,139.77 baht per patient, and the additional length of stay exceeded 2.28 hospital days per patient, this result is similar to that established by Lumpoon Hospital.(100)

Our data suggest that the high average additional cost per case associated with an ADR was estimated to exceed 8,639.80 baht and the additional length of stay exceeded 1 day of patient younger less 1 year (< 1 year of age) found only one case. As reported in previous study, data showed a very different pattern, with the very young and the older patient population demonstrating an increased risk of ADRs.(94)

Our finding shows that the highest overall cost savings and length of stay of patient with an ADR in the older patients age group (≥ 60 years-old). Because the higher number of prescribed medications of older patients used more medications than the younger patients and the influence of the severity of underlying diseases and their complications by considering. That the trend of increasing drug use continued to 80 years of age.(7, 72) In the study by Carbonin et al. of risk factors for ADRs, the incidence was highest between ages 70 and 79 years (6.5%).(73) The patients with ADRs were taking nearly twice as many drugs, which is consistent with result of previous studies.(72-79, 81, 82)

The older patients seem to be more at risk of ADRs, so this group need extra care. Regular medication review, the use of computerised prescribing, involvement of pharmacists in medication review and the use of protocols for shared prescribing between primary and secondary care can reduce the risk.(83)

The UK's National Service Framework for older patient has set standards for medication review in the older. If we wish to prevent ADRs, then the challenge is to recognise the risks of medicines and to extend these standards to healthcare more widely.(84)

No difference in the number of patients with ADRs between male and female was showed in this study. A higher percentage of total cost-savings was estimated in females than males. (see in Table 14) Previous studies, have reported that ADRs are more common in female.(85-89) However, some studies have suggested that this may simply be the consequence of female taking more drug. We found that among the patients with ADRs, female took an average of 3.7 drugs compared with 4.0 drugs taken by male, suggesting that the pattern of drug use in this population was similar in both genders.(73, 87)

From study in Thailand, the preventable adverse drug reaction was 31.40%, using the classification criteria for preventable ADRs of Schumock and Thornton.(3) More than twice as many females as males (68:31%) had ADRs and a higher percentage of preventable ADRs in patients who were 59-78 years (44.74%) than in other groups.(90)

Moreover, the majority of the characteristics of ADRs in this study were classified as non-serious (77.88% of cases) rather than the serious (22.12%), in level of severity. Consequently, the non-serious percentage of total cost-savings were classified at 82.27%, higher than the serious at 17.73%. It is worth noting that one of the likely effects of the prospective, Adverse Drug Reaction Monotoring Program (ADRMP) at Siriraj Hospital is early detection, rapid initiation of corrective action, and mitigation of ADR severity.

On the basis of the Naranjo criteria (2), 58.65% were considered possible and 41.35% probable (See in Table 15), whereas in some studies (53, 59) about 50% or more of ADRs detected were described as possible. The possible mean cost-savings were classified at 7,136.53 baht per patient, higher than the probable at 6,594.83 baht per patient, as related to causality assessment.

Overall, mean cost-savings were classified, according to Rawlins and Thompson (21), as a result of type B reactions (7,208.56 baht per patient) which was higher than type A (2,962.48 baht per patient). (see in Apendix B) Because of the majority of type B ADRs (bizarre, idiosyncratic) could not be explained by the drug's pharmacological action. With respect to the type B reactions, some of them can now be explained by genetic differences, such as, in drug metabolism or in the immune system, so this type were related to increased costs of treating the ADRs-consequences. A major source of discrepancies between studies lies in the distribution of ADRs with respect to their causality assessment, reflecting the different detection systems, different algorithms applied or the way algorithms were handled.

The DRG outlier status of patients with ADRs were considered, twenty-three of the diagnostic groupings represented were different of disorders between the save of cost and length of stay of ADRs-consequences during hospitalization for one-year period of review.

As a result, a higher percentage of cost-savings were for nervous system disorders (17.65% of total cost-savings), followed by musculoskeletal system and connective tissue (12.57% of total cost-savings), and myeloproliferative disorders (9.68% of total cost-savings) than in other diagnoses groups, reflecting the large number of patients with ADRs in this study. (see in Appendix B)

The highest mean savings of length of stay (LOS) in severity ill patients, mostly with hepatobiliary system and pancreas disorders were 11 hospital days per patient, followed by infectious and parasitic disorders (8 hospital days per patient) and mental disorders (6 hospital days per patient) and Human Immunodeficiency Virus (HIV) infections disorders (5 hospital days per patient), respectively.

Wheareas moderate ill patiens, the highest mean savings of length of stay of patients who were associated with an ADR for the musculoskeletal system and connective tissue disorders (4.33 hospital days per patient), followed by blood and immunological disorders (4 hospital days per patient) and injuries, poisonings and toxic drug effects disorders (2.67 hospital days per patient), respectively. This Appendix B lists all the diagnosis codes that, when use as the Principle Diagnosis (PDx) of patient considered as complications or comorbidities (CC) level.

These findings indicated that patient-specific factors could be related to complications and comorbidities (CC) level because of ADRs-consequences. The Diagnosis-Related Group (DRG) categorization of patient clinical complexity level (See in Appendix B) in order to measure the impact of ADRs on the cost of treating and duration of hospitalization.

However, Implementation of the complication and comorbidity index and a severity of disease scale into the estimations further reduces the excess LOS caused by ADRs during hospitalizations.(62) These occurrences emphasise the relevance of adjustment for underlying diagnoses and ADR risk factors to provide for meaningful economic calculations.

Other findings, the hepatobiliary system and pancreas disorders related to severe complications and comorbidities level occurred in a higher mean cost-savings were 9,079.20 baht per patient (See in Appendix B), followed by nervous system disorders (8,691.97 baht per patient) than in other diagnoses groups of severity ill patients.

However, even when comparing investigations in hospitalized patients, the result in different types of ADRs detected by ADR Monitoring Program. In order to compare the cost savings and length of stay effects of ADRs, according to the number of types of ADRs. That is, the highest percentage of total cost-savings were

maculopapular (50.68 % of total cost-savings) followed by rash (14.12%) and urticaria (7.72%). (see in Appendix B)

Additionally, for erythema multiforme and toxic epidermal necrolysis which are the severe forms of drug eruptions had the higher mean cost-savings were 8,639.80 baht per patient (as shown in Table 27), followed by Stevens-Johnson syndrome (8,605 baht per patient) when comparing for all other types.

A majority of the causative drugs represented the most common cause of maculopapular eruptions was caused by phenytoin (12.78% of cases), followed by ceftriaxone (11.11%) and clindamycin (10%), respectively and ceftriaxone also caused rash and urticaria.

