ADVERSE DRUG EVENTS IN MALAYSIA:

MEDICATION-RELATED ADMISSIONS

AND

PHARMACISTS' EXPERIENCES

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ABSTRACT

Adverse drug events (ADEs) are a significant cause of patient morbidity and hospital admissions. There are many studies in this area in Western countries. However, little is known about the prevalence and patterns of such events in Malaysia. Health care professionals are in the best position to reduce and prevent adverse drug events. In order to devise preventive strategies based on the prevalence studies, it is important to understand the current practices of health care professionals in this area. This study aimed to determine the different occurrences of ADEs in a Malaysian public hospital as well as the experiences of some Malaysian pharmacists' of ADEs.

A study of an observational chart review determined the prevalence of adverse drug event-related admissions in a tertiary public hospital and drugs implicated in such. This was achieved through a prospective review of the patients' medical notes and charts in two medical wards. All cases were assessed using a classification tool which was developed after a pilot study. Following this, a postal survey of some Malaysian pharmacists explored their experiences about ADEs: the types of ADEs they have observed, actions taken in response to these incidents and their awareness of and involvement in adverse drug reaction reporting, and their attitudes towards this task.

Both studies revealed that the occurrence of adverse drug events was high in Malaysia – the chart review study found that 39% of admissions to two medical wards were related to ADEs whilst more than half of the sample pharmacists revealed having observed them in their daily work activities. Moreover, cardiovascular drugs, anti-diabetics, anti-asthmatics, and analgesics were responsible for more than 80% of the admissions related to an ADE. Similar drug classes were also associated with ADEs as recounted by the pharmacists. Moreover they claimed to have communicated with patients about ADEs: on the ADE experienced by a patient, proper use of medicine, importance of adherence, alternate medicines and other appropriate measurements. Although more than 80% hospital and clinic pharmacists claimed to have reported adverse drug reactions, less than 20% of community pharmacists have claimed sending a report. This may have resulted from their lack of awareness of the procedures and processes of reporting an adverse drug reaction.

Compared to other countries, the prevalence of ADEs is higher in Malaysia. It remains to be an important cause of patient injury and hospital admissions. Some useful strategies such as educational intervention on main causes of adverse drug events, monitoring of patients, and appropriate prescribing should be targeted at all health care professionals to prevent its likely future occurrences. Pharmacists play an important role in preventing ADEs by providing education and counselling to patients. Furthermore, as they were able to identify ADEs in their daily work activities, they should be included in any prevention programs. Documenting ADEs and interventions taken in relation to those ADEs should be encouraged, as this will be useful in monitoring the occurrence of ADEs and sharing the documented information with others could improve awareness and therefore improve prevention.

PUBLICATIONS

Karuppannan M, Mohd. Ali S, Wong KT, Ting KN and Boardman H. Adverse drug events related medical admissions in Malaysia: A pilot study. Pharm World Sci 2009; 31(4): 494-508.

Abstract presented as a poster presentation at the Pharmaceutical Care Network Europe (PCNE) working conference in Portugal, March 2009

Karuppannan M, Ting KN, Mohd. Ali S, Wong KT and Boardman H. The experiences of Malaysian pharmacists about adverse drug reactions: A pilot study. Int J Pharm Pract 2010; 18(s2):94-95.

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My daughter and son, whose beautiful smiles and inspiring existence, keep me going and meaningful.

Above all, *GOD*, to whom all things are beholden.

DEDICATION

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CHAPTER 2: A CHART REVIEW STUDY OF MEDICATION-RELATED ADMISSIONS TO A HOSPITAL

CHAPTER 3: SURVEY STUDY

LIST OF ABBREVIATIONS

ACEI	Angiotensin-converting enzyme inhibitor
ADE	Adverse drug event
ADR	Adverse drug reaction
ADWS	Adverse drug withdrawal syndrome
CCB	Calcium channel blocker
CPOE	Computerised prescribing order entry
DCA	Drug Control Authority
DO	Drug overdose
DMTAC	Diabetes medication therapy adherence clinic
DRP	Drug-related problem
DRM	Drug-related morbidity
FA	First assessor
GP	General practitioner
ICU	Intensive care unit
IHI	Institutes for Healthcare Improvement
MADRAC	Malaysian Adverse Drug Reaction Advisory Committee
ME	Medication error
MERP	Medication error reporting program
MERS	Medication error reporting system
MOH	Ministry of Health
MPS	Malaysian Pharmaceutical Society
MTAC	Medication therapy adherence clinic
NCC MERP	National Coordinating Committee of Medication Error Reporting and Prevention
NSAID	Non-steroidal anti-inflammatory drug
PDA	Palm assisted digital
PDRA	Preventable drug-related admission
SA	Second assessor
SD	Standard deviation
TF	Therapeutic failure
UK	United Kingdom
US	United States
WHO	World Health Organisation

GLOSSARY

ADVERSE DRUG EVENT	Any untoward medical occurrence that may appear during treatment with a pharmaceutical product, but which does not necessarily have a causal relationship with the treatment
ADVERSE DRUG REACTION	A response to a drug that is noxious and unintended, and occurs at doses normally used in humans for prophylaxis, diagnosis or therapy of disease, or for modification of physiological function
ADVERSE DRUG WITHDRAWAL SYNDROME	A clinical set of symptoms or signs that are related to the removal of a drug
DRUG OVERDOSE	The exposure of an individual (by ingestion or inhalation) to an amount of substance associated with the significant potential to cause harm
DRUG-RELATED PROBLEM	An event or circumstance involving drug treatment that actually or potentially interferes with the patient's experiencing an optimum outcome of medical care
DRUG-RELATED MORBIDITY	The failure of a therapeutic agent to produce the intended therapeutic outcome, or the clinical biosocial manifestation of unresolved drug-related problems

MEDICATION ERROR	Any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems, including the following: prescribing; order communications; product labelling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use
THERAPEUTIC FAILURE	An inadequate therapeutic response to a drug as evidenced by the presence of symptoms of a diagnosed disease state or condition

CHAPTER 1

INTRODUCTION

This chapter describes the background to this thesis. It starts with the problem statement followed by a brief introduction to Malaysia and its health care system. Literature were reviewed to further understand the work that has been done in the area of adverse drug event-related admissions, the terminology and classification of adverse drug events, the types of methods that can be used to identify them, the prevalence of adverse drug events and the role of health care professionals in recognising, resolving, monitoring and preventing them.

1.1 The problem statement

Patient safety and initiatives to develop safety cultures to protect patients from harm are increasingly becoming a major concern in health care quality improvement. Studies of adverse drug reactions and drug-related admissions have been published as early as the 1960s [1, 2] and lately, there is a growing interest in identifying strategies to prevent or reduce adverse drug events (ADEs) [3-6].

In 1999, a report entitled, *To Err is Human* by Institute of Medicine (a United States-based independent and non-profit organization), astonished the medical world by claiming that between 44,000 and 98,000 patients in the US die every year from preventable adverse events [7]. Since then several studies conducted among hospitalised patients reported ADE rates from 2.5% to 30.4% [8-

11], and a meta-analysis revealed that fatal adverse drug reactions (ADR) occurred in 0.32% of patients [12]. There is potential for these percentages to rise with the changes in patterns of diseases and growth in the availability and consumption of medication. ADEs not only cause patient morbidity and mortality, but also contributes substantially to health care costs as a result of prolonged hospital stays and additional interventions [13-16].

The biggest indicator of the Malaysian Ministry of Health's commitment to patient safety is the creation of the Patient Safety Council in 2003 to ensure that its citizens receive safe health care [17]. This council follows closely the recommendation made by World Health Organisation's (WHO) Alliance for Patient's Safety recommendations on patient safety strategies and programs [17]. The council aims to develop a national, electronic database system for reporting and documenting medical errors in hospitals, promote an open and fair system for confidential reporting of incidents, analyse these incidents and learn how to avoid them in the future, devise strategies to improve safety and quality, and publish reports on adverse incidents and patient safety [17]. In line with WHO's patient safety program, the council has implemented various strategies such as improving hand hygiene standards, safety of surgical care, tackling antimicrobial resistance, promoting research for patient safety, and establishing a medical incident reporting system.

Established for more than a decade under the Drug Control Authority (DCA), Malaysian ADR Committee (MADRAC) receives and reviews ADR reports from health care professionals and patients and submits them to the WHO International Centre of Drug Monitoring in Uppsala, Sweden [18]. The reporting rate for ADRs in Malaysia was found to be low by a study in 2003 [19]. However, the number of reports received by MADRAC more recently has been increasing and these reports are mainly submitted by pharmacists [20]. In parallel with MADRAC, the Ministry of Health (MOH) has created the Medication Error Reporting System (MERS) in an effort to encourage health care professionals to report medication errors and to monitor the reports thus enabling the identification of high-risk areas and implementation of safety solutions [21].

The intention of the Patient Safety Council in initiating programs and strategies to improve patient safety is a good start. However, without identifying the extent of the problem and areas that would benefit from interventions, these programs may not be able to eradicate the root cause. The reports received by MADRAC and MERS are not sufficient or suitable to calculate the incidence or prevalence

of ADRs or medication errors (MEs). This is due to incomplete numerators (number of ADEs occurring) and denominators (number of patients exposed to a drug). Additionally, they are not able to identify other types of ADEs which may also compromise patient safety such as drug overdose (DO) and therapeutic failure (TF). A few small-scale studies have addressed the issue of drug-related admissions in Malaysia [22, 23]. However, these studies did not include all types of ADEs and were conducted for a short period of time. The paucity of information regarding the epidemiology of all types of ADEs in Malaysia means that there is potential to identify areas to implement preventive measures that have not been realised.

Therefore, this thesis aims to determine the prevalence of ADE-related admissions in Malaysia, the extent of this problem and the drugs which are the largest target for potential interventions. It also aims to determine the opinions and current practices of health care professionals in Malaysia, and identify whether or not education about ADEs is likely to improve their detection and reporting, and therefore suggest actions to prevent and resolve ADEs.

1.2 Organisation of the study

This thesis is divided into four chapters. The current chapter provides an introduction to the thesis, a brief description about Malaysia and its health care system. Subsequently, it presents the literature review on adverse drug events. The chapter ends with the rationale for the study and presents the aims and objectives of the study.

Chapter 2 describes the methods underpinning the first phase of this study. It describes the development of the method for the chart review study, the development and testing of a classification tool, and implementation of the main chart review study. It illustrates the data collection process, presents the main findings, and discusses the findings.

Chapter 3 describes the methods used in the second phase of the study. It provides explanation on the development and testing of the questionnaire, so as the process of data collection for the main survey study. It presents the main findings, and discussion of those findings.

Chapter 4 summarises the overall findings from both phases of the study and concludes with the implications for practice, policy, and research.

1.3 About Malaysia

Malaysia is located in Southeast Asia. It has 13 states and three federal territories. Kuala Lumpur is the capital of Malaysia. Geographically, it is divided into two regions: West Malaysia (Peninsular Malaysia) and East Malaysia, which are separated by the South China Sea.

In 2010, Malaysia had a population of approximately 28 million [24], with proportion of men and women almost equally distributed (51% versus 49%). The average life expectancy is 74 years, and is higher for women than men. Only 5% of the population are aged more than 64 years whilst 27% are aged less than 15 years. The Malays are the largest ethnic group (64%), followed by Chinese (25%), and Indian (7%)[24]. Islam is the official religion in Malaysia, and is practiced by 60% of the population. Malay language (*Bahasa Melayu*) is the official language and is spoken in all areas of the country.

1.3.1 Health care in Malaysia

The responsibility of health care in Malaysia lies with the Ministry of Health (MOH). The health care system is divided into two sectors – public sector and private sector. These sectors are discussed below. The majority of Malaysians do not have one single general practitioner (GP) who oversees their entire medical care. They can choose to receive medical treatment from several different GPs, clinics, or institutions and there may not be any communication between these different health care professionals.

1.3.1.1 Public sector health care

The government run, public-funded sector is made very affordable to patients because of high government subsidies and is free for civil servants, pensioners, and the poor. Other residents are charged a small amount of money to receive medical treatment. There are four types of health services in the public sector under the MOH: health or community clinics, district hospitals, state hospitals and special medical institutions.

Health clinics provide primary care services for the following: (a) dental care, (b) maternal and child care, (c) family planning, (d) education on health and dietary, (e) elderly health, (f) mental health, (g) adolescent health, (h) health screening and diagnostic services for chronic medical conditions and provide counselling services on food and nutrition, and smoking cessation, (i) follow-up of patients with stable and controlled medical conditions, (j) minor treatment for fever, cough, flu, and other minor ailments and (k) minor treatment procedures such as wound cleaning and stitching. There are also community health clinics providing services to rural residents, as well as mobile health clinics (a van equipped with basic health facilities and personnel) to help the poor and needy residents in rural areas [25, 26]. There are about 3,000 health clinics and 2,300 dental clinics in Malaysia[25].

The district hospitals have around 100 to 200 beds and are normally run by up to ten medical officers. These are secondary care hospitals providing inpatient and outpatient services to the district population. Almost all hospitals have basic diagnostic capabilities. They also receive referrals and further complement the primary health care services in the district. There are two types of district hospitals: with or without specialists. Hospitals without specialists have visiting ones on a regular basis.

State general hospitals have around 500 to 1,500 beds providing tertiary care. Each state in Malaysia has one state hospital, the least. These consist of general and teaching hospitals. These hospitals provide outpatient and inpatient services in general medicine, general surgery, dermatology, ophthalmology, orthopaedics, paediatrics, obstetrics and gynaecology, psychiatry, and pharmacy. In Malaysia, there are three hospitals equipped with total hospital information systems (THIS). It is an electronic information system designed to manage administrative, financial, and clinical aspects of a hospital [25].

There are six special medical institutions in Malaysia. The special medical institutions provide inpatient services for specific medical conditions: (a) National Respiratory Institute (b) National Leprosy Control Centre (c) National Cancer Institute, and (d) three Mental Health Institutes.

1.3.1.2 Private sector heath care

The private sector is funded on a non-subsidised, payment-for-service basis. Those who have private insurance use the services as well. This insurance can be obtained voluntarily or provided by a private company to its workers. Currently, there is no compulsory insurance or national health insurance in Malaysia. The types of private health care services are: private hospitals, maternity homes, nursing homes, hospices, ambulatory care centres, haemodialysis centres, community mental health centres, medical clinics, and dental clinics.

There are about 6,300 private medical clinics and 1,500 dental clinics in Malaysia[25]. Private clinics provide primary care services and the practitioners are registered physicians. Some clinics serve as panel clinics in which a company provides insurance coverage to its employees and allow them to receive treatment at the appointed clinics.

In 2009, there were 209 private hospitals, 21 maternity homes, 21 ambulatory care centres, 12 nursing homes, three hospices, and one community mental health centre in Malaysia. Private hospitals accounted for 25% of Malaysia's hospital beds and are usually located in urban areas [25].

At present, patients can go to any health care facilities to receive treatment. Their medical record database is not linked between the clinics and/or hospitals. This allows patients to receive treatment in any of the clinics or hospitals they prefer, or are comfortable with. However, the disadvantage is that, a patient may end up receiving treatments in different clinics or hospitals and poly-pharmacy could become a problem, as patient details are not communicated.

1.3.2 Pharmacy practice in Malaysia

Malaysia has two types of pharmacy practice – government and private practice. Government pharmacy practice mostly takes place in government hospitals and health care facilities. Pharmacists also work at the National Pharmaceutical Control Bureau, pharmacy regulatory units, and government universities. There are more than 7,000 registered pharmacists in Malaysia and those working in the government sector make up to 59% [27].

Private pharmacy practice is mainly represented by chain-community pharmacies and independent pharmacies. Besides that, pharmacists also practice in private hospitals, industry, and private universities or colleges.

The job scope of hospital pharmacists is wide. Hospital pharmacists may work in an inpatient pharmacy (satellite pharmacy and ward supply pharmacy), outpatient pharmacy, therapeutic drug monitoring unit, parenteral nutrition unit, cyctotoxic drug reconstitution unit, drug information centre, drug store, and pharmaceutical production and pre-packing unit. Pharmacists in the public hospitals usually rotate to different departments regularly. Hospital pharmacists also provide services, such as Medication Therapy Adherence Clinics or MTAC (a pharmacist-based adherence clinic which reviews patients' drug history and assesses their adherence), counselling services for inpatients and outpatients, and Methadone Maintenance Therapy (provides direct observation therapy, education, and monitoring services to patients who are on methadone). There is a growing interest in specialist pharmacists in Malaysia (where pharmacists specialise in certain medical condition or unit such as renal pharmacists and intensive care unit pharmacists).

Hospital pharmacists interact with physicians during medical ward rounds or when there are queries about the medication prescribed to patients. Physicians are usually contacted by telephone or are met at the wards when the pharmacists need to clarify prescriptions. Pharmacists are also contacted by other health care professionals for advice such as the choice of medicine, availability of medicines, side effect queries and appropriate administration methods. Hospital pharmacists have direct patient contact during dispensing at the outpatient pharmacy department, ward rounds, bedside counselling, and patient assessments for clinical monitoring.

There are more than 3,000 community pharmacists in Malaysia [28]. Community pharmacists, also known, as retail pharmacists, provide services such as prescription filling, sales of over-the-counter (OTC) medicines dispensing, patient counselling and education, patient therapy management, and other patient-focused services (blood pressure or blood glucose monitoring, and cholesterol testing). Community pharmacists have minimal interaction with physicians. This is because community pharmacy functions as a unit on its own, and does not have link with any health care institution. The dispensing of prescription medicines in Malaysia still follows a traditional 'dispensing doctors' system, in which general practitioners practicing in private clinics are legally allowed to dispense

medicines as part of their professional practice. Hence, dispensing by community pharmacists is limited. Pharmacists in Malaysia have been seeking to change this situation and move to a model where prescriptions are dispensed by pharmacists rather than doctors. This issue is yet to be resolved. However, the growing number of pharmacists may lead to positive changes in the future.

The pharmacist-population ratio for Malaysia in 2009 was 1: 3,652 [25], which is far from 1:2,000, the ideal ratio recommended by the World Health Organisation [29].There are various government and private institutions in Malaysia that produce pharmacy graduates yearly. Every year, more than 700 graduate pharmacists register with the Pharmacy Board of Malaysia [28]. Due to the shortage of pharmacists in the country, particularly in the government sector, three- year compulsory service was introduced through an amendment to the regulations governing the Registration of Pharmacists Act 1951 in 2003 [28]. However due to increasing numbers of pharmacy graduates in recent years, this compulsory service has now been reduced to one year [30].

1.3.2.1 Pharmacy Board of Malaysia

The Pharmacy Board was established under the Registration of Pharmacists Act 1951. It consists of members from public and private sectors. It is responsible for the registration and deregistration of pharmacists and corporate bodies, registration of provisionally registered pharmacists, recognition of pharmacy degrees, approval of premises for pharmacist training, setting guidelines and standards relating to pharmacy degree, setting and conducting pharmacy jurisprudence examination, and conducting inquiries on unethical practices [28].

1.3.2.2 Malaysian Pharmaceutical Society

The Malaysian Pharmaceutical Society (MPS) is a national association for pharmacists in Malaysia. The membership of this society is voluntary. It regularly provides updates on the pharmacy profession, and scientific research, conducts seminars or conferences for the development of the pharmacy profession and provides continuous pharmacy education for its members [31]. It also provides a platform for communication between its members. Furthermore, MPS promotes and encourages research and publication in the Malaysian Journal of Pharmacy. The society is managed

by council members elected during its annual general meetings. In 2010, there were about 2,000 members in MPS.