An interesting finding in the present study was toxic epidermal necrolysis from imipenem plus cilastatin and fluconazole, rarely reported only two cases of this event. Furthermore, it was found that cephalosporins and aminoglycosides groups caused erythema multiforme and carbamazepine caused Stevens-Johnson syndrome.

In the present study, it was found that the trend of maculopapular eruptions was related to that of previous reports.(91, 92) The previous studies in Thailand, it was found that the trend of maculopapular eruptions was caused by cephalosporins groups followed by phenytoin and phenobarbital respectively.(91-93)

Consequently, the cost savings and length of stay caused by causative drug groups are considered. For drugs, antibiotics represented the highest total cost-savings were estimated to exceed 1,837,846 baht (63.91% of total cost-savings) and the mean savings of length of stay (LOS) were 1.90 hospital days per patient, as reported in previous studies.(91, 92, 99, 100)

Cephalosporins groups (35.41% of cases) were the most common antibiotics groups responsible for causative drug groups, followed by penicillins (19.45%) respectively, similar to published studies. In the present study, it was found that a new generation of antibiotics especially cephalosporins group has replaced penicillins group as the most causative drug groups of ADRs. (as shown in Table 29)

The central nervous system drug class, the obtainable savings were annualized at 411,099 baht (14.30% of total cost-savings). For this drug class, phenytoin was the most commonly involved in ADRs. (see in Appendix B)

When comparing the result of this study, factors contributing to differences in results of types of ADRs and causative drug groups, some aspects of ADR assessment in general and in the context of ADR Monitoring Program setting should be taken into consideration. It is obvious that differences will be observed in the type and frequency of ADRs when collected on the speciality of the department/ward, in Siriraj Hospital. The type of drug class, their rank order for inducing ADRs and consequently the types of ADRs vary extremely. For drugs, causing an ADR-related hospitalizations reflect the 'typical' risk of prescription behaviour. It should be noted that different wards using different types of drugs were involved in ADRs occurring in inpatients.

In contrast, antibiotics groups very often cause ADRs in hospitalized patients (especially allergic reactions), followed by central nervous system drug groups. This result of drugs causing ADRs were related to underlying diseases of patients with ADRs occurred during hospitalization, regarding chronic and delayed effects as well as withdrawal syndromes and therapeutic failures.

If there was the deaths caused by adverse drug reactions of patient who died during hospitalization. Therefore, the death interpretations from the perspective of hospital, we do not have to take benefits because of the nontreatment. In a situation like this it is therefore interesting to look at ADRs caused of death from a societal perspective, if this ADR is prevented by ADR Monitoring Program. We have to take large benefits to society and these benefits could be saved lives. This situation can be found in decisions to optimize patient safety. From a societal perspective, we have only begun to examine the social, economic, and ethical aspects of pharmacovigilances.

For economic considerations, in all instances, where the ADR was not preventable or where there were no treatment alternatives, the risk and cost of nontreatment has to be taken into consideration. In this study, length of stay as an indicator for economic impact of ADRs, this may not be suitable for the perspective of the hospital, depending on the National Health System and reimbursement scheme. Although health insurance in some countries may pay per hospital day, the additional cost of ADRs may not be covered adequately in the Diagnosis-Related Group (DRG) system. In the present of this study, no standards for the estimation of ADR-related

cost for hospitals and the healthcare systems have been established. It has often been claimed that prevention of ADRs by Adverse Drug Reaction Monitoring Program (ADRMP) could result in cost-savings.(19) Prerequisites are preventability of ADRs (roughly 30%), (19, 50), and implementation of prevention program(44, 60), demonstrating the potential economic impact of ADR prevention.

Limitation

This study still has several limitations. First, the present analysis of this study suggests that a benefit is obtainable as difference costs between costs of treatment for detected ADRs (Costs B) and costs of treatment if this ADR is prevented (Cost A) by ADR Monitoring Program, thus leading to cost-savings. That the cost-savings are not representative of net cost or benefit because of the costs of treatment for detected ADRs (Costs B) including costs of treating of preventable and nonpreventable ADRs has been estimated. This suggests that when considering the actual benefits or cost-savings, the expenses associated with the costs of treating of preventable ADRs should also be taken into account. The results allow the assessment of economic performance of benefits or cost-savings in the context of preventable ADRs intervention. This was an attempt to keep the main measures of this study (net cost or benefit) as excluded costs of treating of nonpreventable ADRs in costs of treatment for detected ADRs (Costs B) as possible.

Second, the spontaneous reporting system is employed in Adverse Drug Reaction Monitoring Program (ADRMP) at Siriraj Hospital under the limited of the efficacy of the spontaneous report system leads to determine the true frequency of adverse drug reactions. Our study relied on spontaneous reporting system reported ADRs data, which have numerous limitations including under-reporting, biases reporting, insufficient report quality and grossly underestimate the actual ADR rate. Although spontaneous reporting is the mainstay of passive surveillance and the most widely used technique but it have several limitations. However, a major advantage of the spontaneous reporting system is that it incorporates all drugs, prescribers, dispensers, and patients, casting the broades possible net to capture events. In addition, Intensive pharmacovigilance methods is the very proactive ADR surveilance systems can detect ADRs in the hospital, but it is too expensive for routine use.

Third, in the present study of the ADR Monitoring Program. These include the pressure of routine workloads may prevent a pharmacist spending adequate time with the patients, butget limitation, qualified teamwork and hospital support. This means that economic and hospital policies have to focus on staff numbers and workloads to improve the quality of hospital services.

Forth, in this study was identified by a retrospective review of electronic database by ADR Monitoring Program in a medical university Siriraj Hospital during one-year period of review, focused on patients with ADRs occurred during hospitalization. Documentation of ADRs by pharmacists likely underestimates ADRs incidence and biases selective cases reporting of department/ward, focused on ADRs that were clearly documented, therefore the outcomes of this study cannot represented another hospital.

Finally, the sensitivity analyses investigated changes in baseline results, in order to take into account these limitations with the provision of minimum and maximum values of the estimate.

CHAPTER VI
CONCLUSION

The findings of this study suggest that we should investigate the benefits of the ADR Monitoring Program, in terms of cost-savings and length of stay (LOS) focused on patients with ADRs during hospitalization at Siriraj Hospital in 2006, based on hospital perspective.

The outcomes of an Adverse Drug Reaction Monitoring Program (ADRMP) on benefits to costs ratio was 6.65, which indicated that this program is effective. The cost of the ADR Monitoring Program was 432,499.73 baht (Fiscal year 2006) and the subsequent savings were annualized at 2,875,623 baht. The mean cost-savings were 6,912.56 baht per patient and the mean savings of length of stay 2.11 hospital days per patient. The costs saved by ADR Monitoring Program, it was the difference costs between costs of treatment for detected ADRs (costs B) with a 5,496,500 baht (or 13,212.74 baht per patient) and costs of treatment if this ADR is prevented (Costs A) with a 2,620,877 baht (or 6,300.18 baht per patient).

The classification of the cost savings and the savings of length of stay, showed that the highest percentage of total cost-savings (35.51%) was estimated in the patient's age group who were ≥ 60 years than in other groups and the mean savings of length of stay 2.28 hospital days per patient. Because the older patients seem to be more at risk of ADRs, so this group need extra care and the higher number of prescribed medications of older patients used more medications than younger patients and the influence of the severity of underlying diseases and their complications by considering. No difference in the number of patients who were associated with ADRs during hospitalization between male and female, but a higher percentage of total cost-savings was estimated in females than males. Moreover, the majority of the characteristics of ADRs in this study, the higher percentage of total cost-savings were classified as non-serious (82.27%) than the serious (17.73%), in level of severity. On the basis of the Naranjo criteria (2), the possible mean cost-

savings were classified at 7,136.53 baht per patient, higher than the probable at 6,594.83 baht per patient, as related to causality assessment. The mean cost-savings were classified, according to Rawlins and Thompson (21), as a result of type B reactions (7,208.56 baht per patient) which was higher than type A (2,962.48 baht per patient). Because of the majority of type B ADRs (bizarre, idiosyncratic) could not be explained by the drug's pharmacological action, so this type were related to increased costs of treating the ADRs-consequences.

The Diagnosis-Related Group (DRG) outlier status of patients with ADRs were considered. A higher percentage of total cost-savings were for nervous system disorders (17.65%), followed by musculoskeletal system and connective tissue disorders (12.57%) and myeloproliferative disorders (9.68%) than in other diagnoses groups. For nervous system disorders (16.35% of cases), that the highest percentage of types of ADRs were for maculopapular events (55.88% of cases), followed by rash (19.12%) and urticaria (4.41%) and anaphylactic (4.41%), respectively. This finding is related to result of types of ADRs in this study. This represents the highest percentage of cost-savings were classified by types of ADRs, as a result of maculopapular (50.68%), followed by rash (14.12%) and urticaria (7.72%) when comparing for all other types.

Consequently, a majority of the causative drugs class, represented the highest percentage of total cost-savings were antibiotics groups (63.91%) followed by central nervous system drugs class (14.30%). This suggests that, the three most common antibiotics drugs groups were cephalosporins groups (35.41% of cases) followed by penicillins groups (19.45%) and carbapenems (10.51%).

The outcomes of this study indicated that the ADR Monitoring Program is beneficial in terms of the cost savings and length of stay. Consequent to our finding, the benefits to costs ratio of the ADR Monitoring Program, which indicates that this program is effective and confirm to be successful in this study, it is necessary to maintain early detect and preventable of ADRs during hospitalization for the perspective of the hospital. However, ADR Monitoring Program management may help to develop strategies to detectable and preventable ADRs in hospitalized patients, decrease the incidence and severity of ADRs occurred during hospitalization and reduce cost and length of stay in a medical university Siriraj Hospital. Moreover, the

development of an economic model for ADR Monitoring Program will facilitate the administrator to consider more rationally in this program management.

In summary, the benefits to costs ratio of the ADR Monitoring Program ensures that it would provide better financial and administrative outcomes. So that information serve as a useful for helping to develop standard practice of ADR Monitoring Program, focused on a strategy for preventable ADRs during hospitalization.

Recommendation

First, the benefits to costs ratio of the ADR Monitoring Program ensures that it would provide better financial administrative outcomes for administrator. The ADR Monitoring Program is necessary for early detecting and prevention of ADR and savings hospital resources. Early detection is important, particularly in hospitals where systems for detecting and preventing ADRs by this program will savings of cost and length of stay of ADRs in consequence to hospitalization for the hospital point of views. In the important future challenges, the development of an economic model for ADR Monitoring Program will facilitate the administrator to consider more rationally in ADR Monitoring Program management. ADR Monitoring Program management need to be developed strategies to detectable and preventable ADRs in the face of these important future challenges. Therefore, nonpreventable ADRs may become at least in part preventable. ADRs may be avoided if they are part of the considerations involved in planning and consequently monitoring the therapy, such as patient's groups, causative drug groups, Diagnostic groupings by Diagnosis-Related Groups (DRGs).

Second, for costs, further development of automated signal detection and prevention of ADR systems used in spontaneous monitoring system by this program and to combine some technologies, such as computer databases, patient history record systems. Computer monitoring systems have already proved to be a valid tool in increasing the awareness and preventable ADRs. This suggests considerable, the very proactive intensive pharmacovigilance methods can detect ADRs in strategy planning, but it is too expensive for routine use. Although the passive surveillance of spontaneous reporting is the most widely used technique but it have several limitations. Because of the low costs, most hospitals identify ADRs by spontaneous reporting.

The hospitals policies should perform their services with a good quality, adequate and well-trained staff, and with sufficient budget to improve their ADR screening skills focusing on the maintenance of the effectiveness of the ADR Monitoring Program.

Third, for policy and research development, considering the progress in policy and research development, the attributable risk and developments regarding health economics, the value of ADR detection in hospitals cannot be denied. However, the methods and systems used have to be further evaluated, and more standardization (e.g. with regard to definition of ADR terms, causality assessment and pharmacoeconomic analyses) is required. The incidence and prevalence in terms of ADR prevention is high enough to warrant use of information for pharmacoepidemiological analyses. Depending on the consequences of associated ADRs are severe enough to produce significant changes in clinical or quality of life end points, or lead to significant economic costs. These criteria can guide future research, in considering these issues, and serve as starting points for more comprehensive analyses of the cost-benefits and cost-effectiveness of pharmacovigilance information. This study provides empirical evidence that the use of pharmacovigilances could potentially a reduction of preventable ADRs, a problem of major significance and provides a foundation for future research.

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APPENDIX

APPENDIX A

Criteria for determining preventability of adverse drug reaction

Answering “yes” to one or more of the following implies that an ADR is preventable:

1. Was the drug involved in the ADR inappropriate for the patient’s clinical condition?
2. Was the dose, route, or frequency of administration inappropriate for the patient’s age, weight, or disease stage?
3. Was required therapeutic drug monitoring or other necessary laboratory test not performed?
4. Was there a history of allergy or previous reaction to the drug?
5. Was a drug interaction involved in the ADR?
6. Was a toxic serum drug concentration (or laboratory monitoring test) documented?
7. Was poor compliance involved in the ADR?