1.3.3 Major health problems in Malaysia

According to the Malaysian National Health and Morbidity Survey III (NHMS III) which was conducted in 2006, the prevalence of chronic medical conditions in Malaysia was estimated to be 15.5% [32]. Hypertension was reported to have the highest prevalence and followed by diabetes mellitus (DM), asthma and heart disease [32]. Over the years, the prevalence of these medical conditions has been reported to be increasing [33-36] – the reasons suggested for this increase include poor dietary control and a sedentary lifestyle [36]. For example, the national survey showed that the overall national prevalence of DM among Malaysians aged 30 years and above had increased from 8.3% in 1996 to 14.9% in 2006 [36]. The Malaysian Health Facts 2010 revealed that diseases of circulatory system and of respiratory system were two of the top ten causes of admission to hospitals and these two conditions were the two main causes of death in the hospitals [27].

Across the three main ethnic groups (Malay, Chinese, and Indian), the prevalence of chronic medical conditions was reported to be higher among the Indian ethnic group [32], with the prevalence of DM being the biggest contributor to this figure [33, 36]. The NHMS III also revealed that a higher proportion of people from Malay ethnic group were likely to visit public health facilities compared to the other groups, in contrast, people from the Chinese ethnic group were more likely to seek treatment from private hospitals and clinics [32].

Despite taking drug therapy, more than 70% of patients with chronic medical conditions had poor control of these medical conditions [33, 34]. Inadequate self-management skills, and poor knowledge about their medical conditions and medicines were some of the reasons quoted as causing this [37].

1.4 Definitions of adverse drug event-related hospital admissions

In order to conduct a study in drug safety, it is important to understand the commonly used terminologies in the literature. A number of studies have attempted to define these terminologies [38-42]. One of the problems is that different studies have used different definitions making comparison of findings between studies difficult. Commonly used definitions are presented and discussed.

"Drug related problem" (DRP) is the broadest terminology in drug safety. It has been defined as:

'A*n event or circumstance involving drug treatment that actually or potentially interferes with the patient's experiencing an optimum outcome of medical care'* [42].

This can be divided into events that result in injury and that do not result in injury [43]. The former is known as drug-related morbidity (DRM) which has been defined as:

'*The failure of a therapeutic agent to produce the intended therapeutic outcome, or the clinical biosocial manifestation of unresolved drug related problems*' [42].

The injury caused by the unresolved DRP may be minor or severe which could lead to the need for more medical attention or hospitalisation. This is interchangeable with terms such as drug-related injury [43] and adverse drug event (ADE) [38] . In this thesis, the term ADE will be used.

1.4.1 Adverse drug event

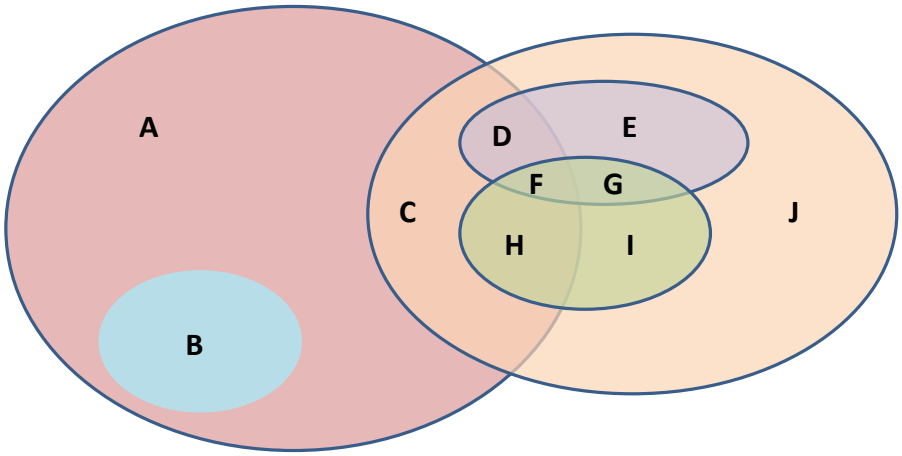
Many attempts have been made to define ADEs (Table 1-1). The American Society of Health-System Pharmacists [38], Bates et al. [13] and Gurwitz et al. [44] have defined ADE as an injury due to the use of a drug. However, these definitions do not include events related to omission of a drug. Whilst, the definition by World Health Organisation (WHO) includes all events occurring during a treatment, which does not necessarily have a causal relationship with the treatment. To ensure that all possible events that occurred during a drug treatment may be investigated the definition by WHO on ADE is adopted in this study.

Table 1-1: Different definitions for adverse drug events

Author	Definition
Bates et al., 1995 [13]	an injury resulting from medical intervention related to a drug
American Society of Health-System Pharmacists (ASHP)., 1998 [38]	an injury from a medicine
World Health Organisation (WHO)., 2000 [45]	any untoward medical occurrence that may appear during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with the treatment
Gurwitz et al., 2000 [44]	an injury resulting from the use of a drug
Hepler., 2003 [3]	a patient injury caused by the drug itself or by an error in how a drug is used

Nebeker et al. [46] have divided ADEs into two major groups; (a) 'harm caused by the drug' which includes adverse drug reaction (ADR) and drug overdose (DO), and (b) 'harm from the use of the drug' which includes therapeutic failure (TF) and adverse drug withdrawal syndrome (ADWS). Medication errors (ME) overlap in both groups [47]. The relationship between the different types of ADEs is shown in Figure 1-1.

Figure 1-1: Relationship between terminologies



A to C :	Medication errors
B :	Potential medication errors
A + B	Medication errors which do not cause harm
D to G :	Adverse drug reactions
C + H+ I+ J :	Other adverse drug events: medication error, therapeutic failure, drug overdose and adverse drug withdrawal syndrome
F to I :	Adverse drug event related admission

Adapted from American Society of Health-System Pharmacists (ASHP)., 1998 [38]

1.4.2 Medication error

An error is defined as:

'*something incorrectly done through ignorance or inadvertence; a mistake, e.g. in calculation, judgement, speech, writing, action, etc*.'[48]

The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) in United States (US) [49] defined ME as:

'*any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems, including the following: prescribing, order communications, product labelling, packaging, and nomenclature, compounding, dispensing, distribution, administration, education, monitoring, and use.'*

This definition specifies where an error could happen and who could make an error. The Malaysian Medication Error Reporting System (MERS) has adopted this definition in its guideline [50]. One of the difficulties in this field is the variety of terms used in the definition and classification of ME. Another recently proposed definition is:

'a failure in the treatment process that leads to, or has the potential to lead to, harm to the patient' [51, 52]

'Failure' signifies that the process has fallen below a standard. 'Treatment process' includes manufacturing or compounding, prescribing, transcribing (when relevant), dispensing, and administration of a drug and monitoring. The definition does not specify who is responsible for the error. It could be a physician, pharmacist, nurse, care taker, or the patient himself [52].

Throughout this thesis, the definition by the NCC MERP will be used due to its being widely accepted in Malaysia. ME is interchangeable with preventable ADE [53] or preventable DRM [54].

According to Helper [3], ME can be categorised into three different categories:

i) An error that has occurred but did not cause any harm to the patient (represented as A + B in Figure 1-1)

ii) An error that has been prevented or corrected in any stages of medication management before causing harm to patients which is called as potential ME (represented as B in Figure 1-1)

iii) An error that has occurred and caused harm to the patient (represented as C + D + F + H in Figure 1-1)

In line with the study aims, this thesis will study all types of MEs. Errors can occur at each stages of the medication use process [55, 56]. There are five main stages in the medication use process as defined by US Pharmacopeia [57]:

1) *Prescribing* – a process of evaluating a patient, establishing the need for a drug, selecting the right drug after determining interactions and allergy history, and prescribing the drug.

2) *Transcribing and documenting* – a process of transcribing a prescription order and transmitting it to the pharmacy.

3) *Dispensing* – a process of reviewing a prescription order, confirming the transcription, contacting the prescriber in case of discrepancies, preparing the drug, and distributing or dispensing the drug.

4) *Administering* – a process of reviewing a prescription order, confirming the transcription, reviewing warnings, interactions or allergies, evaluating the patient and administering the drug.

5) *Monitoring* – a process of assessing a patient's response to a drug, reporting and documenting the result.

Adherence problems can also be classified as ME because non-adherence could result from a human error [58]. In this thesis, however, patient non-adherence to drug will be classified under TF (Section 1.3.4).

1.4.3 Adverse drug reaction

ADR is represented as D to G in Figure 1-1. The most widely used definition for ADR was developed by WHO and is defined as:

'*a response to a drug that is noxious and unintended and occurs at doses normally used in humans for prophylaxis, diagnosis or therapy of disease, or for modification of physiological function*' [45].

This definition has been criticised by Edwards and Aronson [59] because of lack of clarity in the term 'noxious'. For this reason, Edwards et al proposed a new definition for ADR:

'*An appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product*' [59].

However, it is difficult to determine what types of ADR would be considered as 'an appreciably' harmful reaction. The American Society of Health-System Pharmacists has also excluded minor reactions [38] in their definition, whilst Strand et al. have included them [41].

In this thesis, however, the definition by WHO will be applied due to its wider coverage which includes all ADRs no matter how minor, and with the anticipation that all ADRs will be accounted for and not missed.

Some ADRs are unexpected and not preventable, for example, an allergic reaction to an antibiotic where the patient is not known to have the allergy [3, 38]. An ADR can also occur due to an error and cause harm to a patient [38, 55], for example, giving a patient penicillin when the patient's history

shows evidence of allergy to the antibiotic. This type of ADR overlaps with ME and is considered preventable [3, 38]. Thus, an ADR occurring due to an error will be classified as ME in this thesis.

ADRs have been classified as type A or type B reactions by Rawlins and Thompsons [60]. Type A reactions (augmented) are predictable especially where the pharmacological properties of the drug are known. These reactions are dose-dependent, for example, hypoglycaemia caused by insulin. They are also very common and rarely fatal [59]. Type B (bizarre) reactions are rare and unpredictable from the pharmacological properties of the drugs, for example, hypersensitivity reaction due to penicillin intake. This reaction does not show a clear relationship between the dose and the reaction, and can be fatal [59].

1.4.4 Therapeutic failure

Drug therapy is given to a patient to accomplish a positive therapeutic outcome. There are circumstances where the expected outcome is not achieved or accomplished. This is classified as TF. It is also known as 'therapeutic ineffectiveness' [61]. Several reports have attempted to define TF as described below.

Hallas et al. [62] defined TF as

'*an absence of therapeutic response that could be linked causally to a prescribed dose that was too low, to drug non-compliance, recent dose reduction or discontinuation, interaction, or inadequate therapeutic monitoring.'*

Nelson and Talbert. [63] defined TF as

'*an inadequate therapeutic response to a drug as evidenced by the presence of symptoms of a diagnosed disease state or condition*.'

Both definitions have similar concepts. An uncontrolled disease (absence of or inadequate therapeutic response) could occur when the expected outcome of a drug therapy is not achieved [63]. This could be due to patient non-adherence to drugs, recent dose reduction or discontinuation, interactions, too low a dose prescribed or inadequate therapeutic monitoring [62]. Meyboom et al. [64] added that pharmaceutical defect and counterfeit, resistance, and tolerance could also result in TF. The definition by Nelson and Talbert [63] however, is wide and not restricted to certain conditions like the definition by Hallas et al. [62].

One of the challenges in the drug safety field is differentiating between various ADE sub-types. TF overlap with MEs. For example, omission of necessary medication therapy, inadequate dose, interaction, inadequate therapeutic monitoring or pharmaceutical defect and counterfeit which lead to TFs can also be classified as MEs. Thus, it is important to have a clear definition for each type of ADE so that events will not be missed or underestimated. To be consistent throughout the thesis, the

less stringent definition of TF by Nelson and Talbert [63] will be used and TF could result from patient non-adherence to drug resistance or tolerance.

1.4.5 Drug overdose

Camidge et al. [65] have defined drug overdose as:

"*the exposure of an individual (by ingestion or inhalation) to an amount of substance associated with the significant potential to cause harm."*

It occurs when a drug (a pharmaceutical preparation available on prescription or over-the counter) is used in an amount that is higher than its normal dose [66]. This definition will be used throughout this thesis and can be categorised into accidental poisoning and intentional self-poisoning [65].

Accidental poisoning may occur when a patient unintentionally consumes an overdose of drugs and experiences adverse events. Intentional or deliberate poisoning occurs when a patient intentionally consumes an overdose of drugs. If the intentional DO resulted in death, it is diagnosed as suicide [65].

1.4.6 Adverse drug withdrawal syndrome

There are a number of reasons for a drug to be withdrawn: patient experiencing an ADR, inappropriate prescribing, or poor adherence [67-69]. All these could lead to adverse withdrawal syndrome. Occasionally, withdrawal symptoms are missed due to misdiagnosis. The symptoms may mimic a relapse or recurrence of the underlying disease for which the medication was originally prescribed [67]. The symptoms may also be misdiagnosed for adverse effects of a new medication or for TF [67].

Graves et al. [70] defined ADWS as

"*a clinical set of symptoms or signs that are related to the removal of a drug.*"

Edwards and Aronson [59] classified drug withdrawal as a type of ADR. However according to WHO [45], an ADR is a reaction occurring at normal therapeutic doses. Discontinuation of a drug indicates that the drug is not used, which is in contrast to the ADR definition by WHO [45]. Whenever ADWS is mentioned in this thesis, the definition by Graves et al., [70] is being used.

1.4.7 Adverse drug event-related admissions

When a patient experiences an ADE, there are a number of actions which they can take which to a large extent, depend on the severity of the event. Many severe ADEs will result in admissions to hospitals for treatment (an ADE-related admission), which is represented as F to I in Figure 1.1. These admissions can be further classified into ADR, TF, ME, DO or ADWS-related admissions.

1.5 Identifying adverse drug events

There are various ways to detect ADEs depending on the type of events and setting of the studies. These include chart review [9-11, 71] , spontaneous reporting [72, 73], computer surveillance [74, 75], observation [76, 77], intervention documentation [78, 79], and hospital database review [80, 81].

1.5.1 Chart review

In this method, patient medical notes, medication charts, nurses' notes, and laboratory results are reviewed manually to identify events. This can be conducted by a health care professional such as a research nurse, a pharmacist, or a research assistant. The general rule is to look out for any abnormalities in the charts which could indicate an ADE such as, development of new rashes, low blood glucose, or a physician's order for an antidote or sudden cessation of a drug [82]. The assessor needs to be properly trained in how to detect the anomalies and how to interpret the data.

A chart review can be conducted prospectively or retrospectively. Prospective reviews [71, 83, 84] are conducted while the patient is still in the hospital, and allow additional investigations such as patient interviews or new tests to be conducted. For retrospective reviews [15, 85], the patient is not available for more information and the researcher is dependent on the information documented in the chart. Inadequate or incomplete documentation in the chart is one of the major limitations and could result to a wrong interpretation of an event [86-88].

The Institute of Healthcare Improvement (IHI) is an independent, non-profit organisation based in the US which aims to improve the health care system by developing effective practices and models of care in cooperation with patients and health care professionals [27]. This organisation has introduced a trigger tool to make chart reviewing simpler [89, 90]. The tool contains a predetermined list of specified triggers that can indicate whether an ADE has occurred, for example, "rise in serum creatinine," "use of anti-emetics," or "abrupt cessation of a drug." The trigger tool can be used during chart review to assist the identification of any abnormalities in the chart. However, this tool

may have to be modified to suit the study site. For example, medical wards and paediatric wards may have different triggers; or different countries may have different prescribing patterns [89, 91].

Chart reviewing has been found to detect more ADEs compared to other methods [75, 85, 92]. The use of several sources such as medical notes, medication charts, nurses' notes, laboratory results and patient interviews help to compensate for the lack of completeness in each source [93]. Some important information that could confirm the causality for certain types of ADE have been found to be identifiable from nurses' notes [94]. This method also has the advantage of interviewing patients for more information or clarification, if conducted prospectively. It is the preferred method for research on drug safety as it can accurately document the outcome [95]. It can also be used for a more focused review such as about a specific drug or ward.

However, chart review is labour intensive and a time consuming method. It is costly as the assessors may need specialised training. Furthermore, the quality of the information is dependent upon the assessors ability to conduct adequate chart reviews [96]. Although it is a suitable method for this type of research, it was found to be not suitable to detect ADEs in outpatient departments because most events were not recorded in the notes [97].

1.5.2 Incident or spontaneous reporting

This is the primary method which institutions use to identify ADRs. A new drug will only have been tested clinically in a few thousands of patients and millions will be consuming it once it is marketed. The monitoring of ADR reports is necessary to keep track of the drug's safety profile and enable the authorities to issue any warnings regarding the use of a drug. However, this method will not be able to determine the incidence of ADRs due to incomplete numerators (number of ADRs occurring) and denominators (number of patients exposed to a drug). Furthermore, the reporting is essentially voluntary. The reporter will only report when they feel it is important to do so, or they have sufficient interest in reporting ADRs.

Ideally, health care professionals would report reactions to the drug authority that is responsible for collating all such reports, and the reports would be documented and monitored. The reports should also be made by patients and drug companies. The spontaneous reporting system for ADRs is well-established in many countries including Malaysia [18].

The Malaysian ADR Advisory Committee (MADRAC) was established under the Drug Control Authority (DCA) to monitor safety profiles of drugs registered in Malaysia [18]. It provides the DCA with information pertaining to drug safety issues. The National Drug Safety Monitoring Centre, which is the secretariat to MADRAC, was accepted as a member of WHO Drug Safety Monitoring Program in 1990 [18]. Under this program, all ADR reports received and screened by MADRAC are submitted to the Uppsala Monitoring Centre in Sweden for inclusion into the WHO database. MADRAC hold meetings every two months to conduct causality assessments. Members of MADRAC consist health care professionals appointed by the Director General of Health [18]. Initially, pharmacists screen all the cases and conduct causality assessments of common ADRs. Only rare or serious reactions are presented and discussed during the meetings. MADRAC uses the WHO causality assessment scale [98] for all cases and if further investigation is needed for rare or fatal reactions, the Naranjo scale [99] is used as a guideline. Other than its monitoring role, MADRAC promotes ADR reporting and provides information about ADRs to physicians, pharmacists and other health care professionals.

Reporting an ADR can be voluntary and generated. Voluntary reports are sent when a reporter becomes aware of an incident and decides to make one. Generated reports are made when health care professionals or patients are interviewed to seek information on any possible incidents [72, 75]. ADR reporting can also be generated by sending reminders to health care professionals to report incidents [100].

Apart from ADR reporting system, an incident reporting system for ME is also available in some countries [101-103] and this was introduced recently in Malaysia [50]. In 2009, the Pharmaceutical Services Division under MOH embarked on a reporting system called the Medication Error Reporting System (MERS) [50]. The system is managed by a Medication Safety Centre which established a database on MEs that includes all error reports related to medication use process. The reporting is

done on voluntary basis by health care professionals. All reports are reviewed by National Medication Error Committee, which comprises of members from the public and private sectors [50].

Incidents of DO are also documented in some countries [104-106]. In Malaysia, the National Poison Centre is a 24-hour call centre for drug and poisoning information [107]. However poison centres usually document the drug queries and do not collect reports related to overdose. Thus, the data from the centre may not be able to provide the rate of overdoses.

Spontaneous incident reporting is cheap and less-time consuming compared to other methods. This method has been effective in generating signals where rare and serious ADRs have been identified [95]. However, the rate of reporting incidents was found to be low in some countries [108-110]. It is dependent on the reporter choosing to report an event and therefore, the rate derived from this method is not reliable. Furthermore, this method will not be able to identify all types of ADE such as TF and ADWS as there is no system in place to report such incident types.

1.5.3 Computerised surveillance or screening

This method can only be used where there is a comprehensive patient information system in a hospital. This would mean all the records such as clinical, pharmacy, laboratory and administrative, are linked to a common database. Such database can be used to screen for events based on certain rules such as increased or decreased serum creatinine and blood glucose levels [74, 96]. These rules are similar to the 'predetermined list' of trigger tools and are flagged in the database. Alerts are created if any abnormalities occurred. Personnel can see the alerts and perform a targeted chart review to verify the alerts. Classen et al. [111] developed a computerised ADE monitor to detect ADEs. Each day, a list of all potential ADEs is generated and a pharmacist reviews the medical records of all the patients with potential ADEs and interviews them when necessary, to determine the accuracy and causality.

Computerised surveillance is less time-consuming and personnel-intensive compared to chart review studies. Jha et al. [74] compared three methods of identifying an ADE and found that a computer

search strategy required only 11 person-hours per week compared to 55 person-hours per week for a chart review. In addition, Schneider [95] noted that computer screening is capable of detecting errors at the prescribing, dispensing, administration, and monitoring levels. Through this method, events can be detected at the time they occur [95].

However, the disadvantage of this method is that it may not detect events which are not flagged with alerts such as subjective symptoms (headache and dizziness). Moreover, it may trigger false positive alerts, for example, when a drug is stopped [95]. Thus, the sensitivity and specificity of computer alerts depend on the rules or indicators used.

1.5.4 Observational method

Observational methods involve trained researchers observing a practice in a normal setting. For example, an administration of a drug to a patient [76] and documenting the observation. This direct observation method is capable of measuring actual errors [95] by identifying errors unknowingly committed by a health care professional. In a study by Barker et al. [76], the preparation and administration of drugs by nurses in the ward was witnessed by trained observers. One advantage of this method is that researchers can intervene during the drug administration and patient harm could be avoided.

This method can be used to track the performance of an institution [95]. Although it is good for quantitative measurement of types of errors, another method is needed to find the underlying causes of the errors. Taxis and Barber [112] investigated the errors in the administration of intravenous drugs by nurses in a hospital setting through trained observers. They combined the observation method with nurse interviews to identify the causes of the errors.

1.5.5 Intervention documentation method

Another method to identify ADEs is to document interventions made by health care professionals. These interventions are taken in response to an event. This method has been used in a hospital to study the percentage of prescriber contacts documented as pharmacist interventions [113], in an emergency department to determine the pharmacist interventions and potential cost avoidance due to the interventions [114], and in a community setting to document the interventions made by pharmacy personnel with patients and prescribers [115]. Where interventions are routinely documented, it can serve as a method to identify errors and potential errors and determine strategies to improve the current system in an institution. However, the rate of errors generated from this method depends on the quality of the documentation and whether all interventions were recorded [96]. Schneider [95] noted that this method mostly identifies errors made during the prescribing process thus a combination of methods is needed to identify other types of ADEs.

1.5.6 Hospital database review

Hospital databases such as administrative or claims database can be reviewed for ADEs [96]. Using selected codes from the International Classification of Diseases (ICD), the database is searched for events related to drugs. Waller et al. [116] reviewed a hospital database in England by selecting all the 10th International Classification of Disease (ICD-10) codes which included the word 'drug-induced,' diagnoses indicated as 'due to' a drug, or codes which clearly stated that an ADR has occurred.

Hospital database review is less expensive to perform compared to chart review and computerised surveillance [96]. However, the quality of data obtained depends on the quality of data recording and coding [81]. The events identified through this method were found to underestimate the ADEs rate [81, 116] due to incomplete information.

1.5.7 Combining methods to identify adverse drug events

It is challenging to choose the appropriate method to detect ADEs since each method has its own strengths and weaknesses. To overcome the limitations, some studies combined identification strategies to maximise the detection of ADEs. A study by Jha et al.,[75] compared computer monitoring with chart review and practitioner reporting to identify ADEs in a tertiary care hospital. In all the ADEs identified the most effective strategies were chart review (identified 65% of all ADEs) and computer-based monitor (identified 45% of all ADEs). There were overlaps of ADEs identified by both strategies, whist practitioner reporting identified only 4% of it. Similarly, Gurwitz et al., [44] combined chart review with practitioner reporting to identify ADEs in nursing homes. They identified 546 ADEs, of which 17% were done through reporting and the remainder, using chart review. In both studies, chart review was found to have identified more ADEs compared to other methods. In addition, Brvar et al. [85] retrospectively reviewed patient charts, hospital information system and national spontaneous reporting system for ADRs. The detected frequency of ADR-related admissions using chart review was found to be 5.8%, while that using hospital database search was 0.2%. No ADR reports for the studied patients had been sent to the national reporting system. This study highlighted that physicians document an observed ADR in the medical record but rarely code or report it.

1.5.8 Identifying adverse drug event-related admissions

All the methods discussed above can be used to identify ADE-related admissions. However, different methods may identify different types of ADEs. The effect of different study designs on the prevalence estimates of ADE-related admissions have been explored in a few studies [117-120]. Winsterstein et al. [117] explored preventable drug related admissions in a systematic review of 15 papers, whilst Beijer and de Blaey [118] explored the impact of study design on ADR prevalence estimates in a meta-analysis of 68 studies. Similarly, Kongkaew et al. [120] examined the difference in ADR prevalence rates between population groups and methods in 25 studies. Leendertse et al. [119] explored the impact of study characteristics on prevalence estimates of drug-related admissions in 95 studies which included the ones explored by Winsterstein et al. [117]. According to these studies, the prevalence estimates of ADE are influenced by:

a) Study method

Winsterstein et al. [117] and Beijer and de Blaey [118] reported that chart review studies resulted in higher prevalence rates compared to other methods. Chart review is considered to be the 'gold standard' method in identifying ADEs. Studies which did not use chart review generally reported a lower prevalence of ADEs. Referring to the example given above (Section 1.5.7) Brvar et al. [85] reported a prevalence of 5.8% using chart review compared to only 0.2% using computer monitoring. Retrospective chart review studies, on the other hand, have the tendency to report a lower prevalence rate [121, 122] compared to prospective chart review studies [117]. This is attributed to poor documentation in patient notes. Prospective studies which have used chart review as their mode of data collection have been able to interview patients, relatives, and medical teams for more information, where information in the charts was incomplete [9, 11, 123, 124]. Furthermore, studies which used this combination of methods (chart review and interview) reported a higher prevalence estimates compared to chart reviews alone [120]. In addition, Kongkaew et al. [120] reported that studies which have included pharmacists as chart assessors have been shown to detect higher rates of ADEs compared to using other health care professionals.

b) Study population

Winsterstein et al. [117] found that inclusion or exclusion of planned admissions or patient transfers from other wards or hospitals made little difference to the prevalence estimates. Furthermore, they found that studies of patients aged over 70 years reported an almost doubled prevalence estimates than those reported studies including only younger patients. In addition, Beijer and de Blaey [118] reported that the prevalence estimates for studies of elderly patients (aged 65 years and above) were four times higher than those studies of only young patients.

c) Study sample size

Beijer and de Blaey [118] reported that studies with a larger number of patients stated lower prevalence estimates when compared to those with a lower number of patients (varying from 100 to 1,988 hospitalisations). Likewise, Lessing et al. [125] reported that the proportion of adverse event decreased with higher number of sample size, where studies with more than 20,000 patients found a prevalence of less than 1%. However, they did not deny that the quality of data collection methods and publication bias (where smaller studies with higher prevalence rate have a greater chance of being published than larger studies with lower prevalence rate) may have affected the prevalence rates reported.

d) Study outcome

The use of wider definitions of drug-related admissions (including TF and patient non-adherence) result in a higher prevalence rate [117]. Similarly, Leendertse et al., [119] found that studies investigating ADEs reported higher prevalence estimates compared to studies which explored only ADRs, unsurprisingly as ADR is one type of ADE.

1.6 Epidemiology of adverse drug event-related admissions

The prevalence and impact of ADEs have been studied with various outcomes reported due to variation in the definition, classification, causality assessment and detection methods. Of particular interest is the prevalence of ADEs that result in hospital admissions.

Prevalence is the number of cases in the population at a point in time and is calculated by dividing the number of people with the disease or condition at a point in time by the number of individuals studied. Prevalence is often expressed as a percentage, calculated by multiplying the ratio by 100 [126]. Prevalence differs from incidence in that it includes all cases rather than only new cases.

Some studies have explored ADE-related admissions as a whole whilst others have explored its sub-types. The prevalence of the sub-types will be discussed first, followed by the prevalence of ADE.

1.6.1 Adverse drug reaction-related admissions

Studies on ADR are the most extensive and span across a range of different areas, including in-patients [12, 127, 128], primary care [44], paediatrics [129-131], geriatrics [10, 132, 133], and hospital admissions [71, 124, 134]. Table 1-2 lists studies which have investigated the prevalence of ADR-related admissions. The prevalence found in these studies range from 0.7% to 12.8%. The wide range of prevalence, to a large extent, was affected by the differences in methods and populations studied.

Chart review was the most common method of data collection and was often done in combination with patient or health care professional interview, or incident reporting. Studies that used computerised database or surveillance method [74, 80, 81] reported a much lower prevalence, between 1.7% and 3.3%. As reported by Brvar et al. [85] chart review was found to be the most effective and reliable method in identifying ADRs. The prevalence of ADRs is reported to be under estimated if spontaneous reporting or database review methods were used [119].

Most of the studies were conducted prospectively. Only four studies were conducted retrospectively [80, 81, 85, 121] and the prevalence reported was between 1.7% and 3.3%. The information collected through retrospective review is dependent on the quality of the documentation, thus, this mode of data collection probably under-estimates the actual prevalence rate.

Studies conducted in the medical wards [9, 83, 123, 124] reported a higher prevalence compared with studies which included all types of wards within the hospital [80, 81, 121, 135, 136]. Van der Hooft et al. [121] and Hopf et al. [135] reported that in their studies the percentage of ADR-related admissions was highest in the medical wards. The following could be the possible reasons for this: i) medical wards are less likely to have planned admissions compared to other wards such as surgery, ii) patients admitted to medical wards could be hospitalised for diverse medical conditions compared with other wards and iii) patients presenting themselves to hospital could be initially admitted to medical wards and subsequently, after further investigations, are transferred to other specialised wards.

Onder et al. [136] concluded that age *per se* cannot be regarded as a risk factor for ADRs and reported that the increased risks can be attributed to polypharmacy or the number of drugs taken. Elderly patients are more likely to suffer from a number of medical conditions and therefore, require a higher number of drugs – thus, increasing the risk of drug-related events. Onder et al. [136] also suggested that age is of borderline significance only for those hospital admissions related to severe ADRs. Similarly, Zopf et al.,[137] based on a multivariate analysis, found that an increased number of drugs was one of the independent predictors for the occurrence of an ADR (other predictors were increased temperature, decreased erythrocytes, and low thrombocytes). Other studies have also found a similar relationship [138, 139].

Table 1-2: Studies on adverse drug reaction-related admissions

Author (country)	Patient group	Admission type	Number of patients studied	Method	Prevalence of ADR related admission	Most common drug groups
Carrasco-Garrido et al., 2010 (Spain) [81]	All patients	Hospital	20,712,399	Retrospective hospital admission database review	1.7%	Antineoplastic and immunosuppressive agents
Brvar et al., 2009 (Slovenia) [85]	Adult patients aged 19-94 years	Specialised medical departments	520	Retrospective chart review	5.8%	NSAIDs
Schwake et al., 2009 (Germany) [11]	Patients aged >14 years	Medical ICU	1,554	Prospective chart review, and interview	6.4%	antiplatelets
Van der Hooft et al., 2008 (The Netherlands) [121]	All patients	Hospital	2,238	Retrospective computerised medical records review	3.3%	anti-thrombotics
Hopf et al., 2008 (Scotland) [135]	All patients except weekend admissions	Hospital	1,101	Prospective chart review	2.7%	NSAIDs
Alexopoulou et al., 2008 (Greece) [124]	All patients aged 15-100 years	Medical wards	548	Prospective chart review, and interview	12.8%	NSAIDs

table continued.....

Table 1-2 continued: Studies on adverse drug reaction-related admissions

Author (country)	Patient group	Admission type	Number of patients studied	Method	Prevalence of ADR related admission	Most common drug groups
Saha et al., 2008 (India) [140]	All patients aged 18-80 years	Internal medicine department	1,200	Prospective interview and chart review	3.8%	NSAIDs
Rivkin, 2007 (United States) [84]	All patients except weekend admissions	Medical ICU	281	Prospective chart review	7.5%	antiplatelets
Van der Hooft et al., 2006 (The Netherlands) [80]	All acute, non-planned admissions	Hospital	668,714	Retrospective computer database of hospital discharge records	1.8%	anticoagulants
Pirmohamed et al., 2004 (Liverpool, UK) [71]	Patients aged >16 years	Hospital	18,820	Prospective chart review	6.5%	antiplatelets
Bhalla et al., 2003 (Cambrigde, UK) [9]	All patients aged ≥17 years	Medical wards	840	Prospective chart review and interview	6.2%	not reported
Ramesh et al., 2003 (India) [72]	All patients	Hospital	3,717	Prospective chart review, interview, and stimulated reporting	0.7%	cardiovascular drugs

table continued.....

Table 1-2 continued: Studies on adverse drug reaction-related admissions

Author (country)	Patient group	Admission type	Number of patients studied	Method	Prevalence of ADR related admission	Most common drug groups
Onder et al., 2002 (Italy) [136]	All patients	Hospital	28,411	Prospective chart review	3.4%	diuretics
Mjorndal et al, 2002 (Sweden) [123]	All acute admissions	Medicine and cardiology departments	681	Prospective chart review and interview	12.0%	antiplatelets
Jha et al., 2001 (United States) [74]	All adults	Multi-departments	3,238	Prospective computerised and targeted chart review	2.3%	antibiotics
Pouyanne et al., 2000 (France) [141]	All patients	Multi institutional medical departments	3,137	Prospective chart review	3.2%	cardiac stimulants and anti-arrhythmic
Green et al., 2000 (United Kingdom) [134]	Randomly selected patients	Acute medical assessment unit	200	Prospective chart review	7.5%	NSAIDs
Raschetti et al., 1999 (Italy) [8]	All patients	Emergency department	1,833	Prospective chart review	0.8%	cardiovascular drugs

table continued.....

Table 1-2 continued: Studies on adverse drug reaction-related admissions

Author (country)	Patient group	Admission type	Number of patients studied	Method	Prevalence of ADR related admission	Most common drug groups
Schoenemann et al., 1998 (Germany) [73]	All patients	Medical & ICU	4,032	Prospective reporting	2.4%	NSAIDs
Ahmed et al., 1997 (Saudi Arabia) [142]	All patients	Medical	960	Prospective chart review	5.8%	NSAIDs
Hallas et al., 1992 (Denmark) [83]	All patients	Medical	1,999	Prospective interview, and chart review	8.4%	NSAIDs
Hallas et al., 1990 (Denmark) [62]	All patients	Medical	333	Prospective patient interview, and chart review	8.1%	insulin
Bergman et la., 1981 (Sweden) [143]	All patients aged16-97 years	Internal medicine	285	Prospective interview	5.6%	cardiovascular drugs
Hurwitz et al., 1969 (Northern Ireland) [1]	All patients	Hospital	1,268	Prospective chart review and, interview	2.9%	antimalarial

Several studies have found that more women than men experienced ADRs [71-73, 80, 83, 136, 141, 143]. The following reasons were given for this: i) sex affects the drugs to which a patient might react due to their differing health conditions [144], ii) women have increased bioavailability of drugs and greater sensitivity of target organs [145] and iii) women are more aware of the status of their medical conditions [34], thus, seek medical attention more frequently compared to men. The slower and lower renal clearance of drugs in women was also suggested as one of the possible reasons for the higher rate of reaction [144].

Drugs associated with adverse drug reaction-related admissions

The most common drug groups associated with ADR-related admissions include non-steroidal, anti-inflammatory drugs (NSAIDs), and anti-platelets. These drugs were responsible for 70% to 80% of ADR-related admissions. The system most commonly affected by an ADR was gastrointestinal (GI), resulting in GI bleeding. Aspirin was reported the most common single drug causing GI bleeding [11, 71, 84, 123].

1.6.1.1 Studies in Malaysia

There was only one study of ADR-related admissions in Malaysia (not listed in Table 1-3 because of lack of information as published only in abstract form). This study reported that of 110 patients admitted to medical wards due to DRPs, 34% was as a result of ADRs [22]. NSAIDs induced gastritis was the most common cause of these admissions (the percentage was not reported).

1.6.2 Medication error-related admissions

ME-related admissions are also known as preventable drug-related admissions (PDRA) [54] or preventable ADE-related admissions [53]. Up to 92% of all drug-related admissions have been found to be preventable [146]. Table 1-3 summarises studies investigating ME-related admissions. The prevalence of ME-related admissions from these studies was between 1.2% and 10.6%.

All studies were conducted prospectively and chart review was the main mode of data collection (Table 1-3). At least three studies have investigated admissions related to all types of MEs [139, 147, 148], giving prevalence from 1.2% to 4.3%. Studies by Green et al. [134] and Pirmohamed et al. [71] investigated ADR-related admissions and their preventability, whilst, other studies investigated admissions related to ADR, TF, drug-drug interactions, and drug-alcohol interactions. Thus, comparison and among studies is difficult and may not reflect the prevalence of all types of MEs.

Drugs associated with medication error-related admissions

Four studies [83, 134, 147, 148] reported NSAIDs as the drug most frequently associated with ME-related admissions, the most common event being GI bleeding. These errors were reported to have been caused by ignorance of patients and physicians about the said drug. Hardmeier et al [148] divulged that 10% of the patients admitted due to MEs took NSAIDs without consulting a health care professional resulting in GI complications. In contrast, Howard et al. [147] reported that the failure to prescribe a GI prophylaxis in high-risk patients resulted in 12% of ME-related admissions.

Table 1-3: Studies on prevalence of medication error-related admissions

Author (country)	Patient group	Admission type	Number of patients studied	Method	Type of MEs	Prevalence of ME-related admissions	Most common drug group
Leendertse et al., 2008 (Netherlands) [139]	Adults (≥ 18 years)	Hospital	12,793	Prospective chart review, trigger tool, and physician report	Prescribing and administrative errors	2.6%	Anticoagulants
Zargarzadeh et al., 2007 (Iran) [146]	Sampled patients (≤ 21 years)	Hospital	1,000	Prospective chart review	Preventable ADRs and TFs	10.6%	Cardiovascular drugs
Hardmeier et al., 2004 (Switzerland) [148]	All patients	Internal medicine department	6,383	Prospective hospital database "event" review, and physician monitoring	All types of MEs	1.2%	NSAIDs
Howard et al., 2003 (England) [147]	All patients	Medical admission unit	4,093	Prospective chart review, and patient and physician interview	All types of MEs	4.3%	NSAIDs
Pirmohamed et al., 2003 (England) [71]	Adults (>16)	Medical and surgical wards	18,820	Prospective chart review, and interview	Preventable ADRs	4.7%	Not reported
Green et al., 2000 (England) [134]	Random selection of 200 patients	Acute medical admissions	200	Prospective chart review, and interview	Preventable ADRs	6.0%	NSAIDs

table continued.....