Data collection form labor costs of the ADR Monitoring Program

Staff activities and time used in the ADR Monitoring Program (ADRMP)

Activities	Staff responsibility to ADR Monitoring Program	Time used (hour/work-day)
Medical record delivery	Staff	
Patient interview	Pharmacist	
Medical record review	Pharmacist	
Care team rounds	Pharmacist	
ADRs monitoring& follow-up	Pharmacist	
ADRs information	Pharmacist	
	Staff	
Physician's consult	Pharmacist	
ADRs report and ADRs card	Pharmacist	
ADRs record	Staff	

Analysis labor costs of the ADR Monitoring Program (ADRMP)

Staff responsibility to ADRMP	Time used in ADRMP		Salary (baht/month)	Labor costs (baht/year)
	Hour per work-day	Work-day per month		
Pharmacist 1 Pharmacist 2 Pharmacist 3 Pharmacist 4 Staff 1				
Total				

Data collection form costs of an ADR Monitoring Program

Costs of an Adverse Drug Reaction Monitoring Program (ADRMP)

Descriptions	Annual Costs (baht)	Percent (%)
Labor costs **Material costs**		
Total		**100.00**

Data collection form the benefits of an ADR Monitoring Program

The benefits of an ADR Monitoring Program for one-year period of review

age	sex	Causative drugs	Types of ADRs	ICD10 ADRs	ICD10 PDx	Cost A (baht)	Cost B (baht)	Cost savings (baht)	Savings of LOS (day)
					Total				
					Mean				

APPENDIX B

Medications associated with ADRs at Siriraj Hospital 2006 (n = 416)

Causative drugs	No. of ADRs	Percent
Ceftriaxone	37	8.89
Phenytoin	37	8.89
Clindamycin	24	5.77
Vancomycin	21	5.05
Imipenem+Cilastatin	17	4.09
Amoxycillin	16	3.85
Cefazolin	13	3.12
Ciprofloxacin	12	2.89
Piperacillin+Tazobactam	14	3.37
Cefotaxime	12	2.89
Cotrimoxazole	13	3.12
Ampicillin	9	2.16
Ceftazidime	9	2.16
Meropenem	9	2.16
Carbamazepine, Cefepime, Cloxacillin, Omeprazole (each drug = 7 ADRs)	28	6.73
Allopurinol, Ibuprofen (each drug = 6 ADRs)	12	2.88
Celecoxib, Cytarabine, Tramadol (each drug = 5 ADRs)	15	3.61
Cephalexine, Levofloxacin, Paracetamol, Sodium valproate, Cefoperazone+Sulbactam (each drug = 4 ADRs)	20	4.81
Fluconazole, Metronidazole, Nevirapine, Penicillin G , Teicoplanin, Phenobarbital, Indapamide (each drug = 3 ADRs)	21	5.05
Amikacin, Cefpirome, Colistin, Dicloxacillin, Etoricoxib, Furosemide, IVIG, Metformin, Metoclopramide, Morphine, Pethidine, Rifampicin, Risperidone, Simvastatin, Sulfasalazine, Vincristine, Vit.K (each drug = 2 ADRs)	34	8.17

Medications associated with ADRs at Siriraj Hospital 2006 (n = 416) (continued)

Causative drugs	No. of ADRs	Percent
Acetazolamide, Acyclovir, Albendazole, Amifostine, Amphotericin B, Azithromycin, Baclofen, Carboplatin, Cefditoren, Cefminox, Clarithromycin, Codeine, Cyclosporin, Dapsone, Dexamethasone, Diclofenac, Diltiazem, Dimenhydrinate, Ertapenem, Filgastrim, Haloperidol, Itraconazole, Ketamine, Larmotrigine, L-Asparaginase, Lenogastim, Lomefloxacin Eye drop, Mesna, Melthylprednisolone, Naproxen, Nifedipine, Orphenadrine, Oseltamivir, Pacitaxel, Prednisolone, Primaquin, Propranalol, Quatiapine, Rabeprazole, Raubarine+Amitrine, Vidisic, Voluven, Voriconazole (each drug = 1 ADR)	43	10.34
Total	416	100.00

Abbreviations: IVIG, Intravenous immunoglobulin;

Cost and length of stay (LOS) were classified by patient characteristics at Siriraj Hospital 2006 (n = 416)

Characteristics	No of ADRs	Percent(%)	Cost B(baht)		Cost A(baht)		Cost savings(baht)		Savings of LOS(day)	
			Mean	Total	Mean	Total	Mean	Total(%)	Mean	Total
1. Age (year)										
< 1	1	0.24	4479.8	4479.8	-4160	-4160	8639.8	8639.8(0.3)	1	1
1-15	58	13.94	14404.27	835447.6	8171.4	473941	6232.87	361506.6(12.57)	1.33	77
16-33	67	16.11	14816.49	992704.7	7946.38	532407.2	6870.11	460297.5(16.01)	1.42	95
34-46	78	18.75	12193.42	951086.5	5165.77	402929.8	7027.65	548156.7(19.06)	2.46	192
47-59	69	16.59	15058.18	1039014.6	8159.12	562979.3	6899.06	476035.3(16.55)	2.68	185
≥ 60	143	34.37	11704.66	1673766.9	4564.89	652779.4	7139.77	1020988(35.51)	2.28	326
2. Gender										
Male	208	50	13314.18	2769348.4	6472.76	1346334.6	6841.41	1423013(49.17)	2.14	445
Female	208	50	13111.31	2727151.7	6127.61	1274542.1	6983.7	1452609.6(50.83)	2.07	431
Mean (±SD)			13212.74(±7337.95)		6300.18(±8148.40)		6912.56(±2840.39)		2.11(±4.25)	-
Range			3980.6-33874.1		16400.8-33874.1		0-23393.5		0-39	-
Total	416	100		5496500		2620877		2875623(100)		876