Table 1-3 continued: Studies on prevalence of medication error-related admissions

Author (country)	Patient group	Admission type	Number of patients studied	Method	Type of MEs	Prevalence of ME-related admissions	Most common drug group
Raschetti et al., 1999 (Italy) [8]	Adults	Hospital	1,883	Prospective chart review	Preventable ADRs, TFs, drug-drug interactions and alcohol-drug interactions	1.4%	Not reported
Nelson and Talbert, 1996 (US) [63]	All patients	Coronary and medical intensive care unit and internal medicine unit	452	Prospective chart review, and medical team interview	Preventable ADRs, TFs, and DOs	9.6%	Not reported
Hallas et al., 1992 (Denmark) [83]	Adults	Medical wards	1,999	Prospective chart review, and interview	Preventable ADRs and TFs	3.4%	Not reported

1.6.2.1 Studies in Malaysia

The number of studies which investigated ME-related admissions in Malaysia is small. Three studies which have explored different types of ME in hospitals [149-151] reported prevalence of ME between 11% and 25%. However, these studies did not investigate admissions related to ME. Another study which investigated admissions related to drugs reported that 92% of it was preventable [22]. However, no further details on the types and causes of these preventable admissions were given.

1.6.3 Therapeutic failure-related admissions

Comparison between studies that have investigated TF is complicated because of the use of different definitions. As TF overlaps with ME, some of the categories in TF could also be classified as ME.

The studies that have investigated TF are summarised in Table 1-4. All studies were conducted prospectively. Chart review and patient interview were main modes of data collection. Based on these studies, it is estimated that the prevalence of TF-related admission is between 1.1% and 9.3%. TF has many causes including patient non-adherence to drugs, dose reduction or discontinuation, interactions, too low a dose prescribed or inadequate therapeutic monitoring [62], [146]. A study in Iran reported that up to 80% of the drug-related admissions were due to therapeutic failure and this was attributed to low literacy among patients. Zargarzadeh et al. [146] explained that a lack of ability to read drug instructions and failure to seek information about it may have resulted in the high level of therapeutic failure. Other causes reported were drug-drug interactions, inadequate monitoring, dose reduction or discontinuation, too low a dose being prescribed and overdose [8, 9, 83, 152]. In this thesis, drug-drug interactions, inadequate monitoring, dose reduction or discontinuation and too low dose prescribed are classified as MEs.

A few factors increase the risk of admission related to non-adherence including poor recall of drugs taken by patients, seeking medical advice from numerous physicians, female gender, polypharmacy, expensive drugs, and seeking alternative medication or treatment [153]. In addition, Davidsen et al. [154] reported ADRs and discontinuation of the use of drugs (either because patients ran out of it, or felt there was no further need for it) as the reasons for non-adherence [154].

Drugs associated with therapeutic failure-related admissions

Cardiovascular drugs were the most common drug group associated with therapeutic failure probably because they are used widely in clinical practice. Cardiovascular complications such as arrhythmias and congestive heart failure were the most common conditions resulting in admissions [147, 152].

Table 1-4: Studies on prevalence of therapeutic failure-related admissions

Author (country)	Patient group	Admission type	Number of patients studied	Method	Prevalence of TF-related admissions	% of highest cause for TF	Most common drug group
Zargarzadeh et al., 2007 (Iran) [146]	Selected patients	Hospital	1,000	Prospective quota sampling	9.3%	80 %: Non-adherence	Cardiovascular drugs
Franceschi et al., 2004 (Italy) [152]	All patients	Emergency department	607	Prospective patient interview	6.8%	78%: Non-adherence	Cardiovascular drugs
Bhalla et al., 2003 (England) [9]	All patients aged ≥17 years	Medical wards	840	Prospective chart review and interview	2.7%	48%: Non-adherence	Not reported
Howard et al., 2003 (United Kingdom) [147]	All patients	Medical admissions unit	4,093	Prospective chart review, and patient/GP interview	1.3%	(non-adherence cases only)	Cardiovascular drugs
Malhotra et al., 2001 (India) [153]	Elderly patients aged ≥65	Medical emergency department	578	Prospective interview, and chart review	7.6%	(non-adherence cases only)	Cardiovascular drugs
Raschetti et al., 1999 (Italy) [8]	All patients	Emergency department	1,883	Prospective chart review	1.4%	Not reported	Anti-diabetics

Table 1-4 continued: Studies on prevalence of therapeutic failure-related admissions

Author (country)	Patient group	Admission type	Number of patients studied	Method	Prevalence of TF-related admissions	% of highest cause for TF	Most common drug group
Nelson and Talbert, 1996 (US) [63]	All patients	Coronary, medical ICU and internal medicine unit	452	Prospective chart review, and medical team interview	8.9%	Not reported	Not reported
Hallas et al., 1992 (Denmark) [83]	All patients	Medical	1,999	Prospective interview, and chart review	2.8%	64 %: non-adherence	Cardiovascular drugs
Hallas et al., 1990 (Denmark) [62]	All patients	Medical	333	Prospective interview, and chart review	2.7%	56 %: non-adherence	Not reported
Davidsen et al., 1988 (Denmark) [154]	All patients	Cardiology	426	Prospective chart review	3.8%	Not reported	Cardiovascular drugs
Bergman and Wiholm, 1981 (Sweden) [143]	All patients	Internal medicine	285	Prospective interview, and observation	6.7%	58%: non-adherence	Cardiovascular drugs

1.6.3.1 Studies in Malaysia

There are no studies in Malaysia specifically investigating TF resulting in hospital admissions. However, there are studies investigating adherence. These studies focused on specific medical conditions, such as hypertension [155-158], diabetes mellitus [23, 158], tuberculosis [159, 160], renal disease [161], and asthma [158]. The percentage of patients with poor adherence in these studies was between 26% and 56%. The most common reason quoted for poor adherence was 'forgetting to take drugs'[158, 161]. Other reasons were side effects [161], a decision not to take the drugs [161], inability to read instructions on drug labels [158] , and complex, costly or ineffective drug regimens [155]. In addition, in the abstract, Farooqui et al. [22] reported that patient non-adherence accounted for 39% of the identified admissions related to drugs. This study found that patient intent to seek alternative medicine was the main cause for poor adherence.

1.6.4 Drug overdose-related admissions

Drug overdoses whether intentional or not cause significant morbidity and mortality. Poisoning accounted for 3.6% of all deaths registered in England and Wales in 2009 [162]. Drug poisoning mortality rates rose 62% from 1999 to 2004 in US [163].

Studies that have investigated DOs or poisoning-related admissions are summarised in Table 1-5. The prevalence of overdose-related admissions in these studies is estimated between 0.1% and 17.3%. The low prevalence estimates of 0.1% [122], 0.2% [164], and 0.4% [165] were probably due to the study design – retrospective review of patient records. All other studies were prospective. Schwake et al. [11] reported the highest prevalence (17.3%). This was because of the study site (intensive care unit) which serves as a regional toxicology unit, thus, all poisoning cases are treated in this unit before getting transferred to an appropriate ward. Nevertheless, this study raises concerns about the high level of self-poisoning.

Intentional overdoses were reported to be the most common mode of poisoning in some studies [166, 167], although accidental overdoses were found the be more common in children [164]. Most of the studies reported that women and younger patients were found to be at a higher risk of being admitted due to DO. Family conflict was found to be the main risk factor for intentional overdoses in women [142], whilst in young patients, personal and family relationship problems were regarded as causes for intentional overdoses [167]. Ahmed et al. [142] revealed that 70% of DO patients used drugs that had been originally prescribed for another member of the family.

Drugs associated with drug overdose-related admissions

The most common drug groups associated with overdose were analgesics and psychotropics, and these drug types have not changed over the decade. Paracetamol was the most common single causative drug. This is because paracetamol is easily available as an OTC drug. Due to high incidence of paracetamol overdose, the quantity available for individual sale is restricted in some countries [168]. For example, in the United Kingdom (UK), general outlets are limited to selling only 16 tablets of 500mg whereas in pharmacies, only 32 tablets of 500mg can be sold. However in the latter, after further assessment and approval from a pharmacist, the said tablets can still be sold up to 100. There is no restriction on the amount of paracetamol that can be sold in Malaysia. However, they are sold in blister strips.

Table 1-5: Studies on prevalence of drug overdose-related admissions

Author (country)	Patient group	Admission type	Number of patients studied	Method	Prevalence of DO-related admissions	Most common drug group
Liisanantii et al., 2011 (Finland) [169]	All patients	ICU	61,527	Retrospective computer database	4.5%	Not reported
Buykx et al., 2010 (Australia) [170]	All patient	Emergency department	521	Retrospective computer database	1.4%	Not reported
Oguzturk et al., 2010 (Turkey) [166]	All patients aged >15 years	Emergency department	25,070*	Retrospective computer database and, chart review	0.7%	Multiple drugs
Schwake et al., 2009 (Germany) [11]	All patients aged >14 years	Medical ICU	1,883	Prospective chart review, and interview	17.3%	Psychotropic drugs
Rajasuriar et al., 2007 (Malaysia) [165]	All patients	Hospital	5,049,767*	Retrospective computer database review (3 years of computer records)	0.4% (including non-medicinal poisoning)	Analgesics
Al-Jahdali et al., 2004 (Saudi Arabia) [122]	All patients	Hospital	84,946	Retrospective chart review (3 years of records)	0.1%	Analgesics
Bhalla et al., 2003 (England) [9]	All patients aged ≥17 years	Medical wards	840	Prospective chart review, and interview	2.4%	Analgesics

*estimated by researcher

table continued.....

Table 1-5: Studies on prevalence of drug overdose-related admissions

Author (country)	Patient group	Admission type	Number of patients studied	Method	Prevalence of DO-related admissions	Most common drug group
Ab Rahman AF, 2002 (Malaysia) [164]	All patients	Hospital	234,500*	Retrospective chart review (9 years of computer records)	0.2% (including non-medicinal poisoning)	Psychotropic drugs
Tountas et al., 2001 (Greece) [171]	All patients	Internal medicine department	1,705	Not available	8.5%	Psychotropic drugs
Ahmed et al., 1997 (Saudi Arabia) [111]	All patients	Medical wards	960	Prospective chart review	5.2%	Analgesics
Nelson and Talbert, 1996 (US) [63]	All patients	Coronary, medical ICU and internal medicine unit	452	Prospective chart review, and medical team interview	2.0%	Not reported
Bergman and Wiholm, 1981 (Sweden) [143]	All patients	Internal medicine	285	Prospective interview, and observation	3.5%	Psychotropic drugs
Hurwitz et al., 1969 (Northern Ireland) [1]	All patients	Hospital	1,268	Prospective chart review, and interview	2.1%	Psychotropic drugs

* estimated by researcher

1.6.4.1 Studies in Malaysia

In Malaysia, three studies have investigated all types of poisoning resulting in admission to hospitals [164, 165, 172]. Three further studies have investigated other aspects of poisoning – one explored self-poisoning cases [173], the second, the factors associated with adult poisoning [167], and the third the trend of inquiries received by the national poison centre [174]. Poisoning accounted for between 0.2% and 0.4% of admissions [164, 165] and the predominant mode of poisoning was accidental. A study by Fathelrahman et al. [172] conducted in Northern Malaysia estimated an annual incidence rate of poisoning admissions to be 25 per 100,000 persons. They have reported that intentional poisoning was the most common mode of poisoning. The annual rate of self-poisoning was reported to be 15 per 100,000 persons in another study, with an average of 8 patients admitted monthly due to self-poisoning [173].

In the study of self-poisoning, 62% were due to DO [173], but even in studies where accidental poisoning was pre-dominant, more than 45% of cases involved DO [164, 165]. The types of drug classes reported to be involved with DO were non-opioid analgesics, antipyretics, anti-rheumatics, antipsychotics and benzodiazepines [164, 165, 173].

Most admissions occurring due to poisoning involved women. However, the poisoning was more likely to be fatal in men [165, 167, 173]. This is due to the differences in types of substances consumed by each group. Chemical poisoning such as detergent and weed killer was most commonly implicated in men, whereas women were most likely to use medicines. On the other hand, Indian and Chinese ethnicity were found to be significantly associated with poisoning [167]. Rajasuriar et al. [165] added that the fatality rate was highest among Indian ethnicity because they were more likely to use weed killers.

1.6.5 Adverse drug withdrawal syndrome-related admissions

ADWS-related admissions could be due to patient abruptly discontinuing medications or health care professionals discontinuing medications which were found inappropriately prescribed, without tapering down the dose [67, 175].

Studies related to ADWS are not extensive. A systematic review concluded that the withdrawal of some of the drugs such as opioids, beta-adrenoceptor blockers, levodopa and corticosteroid can cause patient morbidity and mortality but studies involving these drugs are lacking [176]. Other than these drugs selective serotonin reuptake inhibitors [67] and other antihypertensives [177] could also cause withdrawal syndromes.

The studies that investigated ADE-related admissions did not include ADWS as one of their study outcomes. This could indicate that the frequency of ADWS could be too small to be identified, or it is difficult to recognise an ADWS. In their study, Mita el at. [175] found that ADWS was not frequently detected and only 0.8% admissions experienced it. Almost half of drug discontinuation cases in the study by Gerety et al. [178] resulted in ADWS but the events were not as serious as other ADEs. Among the 62 patients in a nursing home who experienced ADWS, one was hospitalised and none resulted in death [178].

The issue with drug withdrawal syndrome is that it mimics the medical condition for which the drug was prescribed [67, 178-180]. For example, the withdrawal of antihypertensive agents may produce sympathetic over-activity such as nervousness, tachycardia, headache, agitation, nausea, and rapid increase in blood pressure [177]. However, this syndrome is more common in withdrawals of long-term therapy than short-term [177] . Furthermore, it is difficult to identify which drug has caused the withdrawal syndrome if a patient was prescribed with multiple drugs, or was on alcohol influence or other illicit drugs , since the pharmacological effects of some agents overlap [178, 180]. For example, withdrawal symptoms of alcohol and barbiturates overlap such as seizure and delirium [180].

1.6.5.1 Studies in Malaysia

No study was found that investigated the rate of ADWS or its related admissions in Malaysia.

1.6.6 Adverse drug event-related admissions

Of the studies listed in Table 1-2 to Table 1-5, only 11 studies have investigated more than one sub-type of ADEs. These studies are listed in Table 1-6. The prevalence of ADE-related admissions has been found to be between 0.7% and 30.4% (these include studies which have investigated only one ADE sub-type as listed in Table 1-2 to Table 1-5). For studies which have investigated more than one type of ADEs, the prevalence of ADE-related admissions was 2.5% to 30.4% (Table 1-6). The lowest rate of 2.5% is likely due to the study site (emergency department) where the researcher depended on physicians' diagnoses to identify ADEs[8]. This study used a prospective chart review method. Whilst the highest rate of 30.4% is likely due to the study population (elderly patients aged more than 75 years) and this study combined prospective chart review and patient interview in identifying patients[10].

Comparison between studies in Table 1-6 is difficult because of the difference in the types of ADEs investigated and definitions used. For this reason, each type of ADEs, the prevalence, and drugs associated were discussed separately in the previous sections.

Table 1-6: Studies on prevalence of adverse drug event-related admissions

Author (country)	Admission type (patient group)	Number of patients studied	Method	Type of ADEs investigated	Prevalence of ADE-related admissions
Schwake et al., 2009 (Germany) [11]	Medical ICU (all patients aged >14 years)	1,554	Prospective chart review, and interview	• ADRs • Deliberate self-drug poisoning	23.7%
Saha et al., 2008 (India) [140]	Internal medicine department (all patients aged ≥18 years)	1,200	Prospective interview, and chart review	• ADRs • Drug-drug interaction • Non-compliance • Accidental or intentional overdose	4.2%
Bhalla et al., 2003 (Cambrigde, UK) [9]	Medical wards (All patients aged ≥17 years)	1,000	Prospective chart review, and interview	• ADRs • DTFs • Overdose or abuse	10.1%
Malhotra et al., 2001 (India) [153]	Medical emergency department (Elderly; age ≥ 65)	840	Prospective interview, and chart review	• ADRs • Non-compliance	14.4%
Chan et al., 2001 (Australia) [10]	Acute medical units (Elderly; age≥ 75)	578	Prospective chart review, and interview	• ADRs • Non-compliance	30.4%

table continued.....

Table 1-6 continued: Studies on prevalence of adverse drug event-related admissions

Author (country)	Admission type (patient group)	Number of patients studied	Method	Type of ADEs investigated	Prevalence of ADE-related admissions	Most common type of ADE (%)
Raschetti et al., 1999 (Italy) [8]	Hospital (all patients)	240	Prospective chart review	• ADRs • DTFs • Drug-drug interactions • Drug and alcohol interactions	2.5%	TF (56%)
Ahmed et al., 1997 (Saudi Arabia) [142]	Medical (all patients)	1,833	Prospective chart review	• ADRs • Drug overdose	11.0%	ADR (53%)
Hallas et al., 1992 (Denmark) [83]	Medical (all patients)	960	Prospective interview, and chart review	• ADRs • DTFs • Intentional overdose	11.4%	ADR (74%)
Hallas et al., 1990 (Denmark) [62]	Medical (all patients)	452	Prospective patient interview, and chart review	• ADRs • DTFs	10.8%	ADR (75%)
Bergman and Wiholm 1981 (Sweden) [143]	Internal medicine department (all patients)	1,999	Prospective interview	• ADRs • TF • Poisoning	15.7%	TF (45%)
Hurwitz et al., 1969 (Northern Ireland) [1]	Hospital	333	Prospective chart review, and interview	• ADRs • Overdose	5.0%	ADR (58%)

1.7 Role of health care professionals in adverse drug events

Health care is an integrated process by which physicians, pharmacists, nurses and other health care professionals provide care to patients according to their expertise, and thus patient safety is not an individual responsibility. A health care professional is responsible for recognising and resolving ADEs that occur, monitoring those and developing educational packages to reduce future occurrences.

1.7.1 Recognising adverse drug events

The initial step in identifying ADEs is to be alert to the possibility that a patient may be experiencing one. The next step is to decide the type of interventions. However, it is not an easy task to identify whether or not a patient is experiencing an ADE. Health care professionals sometimes fail to recognise that an ADE has occurred by misinterpreting patients' complaints or symptoms as minor and irrelevant, or related to the progression of their medical conditions. This may explain why many ADEs are never recognised [181].

It is important to listen to the patients as their concerns and complaints may indicate a drug-related problem. The key information for detecting an ADE should be available in the patient's medical and drug history [88]. Health care professionals need to be thorough and comprehensive in taking histories and should include OTC drugs and herbal remedies. If an ADE is suspected, they should investigate whether or not there is sufficient information to link the event to a drug [59, 182]. This can be determined by identifying time relationship between drug intake and the occurrence of the event, and the pattern of the event (whether it is related to a pharmacological effect, an allergy, an insufficient use of a drug, or an error) [59]. Additionally, known drug effects and further investigations such as laboratory tests may caution or rule out a diagnosis. In case of an ADR, an option to confirm that it is an ADR is re-challenging the suspected drug in the patient if the effect is not severe [59, 182, 183].

When these empirical findings fail to produce any causal relationship, algorithms can be used to assist in the assessment of an ADE-probability. Widely used algorithms include Naranjo's algorithm [99], and that of Hallas et al. [62]. Naranjo's algorithm is used for the assessment of suspected ADRs whilst the latter is used to assess suspected TF.

Evidence suggests that inappropriate prescribing (IP) is associated with an increased risk of ADE [184, 185]. This is reported to be relatively common especially in older patients [186]. IP involves the use of medicines that pose more risks than benefits especially when safer alternatives are available. It also involves misuse of medicines (inappropriate dose or duration), prescription of medicines with clinically significant drug-drug and drug-disease interactions, and importantly, the underuse of potentially beneficial medications [185]. In 1992, a UK-based study found that nearly 50% of ADRs were due to inappropriate prescribing, either due to drugs that were contraindicated or were unnecessary [184]. Because older adults are more sensitive to its certain adverse effects, various lists of medicines have been created to guide clinicians. These lists used explicit (criterion-based) or implicit (judgement-based) prescribing indicators. Examples of explicit indicators are the Beer's criteria which is widely used in the US, and the most recent criteria, STOPP (Screening Tool of Older Persons' potentially inappropriate Prescriptions)[186]. Both criteria list the medicines to be avoided in older people. An example of implicit criteria is the Medication Appropriateness Index (MAI) which measures prescribing appropriateness according to ten criteria including indication, effectiveness, dose, administration, drug-drug and drug-disease interactions, and cost [186].

1.7.2 Resolving adverse drug events

Preventing an ADE is a much better option than finding a way to resolve it. However, this may not always be possible because some events occur unexpectedly, particularly ADRs. Surveys have reported that physicians and nurses expect the pharmacists to take the responsibility to resolve drug-related problems [187, 188] and educate patients about safe and appropriate use of drugs [189, 190]. Due to their expertise and knowledge of pharmacology, proactive involvement of pharmacists not only helps in resolving ADEs but in preventing them.

The types of DRP that pharmacists report observing most commonly are related to dosing or drug choice problems [113, 114, 191-193] – inadequate dose or drug, need for dosage adjustment and inappropriate drug selection. Pharmacists most often contacted physicians to resolve these problems [113, 191, 194], however, some managed to do them alone [115, 195]. The most common reasons for pharmacists to contact physicians were to recommend changes to a patient's drug therapy such as addition of a new drug, changes in dosage or stopping to use a drug [113, 114, 191]. Additionally,

pharmacists were reported to be responsible for providing information about drugs to other health care professionals [114, 192] and answering queries from nurses [114].

Patient adherence problems were the primary problem pharmacists reported managing by themselves [195]. Two studies reported that patient counselling and education was the most common intervention used [115, 191]. It is important to highlight that both these studies [115, 191] were conducted in a community setting where pharmacists are not obliged to report to or discuss with other health care professionals. Upon identification of a problem, the interventions recommended by pharmacists in solving a DRP are usually accepted by physicians – the acceptance rate of which was reported to be up to 98% [196]. This high acceptance rates demonstrates the important role of pharmacists in solving DRPs – particularly where this prevents DRP reaching the patient.

1.7.2.1 Studies in Malaysia

Three studies carried out in Malaysia relating to interventions by pharmacists were found. One study was conducted at an outpatient pharmacy department [197], and two were conducted in intensive care units or ICU [198, 199].

Of the 6360 prescriptions received during the one-week study at the outpatient pharmacy department, only 43 required an intervention [197]. Most of these prescriptions had one similar problem, errors of omission of a quantity or dose to be supplied. The most common intervention taken was contacting the physician.

Both studies in ICUs reported that more than 90% of pharmacists' recommendations were accepted by the team [198, 199]. The most common problem identified by the pharmacists was unnecessary drug therapy [198, 199]. This study has also shown that the interventions from pharmacists have resulted in cost-savings [199].

1.7.3 Preventing or reducing adverse drug events

A significant proportion of ADEs are considered to be preventable, thus, approaches to improve patient care and reduce the occurrence of ADEs should focus on this area. The strategies in preventing ADEs can be divided into two types: strategies to improve existing patient care and strategies targeted at high-risk patients of ADE.

A study conducted in paediatric wards evaluated the effectiveness of several prevention strategies in MEs and identified that, i) computerised physician order entry (CPOE), ii) ward-based clinical pharmacists, and iii) improved communication between physicians, pharmacists and nurses have the potential to reduce MEs [200]. Similarly, the studies which assessed the preventability of ADEs in adult patients [13, 78, 128, 201] found pharmacists participation in the rounds [78], and CPOE [201] as the two most effective prevention strategies. These strategies can be targeted to identify DRPs during the process of drug use and may help highlighting problems which could be improved so that ADEs could be minimised.

One of the methods being widely used in the US is the computerised systems in the health care. Computerised systems can be introduced into different stages of the drug use process in order to reduce the probability of an error. CPOE is an electronic system where physicians enter the prescribing order for a patient's treatment. The orders are received by the staff (in the pharmacy, laboratory or ward), through a computer network and they are responsible for completing the orders. Some systems also have a clinical decision-support system (CDSS) which produces drug allergy or drug-drug interaction warnings. Bates et al. [201] evaluated the efficacy of this system and revealed that it was able to show a significant decline in preventable and non-intercepted, potential ADEs – from 10.7 event per 1000 patient-days to 4.68 events.

Pharmacy-led intervention may also help in preventing ADEs due to the pharmacists' expertise and knowledge in pharmacology. Studies have found that pharmacists are capable of reducing the rate of ADEs and their involvement was found to bring positive outcomes to health of patients [6, 78, 79, 196]. Leape et al. [78] conducted a controlled clinical trial that included a pharmacist in a ward round team. They found that the pharmacist was able to reduce the rate of ADEs by preventing and intercepting them. The pharmacist provided information on doses, interactions, indications and drug alternatives to physicians at the time of ordering and 99% of the recommendations were accepted [78]. Similar findings were also observed in a study by Kucukarslan et al. [196] which investigated the

effect of pharmacists in a round team. The rate of ADEs in this study was reduced by 78%. Of the 150 recommendations by the pharmacists, 98% were accepted by the ward round team [196].

These two strategies (CPOE and pharmacists participation in the rounds) may be feasible in hospital settings (provided that the hospital has a computerised system and adequate number of pharmacists), but not in private clinics or community pharmacies. Other examples of strategies where pharmacists can participate to prevent ADEs are pharmacy-led medication review and patient counselling.

Medication review has been defined as a '*structured, critical examination of a patient's medicines with the objective of reaching an agreement with the patient about treatment, optimising the impact of medicines, minimising the number of medication-related problems and reducing waste*' [202].

One example of which is a randomised controlled trial of medication review by pharmacists in care homes that was conducted by Zermansky et al. [203]. A comparison was made between a control group (with usual GP care) and intervention group (where pharmacists conducted medication review). This study concluded that the number of drug changes in the intervention group was high. Furthermore, a significant reduction in the number of falls in the elderly was found. This was achieved by stopping the use of drugs which may cause confusion, sedation, or hypotension and, adjusting or starting a drug that improves mobility (which was thought to have been responsible for this reduction). Additionally, this study reported that the GP reviews occured less frequently than pharmacist reviews (only 19% of patients had a review by the GP during the study).

Pharmacists are not the only professional responsible for conducting medication reviews, but physicians and nurses are equally responsible. GP-made reviews has been found to be as effective as pharmacist-led reviews [204]. One study evaluated the quality of GP and nurse medication reviews during training by a practice pharmacist [205]. It was reported that the quality of review before the training was poor in GP's but the documentation of DRP was improved following the training. The study also found that the nurse reviews were able to identify discrepancies in repeat prescriptions. This study has shown that GPs and nurses are capable of identifying DRP if given the appropriate training.

Although medication review was reported to have produced some health benefits to patients and health care system, the effectiveness of this intervention is still not well-proven. A meta-analysis of 32 studies by Holland et al. [206] revealed that there are some mixed findings from different studies

about medication review (example: one study reported to have reduced hospital admission, while some have shown no significant reduction). Further investigations and improvement may be needed to optimise the benefits of medication review.

One of the important responsibilities of pharmacists is counselling patient on proper medication use. A study by Schnipper et al. [6] evaluated the effects of counselling and follow-up by pharmacists on the rate of preventable ADEs and medication non-adherence after 30 days patients were discharged from a hospital. Only 1% of patients who were in the intervention group experienced ADEs whereas 11% of patients in the control group (no intervention) experienced such [6].

The time spent by pharmacists with each patient might limit the opportunity of implementing pharmacy-led medication review and patient counselling in real life. It may be practical that pharmacists focus on identifying high-risk patients and approach them to tackle the problems.

Apart from the strategies discussed above, inappropriate prescribing which could also contribute to the occurrences of ADE should also be tackled. A qualitative study in UK quoted that '*prescribers need education in how to avoid prescribing when it is not clinically indicated*' [207]. Education is the main strategy to ensure that prescribers are equipped to prescribe appropriately [208]. For many years, guidelines have been created to help prescribers in choosing appropriate therapy for specific conditions. However these guidelines will not be effective unless the users are educated about their use. In UK, an education about the use of guidelines on prescribing nutritional supplements significantly reduced total prescribing by 15% and reduced inappropriate prescribing from 77% to 59% [209]. The study also reported that prior to the educational programme, there was a low level of knowledge and practice in identifying those at risk of malnutrition and their nutritional management. In an attempt to prevent ADEs, it is important that prescribers know the most common medications involved and the demographic patterns of patients who are susceptible to them. These patterns may change over time due to increased numbers of newly marketed medicines and changes in disease patterns. Thus, all this information should be regularly disseminated to the prescribers, accompanied by education on appropriate prescribing.

1.7.3.1 Studies in Malaysia

In Malaysia, pharmacists provide individual or group counselling for outpatients, inpatients and discharged patients. This approach aims to help patients achieve the intended health outcomes through better adherence and providing information about possible ADEs. In 2009, more than 200,000 counselling services have been provided to patients [210]. The number of patients who have received this service has increased by 53% since 2008 [210]. However, to date, there has been no evaluation of the effectiveness of this service.

MTAC has also been introduced in outpatient services. It aims to optimise drug therapy in the management of chronic medical conditions such as diabetes mellitus, asthma, retroviral disease, and warfarin therapy [210]. Patients are selected by pharmacists or referred by physicians. Patients are scheduled to meet pharmacists every one or two months for a total of eight visits and are given individualised counselling and education [211]. During each visit, patient's adherence will be assessed and pharmacists provide recommendations to physicians (for example, addition of a drug, or dosage changes) if necessary. One study has investigated the effectiveness of the Diabetes MTAC (DMTAC) in Malaysia [211]. Patients' medical records and DMTAC forms were assessed retrospectively. The blood sugar control, lipid parameters and medication adherence of patients who had completed all eight visits significantly improved indicating that the service was effective in improving both patients' adherence and outcomes of their condition.

Zaidi et al. [199] have investigated clinical pharmacists' participation in the ICU. The majority of DRPs detected were related to unnecessary drug therapy. The overall recommendations provided by the pharmacists were found to have resulted in a net cost saving of RM 15,277 in the ICU (USD 4,007). Most reduction in the cost resulted from the discontinuation of drug use (70%). This study has provided evidence that a clinical pharmacist in the ICU has the potential to minimise the health service expenditure.

1.7.4 Monitoring adverse drug events

Incident reporting serves as an important tool for monitoring ADEs. Research findings related to ADEs could also provide details of the extent of a problem and lead to changes in practice or increases occurrences of likely problems. Furthermore, computerised systems can also be used to monitor ADEs. An important role of health care professionals in ADE monitoring is reporting an ADE incident after actions are taken to resolve patients' problems, so that they build a database of information that can be used for future prevention or precaution.

Reporting ADRs is important to drug safety surveillance. A drug undergoes clinical trials before it can be submitted for marketing authorisation. Clinical trials are not able to detect all ADRs because they are often conducted over short periods of time and in selected population groups. Once the drug is marketed, it is exposed to a wider population and part of safety monitoring is the spontaneous ADR-reporting system. This system also produces signals for new potential ADRs and is one of the cheapest ways to monitor the safety profiles of all marketed drugs.

In UK, reports of suspected ADR are sent to the Medicines and Health Products Regulatory Agency through the "Yellow Card Scheme"[212]. A similar approach is also practiced in many other countries [18, 213, 214]. Although such reporting systems have been established for many years, under-reporting is a major limitation in many countries. Thus, to identify the reasons for under-reporting, many studies have investigated the possible factors that encourage and discourage ADR-reporting among health care professionals [215-228] . The most common factor encouraging health care professionals in reporting ADRs is a serious or unusual reaction [215-219, 224, 225], followed by reactions involving newly marketed drugs [217, 219]. The most common factors discouraging health care professionals from reporting ADRs include well known reactions [220, 223, 225, 228] , uncertainty of an association between the reaction and the drug [215, 221], and a lack of time [217, 219, 227]. The lack of availability of reporting forms [219], reactions not being clinically significant [216], and a lack of knowledge about the reporting process [222, 226] were other reasons found that discourage health care professionals from reporting ADRs.

Health care professionals were more likely to report a reaction if they could ascertain that the drug has caused the ADR and the reaction was not well-known. However, national pharmacovigilance such as MADRAC in Malaysia, urge health care professionals to report any suspected ADRs. Causality

assessment is usually conducted in the pharmacovigilance unit to determine whether or not there is causal relationship between a drug and an ADR and health care professionals should be made aware of this. Proper communication between the pharmacovigilance unit and health care professionals could clarify this misconception.

More than 40% of hospital pharmacists in UK reported lack of time in completing ADR reports [134]. A survey of community pharmacists in Iran found that lack of time was not a major issue [215] and concluded that different working practices (community compared to hospital) could influence the factors for ADR reporting. However, Herdeiro et al. [229] reported that hospital pharmacists were more likely to report ADRs compared to community pharmacists. Such differences in working practices might be due to the former working closely with other health care professionals and having access to patient notes so they are in a better position to determine whether or not an ADR has occurred. Community pharmacists are reliant on patients informing them of their medical problems.

Pharmacists agree that ADR reporting is a professional obligation [217, 221, 226, 229]. They play an important role in pharmacovigilance, both in hospital and community settings. Greater participation by pharmacists in ADR reporting could considerably reduce the problem of under-reporting [230] and therefore provide better information for the regulators. Several studies concluded that positive ADR reporting attitudes are associated with increased reporting [229] and changing the wrong beliefs and attitudes of pharmacists about the purpose of reporting ADRs could improve it. In some studies, pharmacists suggested that education or training could improve ADR reporting [218, 220, 226, 231]. Granas et al. [232] evaluated the effects of a training on attitudes towards ADR reporting. Compared with a control group that received no training, there was an increase in the percentage of ADR reporting by the pharmacists that received one.

The aims of monitoring spontaneous ADR reporting are to identify previously unrecognised ADRs, identify risk factors that may predispose the development of an ADR, and to maintain a database for sharing of information [18]. These aims were correctly identified by health care professionals in some studies [219, 224]. However, in some studies, it was a matter of concern that they revealed monitoring of ADR reports is able to measure the incidence of ADRs [215, 216]. ADR reporting system is unsuitable to measure such incidence due to incomplete numerators (number of ADR reports) and denominators (number of patients exposed to a drug).

A few countries have developed a ME reporting system or ME reporting program (MERP) at national or hospital level [102, 233, 234]. The Institutes of Safe Medication Practices (ISMP) in the US has listed examples of the impact of the MERP [235] and they were: producing national hazard alerts (e.g. changes in packaging of drugs that could lead to look-alike confusion), disseminating trends of errors and the strategies to reduce them, recommending changes (in drug packaging or labelling, system and individual practices), establishing standards (e.g. national safety guidelines) and promoting public policy advocacy (e.g conducting conferences for health care professionals and participating in national policy discussions). Although the collection of MEs has the potential to reduce future occurrences, a number of factors have discouraged health care professionals from reporting incidents. One study highlighted that the type and severity of a ME influences the likelihood that an error will be reported [236]. Nurses [237, 238] and pharmacists [239] have greater awareness of error-reporting systems and therefore, were more likely to report an incident compared to physicians. Physicians were more likely to report a ME with a severe patient outcome whilst pharmacists and nurses reported all types of MEs [236]. However, most claimed that they would only report a ME that caused harm to the patients [237, 240]. Health care professionals reported that lack of feedback after reporting, the long process of reporting, and incidents that seemed too trivial to report as main barriers to reporting an incident [237]. Other reasons quoted were forgetting to report [237] and not being aware of the occurrence of an error [240].

1.7.4.1 Studies in Malaysia

Malaysia like many countries collects ADR reports on voluntary basis from doctors, pharmacists and nurses. Since 2007, reports from patients have also been accepted. The reports are reviewed and assessed by MADRAC every two months. All are then submitted to the International Centre of Drug Monitoring (WHO) in Uppsala, Sweden [18, 19]. In 2009, the total number of ADR reports received by MADRAC was 5850, which was an increase of 90% since 2007 [241]. A high percentage of reports (57%) were submitted by pharmacists in 2009 and the high number of graduate pharmacists in hospitals due to the three-year compulsory service was suspected to be the reason for the increase.

At least three studies have explored the views of health care professionals to ADR reporting in Malaysia. One investigated the attitudes of physicians towards ADR reporting [223] whilst the other two qualitatively investigated the views of community pharmacists about ADR reporting [226, 231].

Aziz et al. [223] conducted face-to-face interviews using a structured questionnaire among the physicians working in a teaching hospital. More than 80% of the physicians have suspected an ADR but did not report it and 40% were not aware of the existence of a national reporting system. The most common reason for not reporting was either because the ADR was well known or too trivial. Ting et al. [231] and Elkalmi et al. [226] interviewed community pharmacists and both studies reported that most of them were not aware of the existence of a national reporting system and had not reported an ADR. The reason given for the latter was that the reaction was common and mild. When asked to suggest ways to improve ADR reporting, pharmacists from both studies agreed that education and training would improve reporting rates. These three studies have shown that many health care professionals are not aware of the existence of a national reporting system and their obligation to report ADRs.

MERS was established in Malaysia in 2009 [21] and a total of 2,572 ME reports have been received to date [242]. As yet, there has been no published evaluation of the system.

1.8 Rationale for study

A review of the literature has shown that ADEs are a significant problem in many countries and can result in patient harm and hospitalisation. The findings from research on ADEs have produced several preventive strategies. Thus, in order to reduce the number and severity of harm related to medication, and to implement the preventive strategies, it is important to measure and describe the epidemiology of ADEs.

It is evident that the health care professionals have an important role in recognising, resolving, preventing and monitoring ADEs. Various interventions have been introduced to improve patient safety. The two most effective interventions found were CPOE and the involvement of pharmacists in rounds. The concept of clinical pharmacy involves assessment of DRPs and pharmacists play an important role in detecting, solving and preventing the problems. They are well trained in therapeutics and can play a key role in drug surveillance. Changing habits are difficult, thus any attempt to influence the current practice as a means of preventing ADEs should be based on thorough understanding of the current practices of health care professionals in improving patient safety. Many studies of health care professionals' interventions have shown good results for patient safety but how this translates to usual practice is uncertain. Therefore, a study to determine the experiences of Malaysian health care professionals related to ADEs was proposed as part of this thesis.

1.9 Research aims and objectives

This study aimed to determine the occurrence of ADE related admissions to a Malaysian hospital and also investigate experiences of pharmacists of ADEs in the Malaysian health care setting.

The specific objectives of the study are divided into two phases:

Phase 1 – ADE-related admissions

i) To determine the prevalence of ADE-related medical admissions in a public tertiary hospital in Malaysia

ii) To determine the types of ADE-related cases in those medical admissions

iii) To determine the types of drug associated with ADEs

Phase 2 – survey of ADE experiences of pharmacists in Malaysia

i) To investigate whether or not pharmacists are able to observe ADEs during their daily activities in both community and hospital settings

ii) To identify the strategies taken by pharmacists in resolving the ADE-related problems observed

iii) To evaluate whether or not pharmacists are aware about the role of MADRAC and ADR reporting system

1.10 Methodological issues

It was proposed to conduct a study to measure the occurrences of ADEs and determine the drugs associated with them. Following this, a survey was proposed to find about the ADE-related experiences of health care professionals in Malaysia.