Abbreviations: Cost A, cost of treatment if this ADR is prevented would be determined from costs of treatment of PDx with complications and/or comorbidity for each patient, depending on DRGs (Thai DRG version 3.0); Cost B, cost of treatment for detected ADRs would be determined from costs of treating ADRs-consequences during hospitalization plus costs of treatment PDx with complications and/or comorbidity for each patient is assigned a DRG based on their combination of discharge diagnoses; Cost savings, the cost-savings were determined from the difference costs between costs of treatment for detected ADRs(Costs B) and costs of treatment if this ADR is prevented(Costs A), according to the following formula: The cost savings = Costs B - Costs A; The savings of LOS, were determined by the increased LOS of ADRs-consequences, quantified by means of DRG; ADR, adverse drug reaction; DRG, Diagnosis-Related Group; ICD-10, International Classification of Disease, 10th edition; LOS, length of stay; MDC, Major Diagnostic Category; PDx, Principle Diagnosis; SD, Standard deviation;

Cost and length of stay (LOS) were classified by characteristics of ADRs at Siriraj Hospital 2006 (n = 416)

Characteristics	No. of ADRs	Percent(%)	Cost B(baht)		Cost A(baht)		Cost savings(baht)		Savings of LOS(day)	
			Mean	Total	Mean	Total	Mean	Total(%)	Mean	Total
1. Severity of ADRs										
Non-serious	324	77.88	13348.7	4324977.8	6046.59	1959094.8	7302.11	2365883(82.27)	1.92	621
Serious	92	22.12	12733.94	1171522.3	7193.28	661781.9	5540.66	509740.4(17.73)	2.77	255
2. Cause/effect relationship(Naranjo)										
Probable	172	41.35	13259.71	2280670.6	6664.88	1146359.5	6594.83	1134311.1(39.45)	2.32	399
Possible	244	58.65	13179.63	3215829.5	6043.1	1474517.2	7136.53	1741312.3(60.55)	1.96	477
3. Type of reaction(Rawlins&Thompson)										
Pharmacologic(Type A)	29	6.97	15762.05	457099.5	12799.58	371187.7	2962.48	85911.8(2.99)	4.76	138
Idiosyncratic(Type B)	387	93.03	13021.71	5039400.6	5813.15	2249689	7208.56	2789711.6(97.01)	1.91	738
Mean (± SD)	-	-	13212.74(±7337.95)	-	6300.18(±8148.40)	-	6912.56(±2840.39)	-	2.11(±4.25)	-
Range			3980.6-33874.1		16400.8-33874.1		0-23393.5		0-39	-
Total	416	100	-	5496500	-	2620877	-	2875623(100)	-	876

Abbreviations: Cost A, cost of treatment if this ADR is prevented would be determined from costs of treatment of PDx with complications and/or comorbidity for each patient, depending on DRGs (Thai DRG version 3.0); Cost B, cost of treatment for detected ADRs would be determined from costs of treating ADRs-consequences during hospitalization plus costs of treatment PDx with complications and/or comorbidity for each patient is assigned a DRG based on their combination of discharge diagnoses; Cost savings, the cost-savings were determined from the difference costs between costs of treatment for detected ADRs(Costs B) and costs of treatment if this ADR is prevented(Costs A), according to the following formula: The cost savings = Costs B - Costs A; The savings of LOS, were determined by the increased LOS of ADRs-consequences, quantified by means of DRG; ADR, adverse drug reaction; DRG, Diagnosis-Related Group; ICD-10, International Classification of Disease, 10th edition; LOS, length of stay; MDC, Major Diagnostic Category; PDx, Principle Diagnosis; SD, Standard deviation;

Cost and length of stay (LOS) were classified by types of ADRs at Siriraj Hospital 2006 (n = 416)

Types of ADRs	No. of events	Percent(%)	Cost B(baht)		Cost A(baht)		Cost savings(baht)		Savings of LOS(day)	
			Mean	Total	Mean	Total	Mean	Total(%)	Mean	Total
Maculopapular	180	43.27	13779.1	2480237.5	5682.67	1022880.3	8096.43	1457357.2(50.68)	2.07	373
Rash	50	12.02	13742.17	687108.5	5620.76	281037.9	8121.41	406070.6(14.12)	1.76	88
Urticaria	38	9.14	11599.42	440778	5755.58	218712	5843.84	222066(7.72)	1.21	46
Angio-edema	19	4.57	7139.26	135645.9	1646.01	31274.1	5493.25	104371.8(3.63)	0.42	8
Anaphylactic	17	4.09	15341.38	260803.4	10059.25	171007.2	5282.13	89796.2(3.12)	0.59	10
Stevens-Johnson syndrome	13	3.13	9267.1	120472.3	662.1	8607.3	8605	111865(3.89)	2.08	27
Erythema multiforme	10	2.41	12341.42	123414.2	3701.62	37016.2	8639.8	86398(3.00)	1.4	14
Hypersensitivity drug	10	2.41	8990.28	89902.8	1569.88	15698.8	7420.4	74204(2.58)	3.4	34
Erythematous	7	1.68	9409.21	65864.5	2508.81	17561.7	6900.4	48302.8(1.68)	1.14	8
Agranulocytosis	6	1.44	15788.07	94728.4	9236.93	55421.6	6551.13	39306.8(1.37)	7.83	47
Nausea-Vomiting, Constipation	6	1.44	16371.12	98226.7	10651.12	63906.7	5720	34320(1.19)	9.67	58
Eczema	5	1.2	18554.9	92774.5	11654.5	58272.5	6900.4	34502(1.20)	3.4	17
Myopathy drug induced	5	1.2	19912.62	99563.1	19912.62	99563.1	0	0(0.00)	4.2	21
Therapeutic injection	5	1.2	10655.32	53276.6	8018.14	40090.7	2637.18	13185.9(0.46)	0.4	2
Acidosis, Hyponatremia, Hyperkalemia	4	0.96	10191.35	40765.4	7053.8	28215.2	3137.55	12550.2(0.44)	2.75	11
Convulsion, Epilepsy	3	0.72	27261.43	81784.3	22599.63	67798.9	4661.8	13985.4(0.49)	0	0
Edema eyelid, Conjunctiva	3	0.72	11901.93	35705.8	8883.33	26650	3018.6	9055.8(0.31)	0	0
Eruption drug localized	3	0.72	17549.13	52647.4	17549.13	52647.4	0	0(0.00)	0	0
Exfoliative dermatitis	3	0.72	21095.53	63286.6	21095.53	63286.6	0	0(0.00)	3	9
Pruritus	3	0.72	11426.13	34278.4	9126	27378	2300.13	6900.4(0.24)	0.33	1
Renal failure, Acute tubular necrosis	3	0.72	19005.13	57015.4	19005.13	57015.4	0	0(0.00)	2.67	8
Bronchospasm	2	0.48	15984.8	31969.6	15984.8	31969.6	0	0(0.00)	0	0
Extrapyramidal	2	0.48	11823.5	23647	5324.15	10648.3	6499.35	12998.7(0.45)	1	2
Toxic epidermal necrolysis	2	0.48	10293.4	20586.8	1653.6	3307.2	8639.8	17279.6(0.60)	2	4
Toxic liver due to drug	2	0.48	24375	48750	24375	48750	0	0(0.00)	20	40
Vasculitis allergic	2	0.48	9517.95	19035.9	9517.95	19035.9	0	0(0.00)	2.5	5
Aplastic anemia	1	0.24	9284.6	9284.6	2701.4	2701.4	6583.2	6583.2(0.23)	2	2
Dyspnea	1	0.24	13759.2	13759.2	7510.1	7510.1	6249.1	6249.1(0.22)	0	0
Dyshidrosis	1	0.24	9753.9	9753.9	2853.5	2853.5	6900.4	6900.4(0.24)	1	1
Edema localized	1	0.24	11753.3	11753.3	11753.3	11753.3	0	0(0.00)	1	1
Flushing	1	0.24	13755.3	13755.3	13755.3	13755.3	0	0(0.00)	0	0
Nephritis -interstitial acute	1	0.24	11302.2	11302.2	11302.2	11302.2	0	0(0.00)	9	9
Nephropathy drug-induced	1	0.24	16555.5	16555.5	16555.5	16555.5	0	0(0.00)	4	4
Palpitations	1	0.24	8170.5	8170.5	-3770	-3770	11940.5	11940.5(0.42)	0	0