1.10.1 General design

1.10.1.1 Prevalence of adverse drug event-related admissions

Data derived from records of ADR reporting can be a useful tool in identifying areas for intervention. However, the low spontaneous ADR reporting rates may under-estimate the extent of the problem. Furthermore, they may not provide information about other types of ADE – TF, ME and DO. Detecting ADEs through computerised systems is another option. However, the potential study sites like many other Malaysian hospitals, are not equipped with a computerised system and have handwritten documentation.

The most comprehensive method determining the prevalence of ADEs is one which allows detection of ADEs, calculation of prevalence, identification of the type of drugs associated with an ADE, and patient characteristics. All these information can be obtained using the chart review method. Chart review study allows a complete review of patient medical notes and charts. Information gathered from this method is useful in identifying ADEs and classifying them into sub-types. It has the advantage of being able to search for more information in the charts when the initial information is not enough to classify an ADE. Conducting a prospective chart review study also enables the collection or clarification of data from patients and health care professionals.

1.10.1.2 The experiences of health care professionals about adverse drug events

The survey aimed to answer few questions: do health care professionals observe ADEs during their daily work activities? If they do, what types of ADEs were observed and what were the interventions, if needed, taken to solve the ADEs? The best way to understand these experiences is to ask them. This can be done through interviews or survey questionnaires. Interview allows for a two-way communication, where the interviewer is able to clarify answers given by a respondent and the respondent is able to seek more explanation on the questions. However, it is costly and time-consuming to conduct them in a large population yet a smaller sample may not be enough to reflect the views of the population. Hence, a self-administered survey is comparably efficient in collecting information about the types of ADEs observed, the associated drugs, and actions taken in response to those ADEs. Due to high number of physicians and nurses, and with concerns about cost and time, it was decided that the researcher should personally distribute the questionnaires to all physicians and nurses in all medical wards of the studied hospital (including the wards where the chart review study was conducted). This was planned to be carried out during their weekly meetings.

An email-based survey was felt to be the most effective method to obtain information from the Malaysian pharmacists. To enable the views of both community and hospital pharmacists, the MPS was approached to supply details of their members. However, their data confidentiality arrangements meant that they were only able to support a postal survey. Therefore, it was decided to change the method to the latter.

1.10.2 Strengths and limitations

Although chart review is able to provide a complete review of all the notes and charts, the quality of the data in the notes is dependent on a physician's accuracy of recorded details. This can be overcome by adding patient interviews to the chart review where needed. However, chart review is time-consuming, as a researcher must review and record patient notes individually.

Postal surveys use self-completion questionnaires and this method enables the collection of data from a large population within a short time scale. They allow respondents the opportunity to answer the questionnaire at a convenient time. One of the disadvantages of postal survey is the poor

response rate. However, this can be overcome by sending reminders to the respondents. Additionally on the downside, there is lack of control about who completes the questionnaire. Unlike in face-to-face interviews, respondents are not able to clarify immediately from the researcher when they are unsure of question meanings and so, interpretations of such may vary. To minimise this setback, the researcher can provide their contact details in the questionnaire.

1.10.3 Case definition

ADEs as whole have substantial effect on patient morbidity. Rather than investigating one type of ADE, it was decided to investigate all types of ADEs. The reason being that, the sub-types of ADEs overlap with each other and it is difficult to separate one from another. Restricting the study to one type of ADE may result in an under- or over-estimate of the rate due to misclassification of events. Furthermore, the type of drugs associated with different types of ADEs may vary and this information will be useful in developing strategies to improve the current health care system. For the same reasons, health care professionals were asked to report their experiences in observing all types of ADEs.

A chart review study was therefore designed to collect information relating to ADEs in two medical wards in a tertiary public hospital. Following a pilot study, a classification tool was designed to assess and classify the ADEs. The criteria were used in the main chart review study which was conducted over 24 weeks.

1.10.4 Choice of previously published instrument

There was no existing questionnaire exploring pharmacists' experiences of ADEs. However, there are a number of surveys which have investigated health care professionals' attitudes towards and awareness of spontaneous ADR reporting [215-228].

The questionnaire by Consentino et al. [216] was developed to investigate physicians' attitudes to ADR spontaneous reporting system. It explored the physicians' awareness on purposes of ADR

reporting, what types of ADR to report and factors encouraging and discouraging ADR reporting. This questionnaire has also been used in a hospital-based study [243]. Similar criteria were explored in other studies investigating the attitudes towards ADR reporting among health care professionals – experiences of reporting ADRs, aims for ADR reporting system, types of ADR that should be reported, barriers to and factors encouraging ADR reporting [217, 219, 227, 232].

A questionnaire was therefore designed following a discussion with research supervisors to collect information on pharmacists' ADE-related experiences. Following a pilot study, the questionnaires were mailed to all hospital, clinic, and community pharmacists who were members of MPS.

CHAPTER 2

A CHART REVIEW STUDY OF MEDICATION-RELATED ADMISSIONS TO A HOSPITAL

This chapter describes the development of the method for the chart review study. A preliminary study was conducted to determine the type of information available in patient charts, design the data collection form, and modify trigger tool according to the Malaysian context and study objectives. This was followed by a pilot study to design the method for the main chart review study, modify the data collection form, where necessary, and estimate the number of admissions to the study site. Finally, this chapter describes the chart review study which was conducted in two medical wards in a tertiary public hospital. It addresses the prevalence of ADEs, its sub-types, and the drug associated with these occurrences.

2.1 Objectives

The objectives of this study were to:

i) To determine the prevalence of ADE-related medical admissions in a public tertiary hospital in Malaysia

ii) To determine the types of ADEs related to those medical admissions

iii) To determine the types of drugs associated with these ADEs

2.2 Method

2.2.1 Study design

The chart review study was conducted in two medical wards in a tertiary public hospital. It is an 800-bed hospital with 20 clinical disciplines. Patients admitted to emergency department are stabilised and admitted to the wards whilst elective admissions are directly admitted to the wards. The personal data of patients admitted to the hospital is entered into a computer system which is available at the registration counter. Patients or family members of non-civil servants are required to pay a deposit prior to admission and full payment upon discharge, whilst civil servants should provide a guarantee letter from their employer to be exempted from payment. There are a few classes of bed in the public sector – first class, second class and third class. The choice of a class relies upon the salary scale of a civil servant (servants from higher salary scale are eligible for first or second-class wards) or the ability of a non-civil servant to make the full payment. However the choice of wards also depends on their availability. The third-class wards are usually over-crowded, prompting the addition of extension beds if existing beds are fully occupied (40- 50 beds). First and second-class wards have fewer beds (1-6 beds) and more privacy for the patients. This is a typical scenario in almost all the tertiary public hospitals in Malaysia.

There were seven medical wards in the study hospital. The hospital is situated in Selangor state and is the main referral hospital for the surrounding area. Patients admitted to the medical wards were treated for various medical conditions such as cardiovascular diseases, diabetes mellitus, respiratory diseases, renal diseases, haematological conditions, and liver diseases. The majority of adult medical admissions to the hospital were admitted to the medical wards before transferred to the appropriate specialist ward. The selected study site is typical of public hospitals in Malaysia. Two medical wards were selected by the head of medical department in the hospital for the study as they were considered the busiest wards. Patients are usually admitted in these two wards (3^{rd} class wards) before transferred to other wards (2^{nd} class or 1^{st} class wards).

The preliminary and pilot study was conducted between June and July 2008. The main study was conducted between November 2009 and April 2010.

2.2.2 Development of the method

To maximise the sensitivity of the study, a prospective chart review method was chosen. Initially, the preliminary study was conducted to review the medical records. It was then followed by a pilot study to test and develop the chart review method. The following section describes the preliminary and pilot studies which contributed to the development of the main method used for this research.

2.2.2.1 Preliminary study

Prior to the pilot study, a two-day preliminary study was conducted in one medical ward. The preliminary study addressed the following objectives:

- To allow familiarisation with the types of information contained in patient notes on the ward and therefore assist in designing a suitable data collection form
- To test the suitability of a published ADE trigger tool [90] for the Malaysian context

During this preliminary study, all charts of patients admitted over two days were reviewed. The type of information that can be retrieved from patient charts and the location of the different types of information were recorded.

During this, it was noted that patient information such as gender, age, and ethnic group were available in patients' medical notes, as well as the initial diagnosis upon admission, confirmed diagnosis and the investigations carried out. Information about the drugs upon admission and those administered in the ward were available in the medication charts.

All of these information were easily available from the charts. Laboratory test results were not usually updated immediately. However, the results were available the following day.

Based on the information from this preliminary study, the literature, and discussion with research supervisors, a data collection form was designed (Appendix 1). The data collection form was subsequently created in a mobile device called a Personal Digital Assistant (PDA).

The trigger tool developed by Institute of Health Improvement was adapted [90] and it served as a quick check list of important triggers to look out for in screened patients that could lead to identification of ADEs. Some items were added to the list to make it more useful in the Malaysian context and to meet the study objectives. The modified trigger tool is in Appendix 2 and the items added were:

- **T1 Antihistamines:** a wider range of anti-histamines were listed in T1 compared to only diphenydramine in the original trigger tool

- **T4 Anti-emetics:** anti-emetics commonly used in Malaysia were added

- **T5 Anti-diarrhoeals:** anti-diarrhoeal drugs commonly used in Malaysia were added

- **T7 Antacids:** the original trigger list did not contain antacids. Since gastrointestinal disorder was one of the most common ADEs reported in many studies, it was deemed appropriate to add this trigger in the list

- **T10 Abnormalities in laboratory data:** all the abnormalities in the laboratory data were grouped under T10, compared with the original trigger tool which listed limited laboratory tests

- **T13 Uncontrolled disease/ recurrent/ worsening of a disease:** this was not listed in the original tool but was added in accordance with the study objectives

2.2.2.2 Pilot study

Pilot study was conducted prospectively over four weeks between June and July 2008. It addressed the following objectives:

- Assess the feasibility of the chart review method and use the trigger tool to identify ADEs in medical wards of a public hospital in Malaysia
- Determine the availability of charts for review and number of charts that can be reviewed in a day
- Determine the optimum timing of visits to the wards
- Determine the completeness of information in the patient charts
- Determine whether the data collection form is suitable and able to collect the information needed to assess the occurrence of an ADE
- Determine whether any changes should be made to data collection form
- Estimate the number of admissions to medical wards and prevalence of ADEs during the time period of the pilot study
- Determine whether or not the PDA is a suitable way to collect data

Medication charts and medical records of all patients who were admitted to the wards during the previous 48 hours, if available were reviewed. Patient information was initially entered into the PDA and was later uploaded into a Microsoft Access database. The modified trigger tool was used to assist in detecting suspected ADEs during the patient chart review.

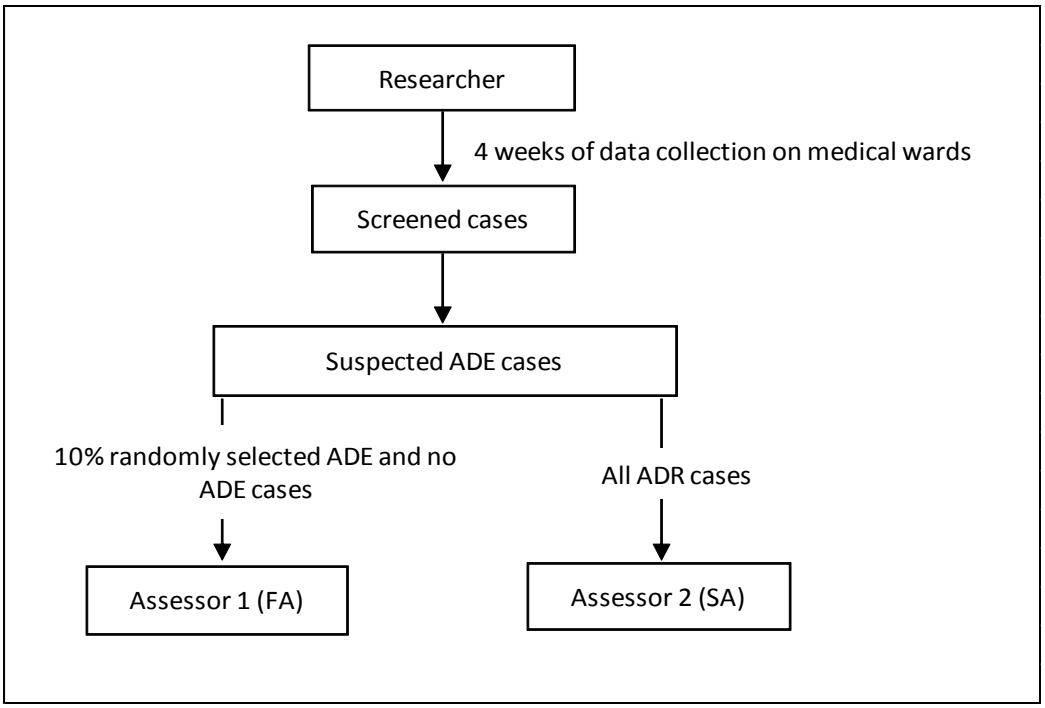
All the clerked cases were classified into 2 main categories:

(i) Suspected ADE cases – admissions that were suspected to have been caused by one or more drugs

(ii) Admissions not related to ADE (no ADE) – admissions that were not related to any drug

A random sample consisting of 10% of all the clerked cases were checked by an assessor (first assessor – FA), to ensure the identification of any ADE cases was appropriate (Figure 2-1). The assessor was one of the research supervisors, who has experience in pharmacovigilance. All suspected ADR cases were sent to a second assessor (SA), a senior pharmacist in MADRAC, to determine the causality. Causality assessment was carried out on all suspected ADR cases using the WHO's causality scale (Appendix 3).

Figure 2-1: Flow chart of the research process



(a) Chart review

During the pilot study, 374 patients were admitted to the medical wards. Of these, 136 (36%) charts were screened. From the information collected, it was possible to determine definite ADEs in 52 cases, no ADEs were suspected in 14 cases, and for the remaining 70 cases classification was not possible. The reason for this was a lack of information in the cases mentioned last. Information such as past medical and medication history, confirmed diagnosis and laboratory results were incomplete or missing. It is important to know which drugs the patients were taking prior to admission, how long they have been taking them, and for what condition to establish whether or not the presenting complaints are related to the drug consumed. Side effects, contraindications, choice of drug, doses and mode of administration need to be assessed to gauge their relation to any event experienced by patients.

Patients without past medication history were considered as admissions not related to drugs by assuming that they were not on any medications. This may not be true in all patients as sometimes, this information may not have been recorded in the chart. Moreover, the patients could not have possibly recalled the information, or that they did not bring their drugs to the hospital.

(b) Completeness of information in the patient charts

As this study relied on patient charts and medication records, incomplete information and poor documentation were major limitations. Interviewing patients though, may have provided some missing information. However, quality of data would depend on their ability to recall information, their willingness to be interviewed, or their physical or health condition (for they may be too sick to even engage in an interview). Count in the fact that patients in Malaysia may visit more than one general practitioner, and so clarifying any medication history from these very patients may have been complicated.

(c) Availability of charts for review and number of charts reviewed daily

During the four-week period, the mean number of charts reviewed per day was six (ranging from three to 12). Some charts were not available for screening for a number of reasons including patients being away from the ward for procedures such as scans and X-rays, or them being discharged or transferred to another ward.

The advantages of reviewing patients admitted in the previous 48 hours was that the information in the charts was more likely to be complete, with laboratory results, diagnosis, and further investigations. The disadvantage, however, was that patients admitted for short periods of time or were quickly transferred to other wards were missed. The only available record of all admitted patients was a daily record book which had minimal information on patients. Therefore, clerking patients admitted previous 24 hours will increase the number of cases screened per day. In case of missing or incomplete information, the case can be followed up the next day.

(d) Trigger tool

The list of triggers which was modified from the IHI trigger tool was not able to detect all ADEs. There were no triggers for MEs, DOs or ADWS. It would have been possible to add more triggers to the list to include all the possible ADEs. However, the usefulness of a trigger tool may reduce as the number of items for checking increases.

(e) Visiting time

Both the wards in the study had a routine of patient care. In the morning physicians and specialists conduct their ward rounds. During this time, patient charts were placed by the foot of patients' beds to aid review of patients during the rounds. However, later in the afternoon, charts were moved to the nurses' station for final review and duty hand-over, thus, making this the best opportunity to gain access to the medical charts.

During the study, the researcher visited each ward on alternate days. However, during the case assessment at the end of each day, there was a need to clarify incomplete information. Information such as confirmed diagnosis and laboratory data were either not available or incomplete. For this

reason, the researcher visited the same ward the next day to clarify the incomplete information and increased the time needed to review each patient.

(f) Suitability of the data collection form

The data collection form was able to collect basic information. However, in order to conduct an ADR causality assessment and classify cases into ADE category, more information is needed. Additional information needed were: dates when past medication were started and stopped, changes in vital signs and laboratory results, other laboratory findings (such as computerised tomography (CT) scan, X-ray, and drug therapeutic monitoring), and progress of patients after any medical intervention.

(g) Suitability of Palm PDA to collect data

The PDA delayed the data collecting process because it did not always recognise handwriting, so data needed to be entered more than once before it was correctly interpreted. PDA only recognised the letters if they were written slowly and clearly. Hence, writing on data collection form using the traditional pen and paper would be quicker. However, the disadvantage of these forms is that the all data then need to be manually entered into the database at a later time.

(h) Suspected adverse drug event cases

Patients with past medication history and were admitted to the hospital due to some unwanted event were initially grouped as suspected ADEs. Further evaluation was conducted to ensure whether or not the events leading to the admissions could have been related to any of the drugs a patient was taking. Patients without recorded drug history were assumed as not taken any drugs. This aligns with the definition of ADE by WHO [45], where an undesirable event occurs while the patient is taking drug therapy whether or not there is a causal relationship between the medication and the event.

Out of 136 patients, 66 (49%) were suspected as having been admitted due to ADEs. There were four planned admissions – when patients were admitted electively for dialysis. These patients were excluded as being admitted due to ADEs. All 62 remaining cases were then assessed by looking at the presenting complaints, symptoms, and laboratory tests. Such steps were taken in order that they can be classified into different categories, based on each ADE-type definition.

However, during the pilot study it was found that classifying each case was difficult due to lack of information. More information was needed to identify each case into one type of ADE. All the cases were classified using only the available information and thus, this may not indicate the true percentages.

After the assessments, 52 were classified as drug-related admissions and ten were not. These ten patients were admitted due to infections or newly diagnosed medical conditions. Within the drug-related admissions, 45 (87%) of them were classified as TF, ten (19%) as ADRs, three (6%) as MEs, and one (2%) as DO. There were seven patients admitted with more than one type of ADE. This pilot study, however, did not identify any ADWS.

(i) Inter-assessor reliability of adverse drug event classifications

The following figures represent the ten percent of each classified group: suspected drug-related admissions (n=5), admissions not related to a drug (n=1) and patients' without past medication history (n=7); were randomly selected and assessed by the assessor (FA). All the suspected ADR cases (n=10) were assessed by a pharmacist from MADRAC (SA). The agreement on "ADE and no ADE" classifications between the assessor and researcher was excellent – the agreement percentage being 92.

The causality assessments of ADR cases using the WHO's causality assessment scale (Appendix 11) are shown in Table 2-1. The pharmacist from MADRAC reported the difficulty of carrying out the causality assessment for all suspected ADR cases due to some missing information (such as when exactly the drug was taken or stopped, and the name of the traditional medicine and its indication). For most of the reactions, a temporal association was not possible due to incomplete data.

Table 2-1: Second assessor's adverse drug reaction causality assessment (n= 10)

Number	Suspected ADR	Pharmacist's assessment
1	Hypoglycaemia secondary to insulin	C5- Possible
2	Rash secondary to warfarin	C5- Possible
3	Hypokalemia secondary to traditional medicine	C6- Not enough information
4	Hyponatremia secondary to diuretic	C6- Not enough information
5	Anemia secondary to UGIB[i] – aspirin induced	C6- Not enough information
6	Anemia secondary to UGIB[i] – aspirin induced	C6- Not enough information
7	Itchiness secondary to amlodipine	C6- Not enough information
8	Renal impairment secondary to perindopril	C6- Not enough information
9	Hyponatremia secondary to captopril	C6- Not enough information
10	Cough secondary to perindopril	C6- Not enough information

[i] *UGIB – upper gastrointestinal bleed*

Amendments prior to the main study

Based on the pilot study, the following amendments were made for the main study:

- **Prescriber appointed to assess classification**

Since the researcher and the assessor involved in the pilot study are pharmacists (FA and SA), and to avoid bias, it was decided appropriate to include a prescriber in the main study.

- **Research assistants for data collection**

Chart review is a time-consuming method. Involving more personnel during data collection would reduce the time spent by the researcher on the wards and therefore, may increase the number of patients reviewed in a day. However, training of the data collectors in the use of the form would be required.

- **Use of trigger tool**

As discussed earlier, the trigger tool was not able to detect all types of ADE. Thus, it was realised and decided that its benefit of detecting ADEs would diminish if it was expanded to include all types of ADEs.

- **Patients screened**

As discussed in the previous section, many patients were missed because of the 48-hour time frame upon admission. It was already anticipated that reviewing patients admitted in the previous 24 hours would reduce the number of patients missed. Though such were the cases, this meant too, that patients' data needed to be updated the next day, had there been missing lab results or other ongoing tests.

ADWS were not identified in the main chart review study due to the difficulty in recognising it using only the information from patient notes. Furthermore it may need further investigation on

associating the drugs responsible for the event: on the patient's medical and medication histories and adherence behaviour.

- **Patients interviews**

This pilot study found that in 70 cases, past medical and medication histories were incomplete or missing. Interviewing patients was considered a suitable method for collecting this information.

- **Use of Palm PDA**

As the use of PDA limited the charts that could be reviewed each day, to increase the efficiency, a paper data collection forms were used.

An attempt was made to include research assistants for assisting in the collection of data as suggested upon completion of the pilot study. However, this attempt failed and led to the development of a classification tool as discussed in the next section (Section 2.2.2.3).

2.2.2.3 Development and testing of the classification tool

Two pharmacists were appointed to help in collecting data for the main chart review study. They were given a briefing about what information to collect and were given the data collection forms. However, after a collection of 600 cases, it was found that the information collected by the pharmacists was insufficient in determining whether or not an ADE has occurred. Due to this, all 600 clerked cases were discarded.

However, during the assessment of the 600 cases by the researcher, it was found that there was a need for a more systematic approach in reviewing and classifying each case in the same manner. The researcher found that it was difficult to rely only on the ADE definitions to assess all the cases as they do not state what type of information is needed to suspect an event. Furthermore, the information collected from the patient notes were usually not complete (as reported in the pilot study). On the other hand, it was found out a tool could help the researcher scrutinise all the available information, identify any extra information as needed in classifying the cases, and gauge whether or not a patient interview was still needed. Upon the development of a tool to recognise and classify ADEs, all 600 cases collected by the pharmacists were discarded and the data collection was restarted. However, the two pharmacists appointed to collect data were not available for re-collection due to changes in their work schedules. Thus, the researcher collected all the data herself for the main study.

Development of the classification tool

Although the types of information collected by studies investigating ADEs were similar, the way this information was assessed to identify an event differed between studies. Most studies identified or detected ADEs based on their definitions [9, 143, 244, 245]. Some used the criteria proposed by Hallas et al. [62] or Naranjo et al. [99] that sought to associate an event with a drug and classify those events [134, 135, 246]. However, the criteria were used only where an ADE was already suspected and not on all the screened patients. In some studies, a list of triggers has been used to detect ADEs from charts [139, 246, 247]. However, as discussed earlier, the trigger tool was not able to identify all types of ADEs without substantially increasing its length, therefore, decreasing its usability. It also contains only specific triggers related to specific medications (for example, asthma exacerbation due to NSAIDs or aspirin however, this exacerbation could also be due to TF). Although

a trigger tool can be used as a guideline to help detect ADEs, the stringent criteria in the list may limit the type of ADEs detected.

In order to be consistent in assessing all cases, a step-by-step approach to identifying ADEs was proposed. In each case where there is medication, history was assessed using the classification tool to reduce the possibility of missing an ADE.

Based on the literature and discussions with research supervisors, a classification tool that contains five criteria determining whether or not an ADE was present in a case was developed (Figure 2-2). The said criteria are detailed on the next page.

Figure 2-2: The classification tool

Criteria		Criteria that indicates the ADE type
1	Review patient's complaints and symptoms. Assess whether or not they may be related to patient's medication prior to admission.	Relate to the side effect of a drug (ADR)
		Appear at insufficient dose (TF)
		Appear due to prescribing error: wrong drug/dose/frequency etc (ME)
		Appear due to drug-drug interaction (ME)
		Appear at overdose of a drug (DO)
2	Review patient's complaints and symptoms. Assess whether or not they may be related to past medical condition.	Appear due to exacerbation of a past medical condition which usually appear at insufficient dose (TF)
		Appear due to drug-disease interaction, drug contraindicated for patient's medical condition or age (ME)
3	Review medication changes on admission.	Addition of a new drug (TF or ADR)
		Substitution to a different drug (TF or ADR)
		Abrupt cessation of a drug (ADR or DO)
		Dose was increased or decreased (TF, ADR, ME or DO)
		An antidote was prescribed (DO)
4	Review the laboratory tests and other findings.	Abnormalities in blood test
		Abnormalities in vital signs
		Abnormalities in other findings eg X-ray, CT scan, ECG etc
5	Review the diagnoses.	The diagnosis is related to the side effects of patient's medication (ADR)
		The diagnosis is related to insufficient dose of patient's medication (TF)
		The diagnosis is related to prescribing error (ME)
		The diagnosis is related to interactions of patient's medication (ME)
		The diagnosis is related to overdose of patient's medication (DO)
		The diagnosis is related to drug contraindication / drug-disease interactions (ME)

Morimoto et al. [82] have discussed different methods in identifying ADEs and key factors in determining whether or not an event is related to a drug. The first important step was to look for any signs and symptoms in patients that could be related to a drug, by reviewing patient's complaints. For example, if a patient complains of gastric pain, there could be several possible reasons – an exacerbation of previous gastric disorder, an adverse effect of a drug or a new medical condition.

The next stage is determining whether or not an event is associated with the patient's past medication history. Illustrating this using the same example above: If the patient was prescribed aspirin prior to admission, it could be suspected as the cause of patient's gastric pain (an ADR may be the cause), on the other hand, if patient had a history of gastritis, and if antacid was listed in the past medication history, TF could be suspected after all. However, if none of the patient's medication could be associated with patient's gastric pain, the patient's admission may not be drug-related and the pain could have resulted from a new condition. For an ADR to be suspected, a reasonable timing of drug intake and the reaction need to exist.

Following these, the first criterion in assessing a screened case was to seek for and observe "*patient's complaints and symptoms, and consider whether or not they might be related to patient's medication prior to admission (criterion one)"*. Based on the definition of different types of ADEs that were discussed in Chapter 1, patient's symptoms or complaints should be assessed as to whether or not they: are related to the side effects of a drug (which may indicate an ADR had occurred), appear at insufficient dose (which may indicate a TF had occurred), appear due to prescribing errors: wrong choice of drug or dose or frequency and etc. (which may indicate a ME had occurred), appear due to drug-drug interaction (which may indicate a ME had occurred), or appear at overdose (which may indicate DO had occurred).

Using the same example above, if patient was found to have had a history of gastritis that was overlooked when aspirin was prescribed, this could be suspected as a ME. This shows that patient's medical history is also as important. It could provide information on previous drug allergies, medical conditions or history of disease management. For this reason, the second criterion was to "*assess patient's complaints and symptoms and consider whether or not they might be related to patient's past medical conditions (criterion two)*". This was to find out whether or not the symptoms appear due to exacerbation of a past medical condition which usually appear at insufficient drug or dose (which may indicate a TF or ME had occurred); or appear due to drug-disease interactions or drugs contraindicated for patient's medical condition or age (which may indicate a ME had occurred).

Where the two above criteria were not met, the admission was not considered as related to a drug. If a patient's complaints or symptoms do not relate to their past medication or medical history, there could be other reasons that could have caused the patient's admission, such as newly diagnosed medical condition or infection not related to past medication or medical history.

Assuming that one or both criteria were met, the next criterion to assess was the changes in patient's medication as derived from criterion three, (*assessing medication changes on admission).* The essential step in managing a patient presenting with an ADR is to withdraw all the suspected drugs, if possible and provide symptomatic treatment [59, 182]. If the effect is dose-related, dose of the suspected medication should be reduced or substituted with another drug [59, 182]. Usually a drug re-challenge is recommended if the reaction is not severe. Similarly, in case of a DO, the suspected drug is removed and an antidote or symptomatic treatment is given, if necessary. In contrast, if a TF is suspected, the usual management is to add a drug, increase the dose or substitute with a different drug. Hence this criterion was aimed to look for interventions such as an addition of a new drug (which may indicate a TF or ADR had occurred), substitution to a different drug (which may indicate a TF or ADR had occurred), abrupt cessation of a drug (which may indicate an ADR or ME had occurred), dose were increased or decreased (which may indicate a TF, ME, or DO had occurred) or an anti-dote (which may indicate a DO had occurred). Referring to the example given above, if aspirin was withdrawn (abrupt cessation of a drug) and an antacid was given to the patient (addition of a new drug), this may indicate an ADR or a ME could had occurred. In contrast, if a proton pump inhibitor was substituted for magnesium trisilicate mixture the patient was prescribed prior to admission, this may indicate a TF had occurred.

The fourth criterion (*assess the laboratory tests and other findings)* was based on the investigations carried out after admission. Results from laboratory test or other tests can confirm the symptoms reported by the patients. For example, a complaint of gastric pain can be confirmed through an endoscopy, if available. The laboratory tests may be helpful for some types of ADE, especially when it involves specific organs. Abnormalities in tests, such as renal profile test, liver function test, or complete blood count or blood sugar level may indicate a problem that is potentially related to medication prior to admission.

The fifth criterion was to "*assess the diagnoses (criterion five)*". Admitted patients are sometimes assigned an initial diagnosis until a confirmed diagnosis can be made. Both diagnoses can assist in determining whether or not an ADE is present by relating it to the patient's past medical and medication histories. Referring back to the example above, if gastritis is documented as the diagnosis, this could confirm the occurrence of an event.

After the criteria assessment, patients are categorised into each type of ADE based on the classification listed in Figure 2-3.

Figure 2-3: Classification of adverse drug events

ADE	Classification
Adverse drug reaction	Symptoms are related to the side effects of a drug
Overdose	Symptoms appear at overdose
Therapeutic Failure	Symptoms appear at insufficient dose or due to exacerbation of past medical condition which usually appear at insufficient dose
Medication error	Symptoms appear due to wrong choice of drug and dose, drug-drug interaction, drug-disease interactions or drug contraindicated for patient's medical condition or age

Testing the classification tool

The classification tool was tested to determine whether it was suitable and efficient in categorising ADEs. The test was conducted in cases screened during the first week of the main chart review study (male medical ward). The cases from the pilot study were not used because of incomplete or missing information in most cases. Information such as demographic data, presenting complaints, drugs on admission, laboratory test, and other findings and diagnoses were collected as intended for the main study. The criteria were used to review each patient and identify whether or not he or she was admitted due to an ADE.

Of the 44 patients, 17 did not have past medication or medical histories and six were planned admissions for dialysis, review of renal, or blood profile; these cases were excluded from further assessment. Thus, using the classification tool (Table 2-2), 21 potential cases were assessed to determine whether or not an ADE had occurred in such.

Table 2-2: The assessment of cases using the classification tool (n= 21)

Case number	Criterion					Number of criteria met	ADE type
	1	2	3	4	5		
1	√	×	√	x	×	2	None
2	√	√	√	×	√	4	TF, ME
3	×	√	√	√	√	4	TF
4	×	×	-	-	-	NA	None
5	√	×	√	x	×	2	None
6	√	√	√	√	√	5	TF
7	√	√	√	√	√	5	TF, ADR
8	√	√	√	√	√	5	TF, ME
9	√	√	√	√	√	5	TF, ADR
10	×	×	-	-	-	NA	None
11	√	√	√	√	√	5	TF, ADR, ME
12	√	√	√	√	√	5	TF, ADR
13	√	√	√	√	√	5	TF
14	√	×	√	√	×	4	ADR, ME
15	√	√	√	√	√	5	TF
16	√	×	√	√	√	4	ADR
17	√	√	√	√	√	5	TF
18	√	×	√	√	√	4	ADR
19	√	√	√	√	×	4	TF
20	√	√	√	√	√	5	TF
21	√	×	√	√	√	4	ADR

NA – not applicable

A total of 25 ADEs were identified using the classification tool (where one patient may have more than one type of ADEs). Thirteen patients were identified to have been admitted due to a TF, eight due to an ADR and four due to a ME. All these cases met four or more criteria. Out of 21 cases seven met four criteria whilst ten cases met all five criteria. Criteria one and two were not met in two cases (case four and ten), indicating that the patient's complaints were not related to patients' past

medical and medication histories. Thus these admissions were classified as not drug-related. Furthermore, cases one and five met criteria one and three (Figure 2-4). Fulfilling criterion one indicated that the patients' complaints were related to their past medication history, and meeting criterion three indicated that there were some changes in their medication. However, evidence was not enough to be able to determine that their admission was drug-related.

Figure 2-4: Summary of cases 1 and 5

Case one: The patient was discharged one month ago and diagnosed with tuberculosis.He was prescribed anti-tubercular drugs. He complained of poor oral intake (anorexia) and body weakness for the past two days. Poor oral intake is one of the side effects of anti-tubercular drugs but it is also a sign of active tuberculosis. An antibiotic was added to patient's medication in the ward. CT scan showed a mid-line shift and, the patient was diagnosed with brain abscess and suspected with cerebral toxoplasmosis. There was no evidence to support his complaints, hence, this case was classified as 'not drug-related'.
Case five: The patient was admitted with complaints of bed sore with pus discharge mixed with blood and foul smell for the past two weeks. Patient was bedridden since 2008 and was unable to move upper and lower limb. Patient was tolerating tube-feeding and had diabetes mellitus and hypertension. He was prescribed anti-diabetics and anti-hypertensive agents. Two antibiotics were added to patient's medication in the ward. Patient was diagnosed with grade II bed sore secondary to prolonged bed-ridden. Although, poor control of diabetes mellitus can be suspected as the cause of patient's bed sore, there was no evidence supporting this suspicion. Hence, this case was classified as 'not drug-related'.

All the information collected from the ward were reviewed systematically to decrease the likelihood of missing an ADE. All cases were reviewed in the same manner using the criteria. In using the criteria, it was possible to determine whether or not the information collected were sufficient to complete the assessment. Hence, when there was not enough collected information, the researcher could go back to the ward the next day to locate any missing information.

Criterion three needs to be evaluated carefully. Although there are changes in the medication particularly the addition of a new drug, it may not mean that an event has occurred. Changes in medication could also indicate that a patient has been diagnosed with a new condition.

Criterion four investigates whether or not there is any abnormality in the laboratory tests or other findings that could indicate an event may have occurred. However, this criterion is difficult to apply to subjective symptoms such as cough, constipation or headache. These symptoms cannot be measured by laboratory testing and may not be reported in the medical notes. Thus, criterion four is reliant on the quality of documentation in the medical notes.

The definitions of ADE sub types overlap and it can be challenging to differentiate one from another. This further emphasises the need for clear definitions and system of classification is just as important to avoid misclassification of any ADEs.

Seven out of 21 cases assessed using the classification tool met four criteria – meaning there was only one criterion not met by these cases. Criterion 2 was not met in four of these cases. This could be due to missing or incomplete information. The remaining cases did not meet criterion one, four or five. Part of this could be because patient details were not followed-up until discharge, where more investigations would have been conducted and a confirmed diagnosis might have been stated.

Referring to the WHO's ADR causality scale [98], for an event to be classified as possible, probable, or certain, it is important that some of the criteria are fulfilled: (a) a clinical event, (b) laboratory test abnormality with a reasonable time sequence, (c) clinically reasonable response on withdrawal, and (d) satisfactory reasonable procedure. Although, patients' complaint is enough to suspect an ADE, in order to confirm the causality of an event, it is important to get more evidence to support this. Similar approaches have also been used by Hallas et al. [62] and Naranjo et al. [99] where a list of criteria was scored to determine the causality of an event. Based on these approaches and the testing conducted on 21 cases using the classification tool, it was decided that cases that meet four

criteria will be considered as 'drug-related', meaning, the event may be considered as certainly or probably caused by a drug. None of the 21 cases met only three criteria. However cases meeting 3 criteria should also be considered as 'drug-related', as the remaining two criteria may not be met partly due to incomplete or missing information, and these cases may be considered as possibly caused by a drug. Cases which meet less than three criteria are considered as not drug-related, as there was not enough information to conclude that the event leading to the admission was related to a drug. These cases may be considered as unlikely, unclassified or unclassifiable according to WHO's scale.

Limitations

The classification tool was tested only in a small number of patients due to time constraints. Furthermore the classification tool was developed using retrospective cases (the 600 that were discarded) and the tool then was tested prospectively to ensure it could be applied in practice. This was done using all suspected ADE cases for the first week of the main study (n=21). The number cases used to test the tool was small but this test also served as an exercise for the researcher to get familiarised with the components in the tool.

Not all types of MEs are identified through this chart review study. This is because only ME which have caused hospital admissions were investigated. Other MEs such as wrong dosage or frequency in the prescriptions may not be captured during the admissions because they are preventable and may have been intercepted before causing any harm. This chart review study will only be able to identify MEs that have caused harm and thus, only those MEs are included in the classification tools.

Amendments made to the criteria

The findings from testing of the classification tool in 44 patients and discussion with research supervisors were considered for amendments. Where a new drug is added, a further review of the laboratory test and diagnosis should be made to determine whether or not the new drug was added due to an ADE. An extra section was added to criterion four for the assessor to consider changes in

subjective symptoms such as cough and headache. Although the subjective symptoms should be reviewed in criterion one, the progression of the symptoms (for worse or better) which may indicate the success or failure of the new therapy given to the patient, may be the key point to indicate that changes made to patient medication have improved or worsened the patient's condition. If the condition worsens, suspicion could be raised as to whether or not the suspected drug or suspected event was the actual reason for the admission.

2.2.3 Sample size calculation

The prevalence of ADE-related medical admissions in the pilot study was estimated as 38%. There were 374 admissions during the four-week pilot study. It was estimated that in 24 weeks, the number of admissions (population size) would be around 2,300 patients. The sample size was calculated using a formula designed by Naing et al. [248], which allows calculation of sample size of studies estimating prevalence. The required sample size was estimated to be 1141 at 95% confidence level and with 2% precision. A total of 1200 patients were included in the study.