Cost and length of stay (LOS) were classified by types of ADRs at Siriraj Hospital 2006 (n = 416), (continued)

Types of ADRs	No. of events	Percent(%)	Cost B(baht)		Cost A(baht)		Cost savings(baht)		Savings of LOS(day)	
			Mean	Total	Mean	Total	Mean	Total(%)	Mean	Total
Peripheral vascular	1	0.24	14036.1	14036.1	14036.1	14036.1	0	0(0.00)	14	14
Polyneuropathy drug-induced	1	0.24	10908.3	10908.3	-1948.7	-1948.7	12857	12857(0.45)	1	1
Respiratory failure	1	0.24	6193.2	6193.2	-6990.1	-6990.1	13183.3	13183.3(0.46)	1	1
Thrombocytopenia	1	0.24	6992.7	6992.7	-16400.8	-16400.8	23393.5	23393.5(0.81)	4	4
Thrombosis deep vein	1	0.24	11766.3	11766.3	11766.3	11766.3	0	0(0.00)	6	6
Mean (±SD)			13212.74(±7337.95)		6300.18(±8148.40)		6912.56(±2840.39)		2.11(±4.25)	-
Range			3980.6-33874.1		16400.8-33874.1		0-23393.5		0-39	-
Total	416	100	-	5496500	-	2620877	-	2875623(100)	-	876

Abbreviations: Cost A, cost of treatment if this ADR is prevented would be determined from costs of treatment of PDx with complications and/or comorbidity for each patient, depending on DRGs (Thai DRG version 3.0); Cost B, cost of treatment for detected ADRs would be determined from costs of treating ADRs-consequences during hospitalization plus costs of treatment PDx with complications and/or comorbidity for each patient is assigned a DRG based on their combination of discharge diagnoses; Cost savings, the cost-savings were determined from the difference costs between costs of treatment for detected ADRs(Costs B) and costs of treatment if this ADR is prevented(Costs A), according to the following formula: The cost savings = Costs B - Costs A; The savings of LOS, were determined by the increased LOS of ADRs-consequences, quantified by means of DRG; ADR, adverse drug reaction; DRG, Diagnosis-Related Group; ICD-10, International Classification of Disease, 10th edition; LOS, length of stay; MDC, Major Diagnostic Category; PDx, Principle Diagnosis; SD, Standard deviation;

Cost and length of stay (LOS) were classified by Diagnosis-Related Groups (DRGs) of PDx at Siriraj Hospital 2006 (n = 416)

MDC	DRGs of PDx	No. of ADRs	Percent)%)	Cost B(baht)		Cost A(baht)		Cost savings(baht)		Savings of LOS(day)	
				Mean	Total	Mean	Total	Mean	Total(%)	Mean	Total
1	Nervous system	68	16.35	15367.05	1044960	7904.25	537488.9	7462.8	507470.6(17.65)	1.85	126
8	Musculoskeletal system & connective tissue	50	12.02	11857.79	592889.7	4628.31	231415.6	7229.48	361474.1(12.57)	2.58	129
17	Myeloproliferative disorders	45	10.82	29318.61	1319338	23132	1040940	6186.61	278397.6(9.68)	2.82	127
5	Circulatory system	31	7.45	11505.46	356669.3	5530.62	171449.2	5974.84	185220.1(6.44)	2.87	89
4	Respiratory system	30	7.21	9895.77	296873.2	3059.85	91795.6	6835.92	205077.6(7.13)	1.17	35
9	Skin, Subcutaneous tissue & breast	28	6.73	8244.55	230847.5	229.82	6435	8014.73	224412.5(7.80)	1.43	40
21	Injuries, Poisonings & toxic drug effects	24	5.77	7320.79	175698.9	396.99	9527.7	6923.8	166171.2(5.78)	1.29	31
11	Kidney & urinary tract	19	4.57	9351.72	177682.7	3074.5	58415.5	6277.22	119267.2(4.15)	2.63	50
7	Hepatobiliary system & pancreas	17	4.09	12086.71	205474.1	5250.93	89265.8	6835.78	116208.3(4.04)	1.82	31
3	Ear, Mouth & throat	16	3.85	11210.06	179361	3769.19	60307	7440.87	119054(4.14)	1.25	20
25	Human Immunodeficiency Virus (HIV) infections	15	3.61	11302.2	169533	4546.36	68195.4	6755.84	101337.6(3.52)	3.13	47
18	Infectious & parasitic diseases	14	3.37	10178.07	142493	3280.09	45921.2	6897.99	96571.8(3.36)	2.5	35
14	Pregnancy, Childbirth & puerperium	12	2.88	8446.42	101357.1	1518.94	18227.3	6927.48	83129.8(2.89)	3.25	39
6	Digestive system	11	2.64	7561.51	83176.6	99.39	1093.3	7462.12	82083.3(2.85)	0.91	10
13	Female reproductive system	8	1.92	10257.33	82058.6	4719.65	37757.2	5537.68	44301.4(1.54)	0.75	6
16	Blood & Immunological	8	1.92	9015.83	72126.6	2684.34	21474.7	6331.49	50651.9(1.76)	1.63	13
10	Endocrine, Nutritional & metabolic	7	1.68	11837.99	82865.9	3859.14	27014	7978.84	55851.9(1.94)	3	21
2	Eye	4	0.96	10034.05	40136.2	2690.68	10762.7	7343.37	29373.5(1.02)	1.75	7
12	Male reproductive system	3	0.72	17851.6	53554.8	13058.07	39174.2	4793.53	14380.6(0.50)	1	3
15	Newborns & other neonates	2	0.48	12455.3	24910.6	6145.1	12290.2	6310.2	12620.4(0.44)	2.5	5
19	Mental disorders	2	0.48	10593.7	21187.4	6500	13000	4093.7	8187.4(0.29)	4.5	9
22	Burns	1	0.24	26782.6	26782.6	18595.2	18595.2	8187.4	8187.4(0.29)	1	1
24	Multiple significant trauma	1	0.24	16524.3	16524.3	10331.1	10331.1	6193.2	6193.2(0.22)	2	2
	Mean (± SD)		-	13212.74(±7337.95)	-	6300.18(±8148.40)	-	6912.56(±2840.39)	-	2.11(±4.25)	-
	Range			3980.6-33874.1		16400.8-33874.1		0-23393.5		0-39	
	Total	416	100	-	5496500	-	2620877	-	2875623(100)	-	876

Abbreviations: Cost A, cost of treatment if this ADR is prevented would be determined from costs of treatment of PDx with complications and/or comorbidity for each patient, depending on DRGs (Thai DRG version 3.0); Cost B, cost of treatment for detected ADRs would be determined from costs of treating ADRs-consequences during hospitalization plus costs of treatment PDx with complications and/or comorbidity for each patient is assigned a DRG based on their combination of discharge diagnoses; Cost savings, the cost-savings were determined from the difference costs between costs of treatment for detected ADRs(Costs B) and costs of treatment if this ADR is prevented(Costs A), according to the following formula: The cost savings = Costs B - Costs A; The savings of LOS, were determined by the increased LOS of ADRs-consequences, quantified by means of DRG; ADR, adverse drug reaction; DRG, Diagnosis-Related Group; ICD-10, International Classification of Disease, 10th edition; LOS, length of stay; MDC, Major Diagnostic Category; PDx, Principle Diagnosis; SD, Standard deviation;

Cost, length of stay (LOS) of Diagnosis-Related Groups and complication index at Siriraj Hospital 2006 (n = 416)

DRGs of PDx	No. of ADRs(%)	Complication index				Mean cost (baht)			Mean savings of LOS
		No CC	Moderate	Severe	Catastrophic CC	Cost B	Cost A	Cost savings	(day)
Nervous system	68(16.35)				11	14468.88	7687.85	6781.04	1.91
				15		19027.06	10335.09	8691.97	2.73
			2			9117.55	3033.55	6084	1
		40				14554.02	7295.73	7258.29	1.55
Musculoskeletal system	50(12.02)				8	12411.91	4054.86	8357.05	0.88
				11		12600.07	4428.63	8171.45	1.91
			3			10276.93	2216.93	8060	4.33
		28				11577.24	5128.96	6448.28	3.14
Myeloproliferative disorders	45(10.82)				26	29649.3	23750	5899.3	3.62
				4		27008.8	22802	4206.8	0.5
			1			33874.1	26881.4	6992.7	0
		14				29039.03	21810.75	7228.28	2.21
Circulatory system	31(7.45)				11	11571.3	5865.6	5705.7	0.91
				7		12344.61	5387.39	6957.23	1.86
		13				10997.9	5324.3	5673.6	5.08
Respiratory system	30(7.21)				11	9072.58	1348.93	7723.65	1
				4		12262.58	10215.73	2046.85	0.25
			4			10727.93	2925.98	7801.95	1.25
		11				9555.71	2217.33	7338.38	1.64
Skin, Subcutaneous tissue & breast	28(6.73)				8	9177.68	1384.99	7792.69	1.13
				6		8170.5	-318.5	8489	3.5
			7			7397.37	-1048.54	8445.91	0.43
		7				8088.79	657.99	7430.8	1

Cost, length of stay (LOS) of Diagnosis-Related Groups and complication index at Siriraj Hospital 2006 (n = 416), (continued)

DRGs of PDx	No. of ADRs(%)	Complication index			Mean cost (baht)			Mean savings of LOS
		No CC	Moderate	Severe	Catastrophic CC	Cost B	Cost A	Cost savings	(day)
Injuries & toxic drug effects	24(5.77)				5	8998.08	2756.52	6241.56	1.8
				3		7217.17	-310.27	7527.43	0.33
			3			6386.9	-1106.3	7493.2	2.67
		13				6915.1	-0.4	6915.5	1
Kidney & urinary tract	19(4.57)				11	9910.02	4659.44	5250.58	3.36
				2		7580.3	-607.1	8187.4	2
			2			7856.55	666.25	7190.3	1
		4				9449.7	1760.85	7688.85	1.75
Hepatobiliary system & pancreas	17(4.09)				1	10181.6	1994.2	8187.4	11
				3		12182.73	3103.53	9079.2	0.67
			1			14731.6	8538.4	6193.2	1
		12				12001.06	5785.22	6215.84	1.42
Ear, Mouth & throat	16(3.85)				1	14959.1	6319.3	8639.8	0
				1		14959.1	6771.7	8187.4	0
			2			14959.1	10865.4	4093.7	1
		12				9960.38	2123.77	7836.62	1.5
HIV infections	15(3.61)				8	11302.2	4888.65	6413.55	5
				3		11302.2	2813.2	8489	0.67
		4				11302.2	5161.65	6140.55	1.25
Infectious & parasitic diseases	14(3.37)				8	12550.04	5683.11	6866.93	3
				1		7077.2	884	6193.2	8
		5				7003.1	-85.54	7088.64	0.6

Cost, length of stay (LOS) of Diagnosis-Related Groups and complication index at Siriraj Hospital 2006 (n = 416), (continued)

DRGs of PDx	No. of ADRs(%)	Complication index			Mean cost (baht)			Mean savings of LOS
		No CC	Moderate	Severe	Catastrophic CC	Cost B	Cost A	Cost savings	(day)
Pregnancy, Childbirth & puerperium	12(2.88)			1		9522.5	1335.1	8187.4	3
			1			11198.2	5005	6193.2	1
		10				8063.64	1634.62	6874.92	3.5
Digestive system	11(2.64)				2	10888.8	3698.5	7190.3	0.5
				3		6536.83	-1136.63	7673.47	1.67
		6				6964.75	-482.3	7447.05	0.67
Female reproductive system	8(1.92)				5	10559.38	3427.06	7132.32	1
		3				9753.9	6873.97	2879.93	0.33
Blood & Immunological	8(1.92)				2	6583.2	-1830.4	8413.6	0.5
			1			9826.7	1639.3	8187.4	4
		5				9826.7	4699.24	5127.46	1.6
Endocrine, Nutritional & metabolic	7(1.68)	7				11837.99	3859.14	7978.84	3
Eye	4(0.96)				1	13336.7	5149.3	8187.4	4
		3				8933.17	1871.13	7062.03	1
Male reproductive system	3(0.72)		1			17851.6	17851.6	0	0
		2				17851.6	10661.3	7190.3	1.5
Newborns & other neonates	2(0.48)			1		12550.2	8569.6	3980.6	2
		1				12360.4	3720.6	8639.8	3
Mental disorders	2(0.48)				1	9421.1	1233.7	8187.4	3
				1		11766.3	11766.3	0	6

Cost, length of stay (LOS) of Diagnosis-Related Groups and complication index at Siriraj Hospital 2006 (n = 416), (continued)

DRGs of PDx	No. of ADRs(%)	Complication index				Mean cost (baht)			Mean savings of LOS
		No CC	Moderate	Severe	Catastrophic CC	Cost B	Cost A	Cost savings	(day)
Burns	1(0.24)	1				26782.6	18595.2	8187.4	1
Multiple significant trauma	1(0.24)				1	16524.3	10331.1	6193.2	2
Mean (± SD)						**13212.74(±7337.95)**	**6300.18(±8148.40)**	**6912.56(±2840.39)**	**2.11(±4.25)**
Total(%)	**416(100)**	**201(48.32)**	**28(6.73)**	**66(15.86)**	**121(29.09)**	**5496500**	**2620877**	**2875623**	**876**

Abbreviations: Cost A, cost of treatment if this ADR is prevented would be determined from costs of treatment of PDx with complications and/or comorbidity for each patient, depending on DRGs (Thai DRG version 3.0); Cost B, cost of treatment for detected ADRs would be determined from costs of treating ADRs-consequences during hospitalization plus costs of treatment PDx with complications and/or comorbidity for each patient is assigned a DRG based on their combination of discharge diagnoses; Cost savings, the cost-savings were determined from the difference costs between costs of treatment for detected ADRs(Costs B) and costs of treatment if this ADR is prevented(Costs A), according to the following formula: The cost savings = Costs B - Costs A; The savings of LOS, were determined by the increased LOS of ADRs-consequences, quantified by means of DRG; ADR, adverse drug reaction; CC, Complication and Comorbidity; DRG, Diagnosis-Related Group; HIV, Human Immunodeficiency Virus;
ICD-10, International Classification of Disease, 10th edition; LOS, length of stay; MDC, Major Diagnosis Category; PDx, Principle Diagnosis;

Cost and length of stay (LOS) were classified by causative drug groups at Siriraj Hospital 2006 (n = 416)

Therapeutic drug class	No. of ADRs	Percent(%)	Cost B (baht)		Cost A(baht)		Cost savings(baht)		Savings of LOS(day)	
			Mean	Total	Mean	Total	Mean	Total(%)	Mean	Total
Anti-biotics	257	61.78	12752.63	3277426.00	5601.48	1439580	7151.15	1837846(63.91)	1.9	489
CNS-Psychiatric	53	12.74	12890.97	683221.50	5134.39	272122.5	7756.59	411099(14.30)	2.92	155
Unclassified therapeutic agent	23	5.53	13778.13	316897.10	8782.40	201995.3	4995.73	114901.8(4.00)	0.52	12
Musculoskeletal:NSAIDs	17	4.1	9423.55	160200.30	2334.88	39692.9	7088.67	120507.4(4.19)	1.12	19
Hematologic-oncologic	14	3.37	26977.79	377689.00	18943.51	265209.1	8034.28	112479.9(3.91)	1.71	24
Gastro-intestinal	9	2.16	12268.1	110412.90	5111.46	46003.1	7156.64	64409.8(2.24)	2.11	19
Musculoskeletal:misc	9	2.16	8600.08	77400.70	3068.14	27613.3	5531.93	49787.4(1.73)	1	9
Cardiovascular	7	1.68	9839.89	68879.20	3186.30	22304.1	6653.59	46575.1(1.62)	3.43	24
Endocrine	7	1.68	19631.11	137417.80	19631.11	137417.8	0	0(0.00)	2.86	20
Musculoskeletal:gout, DMARDs	7	1.68	9269.74	64888.20	3346.94	23428.6	5922.8	41459.6(1.44)	2.86	20
Anti-fungals	6	1.44	23841.35	143048.10	20373.38	122240.3	3467.97	20807.8(0.72)	10	60
Anti-virals	5	1.2	9704.76	48523.80	1829.88	9149.4	7874.88	39374.4(1.37)	5	25
Anti-tuberculous	2	0.48	15247.7	30495.40	7060.30	14120.6	8187.4	16374.8(0.57)	0	0
Mean (±SD)			13212.74(±7337.95)		6300.18(±8148.40)		6912.56(±2840.39)		2.11(±4.25)	
Range			3980.6-33874.1		16400.8-33874.1		0-23393.5		0-39	
Total	416	100		5496500.00		2620877		2875623(100)		876

Abbreviations: Cost A, cost of treatment if this ADR is prevented would be determined from costs of treatment of PDx with complications and/or comorbidity for each patient, depending on DRGs (Thai DRG version 3.0); Cost B, cost of treatment for detected ADRs would be determined from costs of treating ADRs-consequences during hospitalization plus costs of treatment PDx with complications and/or comorbidity for each patient is assigned a DRG based on their combination of discharge diagnoses; Cost savings, the cost-savings were determined from the difference costs between costs of treatment for detected ADRs(Costs B) and costs of treatment if this ADR is prevented(Costs A), according to the following formula: The cost savings = Costs B - Costs A; The savings of LOS, were determined by the increased LOS of ADRs-consequences, quantified by means of DRG; ADR, adverse drug reaction; CNS, Central Nervous System; DMARDs, Disease-Modifying Anti-Rheumatic Drugs; DRG, Diagnosis-Related Group; ICD-10, International-Classification of Disease, 10th edition; LOS, length of stay; MDC, Major Diagnostic Category; NSAIDs, Nonsteroidal Anti-inflammatory Drugs; PDx, Principle Diagnosis; SD, Standard deviation;

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