2.2.4 Ethical approval

Ethical approval was obtained from the Malaysian Research Ethical Committee, Ministry of Health to conduct the pilot study (reference number: NMRR-08-260-1415) (Appendix 4) and main study (NMRR-08-1532-2877) (Appendix 5). Permission was also obtained from the hospital director and ward sisters to have access to patients' medical and medication charts.

2.2.5 Data collection

Medication charts and medical records of patients admitted to two medical wards were reviewed prospectively from Nov 2009 to April 2010. Each ward was visited by the researcher on alternate

weeks. Data were collected for all patients admitted to the ward during the previous 24 hours, where their charts were available for review. The data collected were:

- Demographic information (patient's age, gender and ethnic group)
- Presenting complaints (complaints recorded on the chart at admission)
- Vital signs and other investigations since admission (results of investigation on patients since admission)
- Medication since admission (medication patient was given since admission)
- Past medical and medication history (medical and medication history recorded in the notes and if not satisfactory, the patient was interviewed for more information)
- Initial and confirmed diagnoses (the initial diagnosis on admission and confirmed diagnosis after investigations)
- Laboratory results and other findings (results from the laboratory and other tests recorded in patient's notes since admission)

All data gathered were handwritten on a data collection form which was designed and modified following the pilot study (Appendix 6). Data was subsequently entered into a prepared Microsoft Office Access (2007) database.

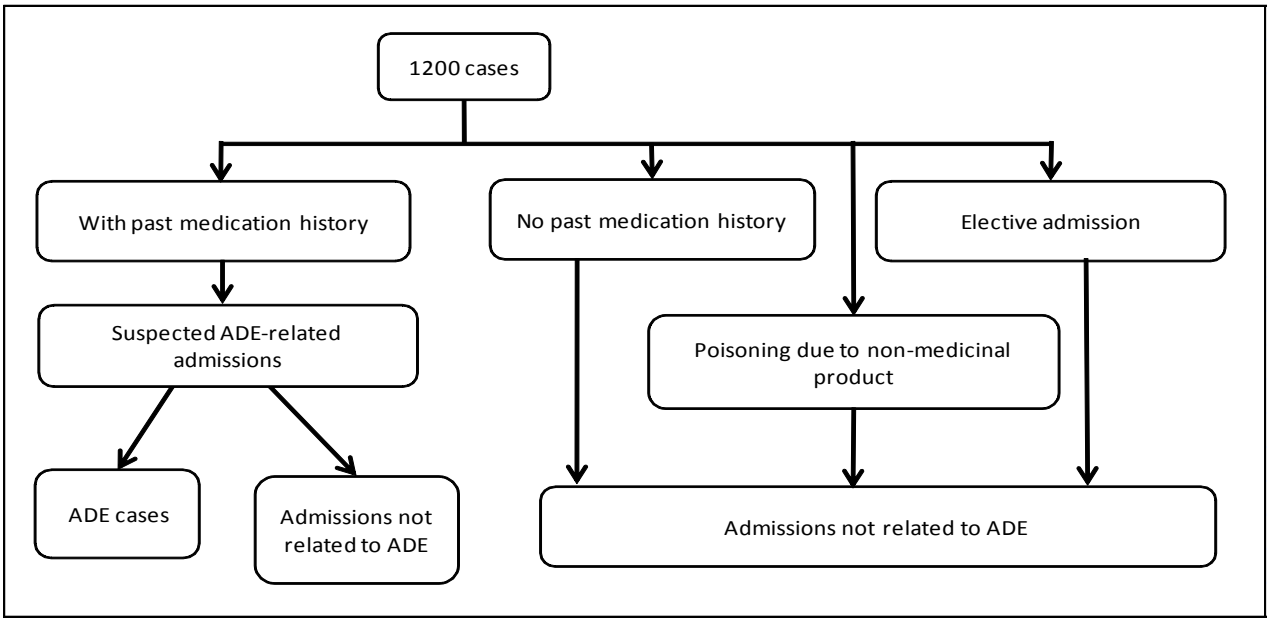
2.2.6 Case screening and classification

All cases were screened by the researcher and were classified into two groups; admissions not related to ADE and suspected ADE-related admissions. The characteristics which distinguish these two groups are shown in Figure 2-5. Patient admissions without past medication history, elective admissions and those due to poisoning with non-medicinal product (such as detergent or weed killer) were classified as "admissions not related to ADE".

All patients admitted with past medication history were suspected as having an ADE. These patients were then assessed by the researcher using the ADE classification tool and subsequently classified as either:

- Suspected ADE cases if three or more criteria were met (criteria one and/ or criteria two and one or more of the other criteria)
- Admissions not related to an ADE if fewer than three of the five criteria were met

Figure 2-5: Characteristics distinguishing ADE-related admissions from admissions not related to ADEs



All ADE cases were then classified into four different types of ADEs:

i) Therapeutic failure – defined as an inadequate therapeutic response to a drug as evidenced by the presence of symptoms of a diagnosed disease state or condition [63]

ii) Adverse drug reaction – defined as a response to a drug that is noxious and unintended and occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease, or for modification of physiological functions [45].

iii) Drug overdose – defined as an exposure of an individual, by ingestion or inhalation, to an amount of substance associated with the significant potential to cause harm [65].

iv) Medication error – defined as any preventable event that may cause or lead to inappropriate medication use or patient harm, while the medication is in the control of the health care professional, patient, or consumer[49].

2.2.7 Independent assessment and inter-assessor reliability

As a process of checking the reliability of the classification tool used to identify and classify ADE cases, and to ensure the identification and classification of any ADE was appropriate, 10% of each ADE cases (n= 46) and admissions not related to ADE (n= 19) were assessed by two assessors. These cases were generated randomly using the Predictive Analytics SoftWare (PASW) Statistics 18.0 (© SPSS, Inc., 2009, Chicago, IL). The reliability could have been increased if the assessors were able to assess all the cases. However due to their work commitments; they were not able to look at all 1200 cases. Thus only 10% of cases were selected. The assessors were:

- A physician who has experience working on medical wards and
- An academic who is a pharmacist and has experience in pharmacovigilance (FA); also a research supervisor.

Both assessors were given an explanation about the study and its purposes. They were given training on the application of the ADE classification tool using a few sample cases.

Each assessor was given:

- A set of all the randomly selected cases
- A list of ADE classification tool

- A British National Formulary [249]
- A password to access online Martindale[250] and Stockley's Drug Interactions[251]

Inter-assessor reliability was used to identify whether same results can be obtained by two or more assessors using similar method of assessment or instrument. It is a measure of the level of agreement between assessors. Percentage agreement and kappa statistic can be used to measure this level.

Calculating the percentage of agreement is simple. Observed percentage agreement (P_o) = total agreement (T) divided by total number of cases assessed (N) [252, 253]:

$$P_o = T/N$$

However, some researchers believe this is not the best measure as it does not take into account the chance of agreement [253, 254]. Kappa statistic overcomes this limitation by taking into consideration the amount of agreement that could be expected by chance [255]. Chance agreement can occur for example when the assessor knows in advance that most of the cases are not related to ADEs and they adopt a strategy reviewing the cases as negative whenever they are in doubt [252]. Thus, the percentage of negative agreement will be large because of prior knowledge of the prevalence of ADE, not because of the information reviewed in the cases. Kappa (κ) is calculated by subtracting the percentage of expected agreement (P_e), which occur by chance, from the total agreement (P_o), then divided by percentage agreement which is not expected to occur by chance (1-P_e) [252, 253, 256]:

$$\kappa = P_o - P_e / 1 - P_e$$

A kappa of one indicates perfect agreement, whereas a kappa of zero indicates agreement equivalent to chance and kappa of <0 indicates agreement which is worse than chance. There is no universal standard in classifying the kappa value that reflects reliable judgement, but the commonly applicable ranges are by Landis and Koch [257] (Table 2-3).

Table 2-3: Classification of level of agreement

Range of κ	Description of agreement level
< 0.00	Poor agreement
0.01 - 0.20	Slight agreement
0.21 - 0.40	Fair agreement
0.41 - 0.60	Moderate agreement
0.61 - 0.80	Substantial agreement
0.81 - 1.00	Almost perfect agreement

Source: Landis and Koch [257]

Kappa has been criticised for a number of reasons. Kappa is sensitive to the distribution of proportion in each subject category and may not be reliable for rare observations. So caution has to be taken when comparing kappa between studies. Kappa treats all disagreements equally. When the categories are ordered, it is important to use the weighted kappa. However, this is not relevant for assessment of ADE and types of ADE in this study. The kappa statistic was used in this study to assess the level of agreement between assessors in identifying the occurrence of ADEs and classifying the type of ADE observed.

It was found that percentage of agreement was slight to fair when the academic assessments were compared to the researcher's and physician's. Therefore, it was decided to use a second pharmacist to assess all the cases – a clinical pharmacist who has experience working on medical wards.

During the course of this study, the pharmacist (SA) from MADRAC was promoted and transferred to another department. Upon discussion with a new pharmacist who was appointed to replace the previous pharmacist, all suspected ADR cases were sent to MADRAC using the online reporting form [258]. Whilst sending some of the reports using the online reporting form, errors occurred on the webpage. The webpage could not be retrieved and it was not possible to determine whether or not the report had been sent. For this reason, a hardcopy of each case was also handed personally to a pharmacist in MADRAC by the researcher, to ensure that the committee received all suspected cases. The causality of each case was assessed by the MADRAC. MADRAC conducts meetings every two months to review all the reports received and for causality assessments. After the causality

assessment, one of the pharmacists from MADRAC contacted the researcher with the outcome of their assessment.

2.2.8 Data analysis

Statistical analysis was performed in Predictive Analytics SoftWare (PASW) Statistics 18.0 (© SPSS, Inc., 2009, Chicago, IL). Descriptive statistics are shown as means, frequencies and percentages. The admissions identified as related to ADE, its sub-categories, and the drugs implicated are shown in frequencies and percentages. The influence of patients' characteristics on the percentage of admissions due to ADE and its sub-type was assessed using Chi-square. Differences were considered statistically significant when the p-value was less than 0.05.

2.3 Results

2.3.1 Characteristics of patients

During the study period, 1200 patients were reviewed by the researcher. Half of the patients reviewed were men (n= 605, 50%) and 46% (n=551) of them were from the Malay ethnic group. The mean age was 50 (SD 18) ranging from 12 to 101 years. Patients aged up to 12 years are usually treated on paediatric wards whilst patients aged 13 years and above are treated on the adult wards. However depending on the availability of beds in the paediatric wards, patients aged 12 years may be admitted to adult wards.

2.3.2 Case assessment and classification

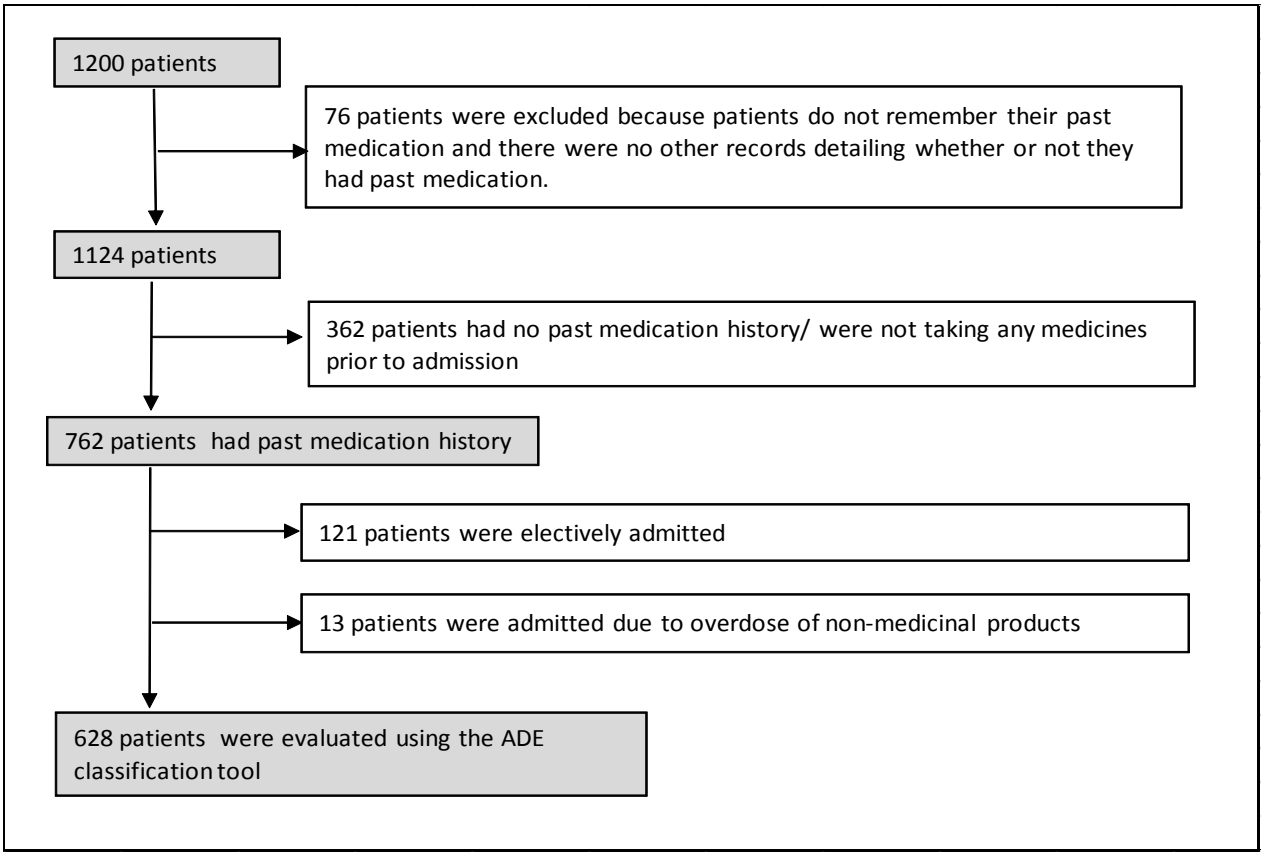
Of the 1200 patients, 76 (6%) were excluded due to incomplete past medication history. These patients could not remember the names of the drugs they took prior to admission and/ or there were no records detailing whether or not they had past medication. Therefore, a total of 1124 patients were assessed for possible ADEs and the characteristics of these patients are shown in Table 2-4.

Table 2-4: Characteristics of assessed patients (n=1124)

	Number of patients	Percentage (%)
Gender		
Male	565	50.3
Female	559	49.7
Age		
< 15	16	1.4
15-39	316	28.1
40-64	552	49.1
≥65	240	21.3
Ethnic group		
Malay	515	45.8
Indian	403	35.9
Chinese	141	12.5
Other	65	5.8

Of 1124 patients included in the study (Figure 2-6), 362 (32%) had no past medication history. Although these patients were not on any drugs prior to admission, this does not preclude them from having an existing medical condition. Thirteen patients were admitted due to an overdose of non-medicinal products. These patients were admitted for intentional or unintentional household poisoning such as detergents or weed killers. None of these 13 patients had a past medication history. A total of 121 patients were admitted electively. These admissions were for planned dialysis, scans, surgery, or reviews on blood tests or renal profile results. These patients were on medication prior to admission and, although admitted electively to the admission wards, sometimes present with complains suspected to be related to the medication they were prescribed. Thus, they were not excluded from being reviewed by the researcher. However, none of their complaints turned out to be related to the medication they have been taking. Thus, they were categorised as admissions not related to drugs. After accounting for all these patients, a total of 628 (56%) of them were suspected as having ADEs.

Figure 2-6: Flow chart of case assessment

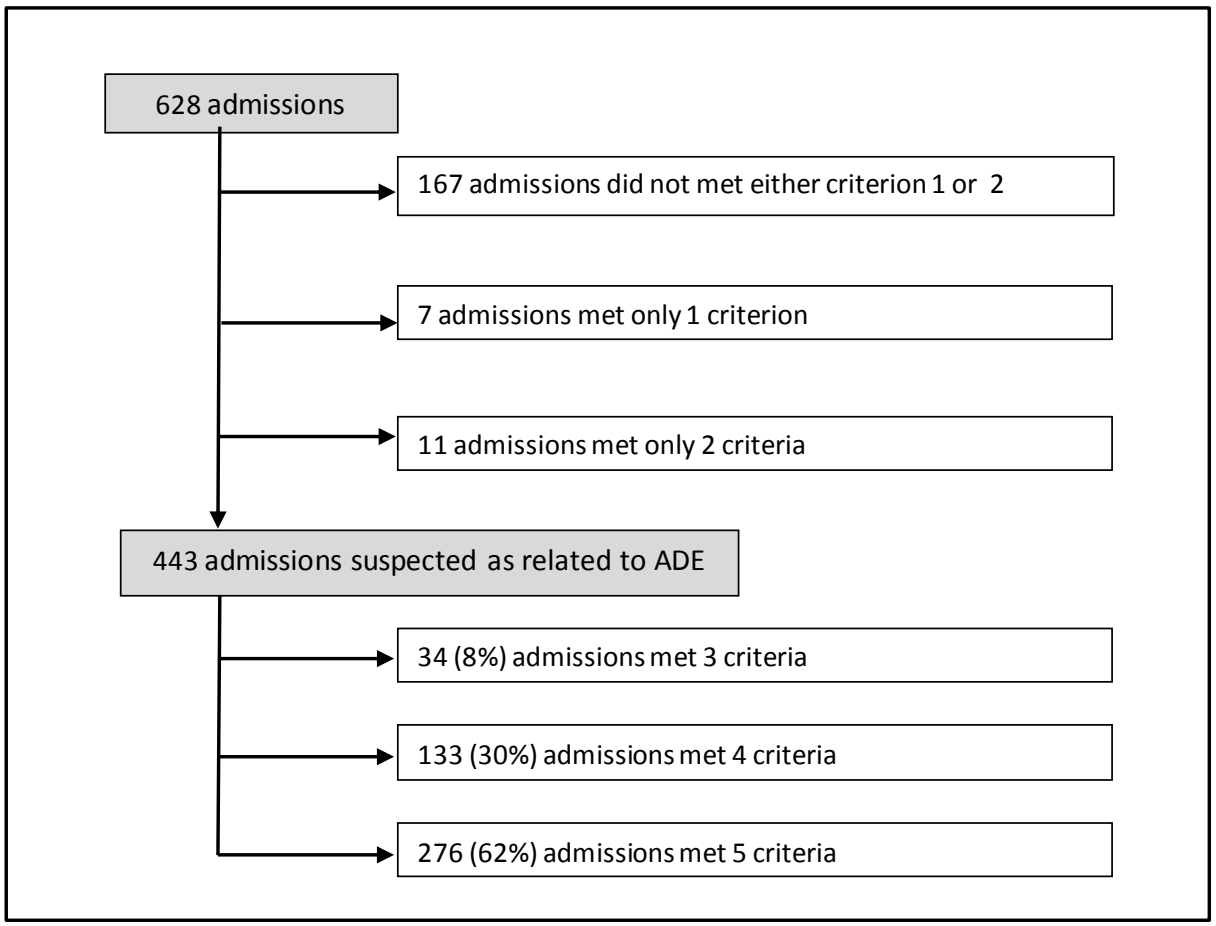


2.3.3 Adverse drug event-related admissions

All patients who had past medication history (after excluding elective admissions and those due to overdose of non-medicinal products; n= 628) were evaluated using the ADE classification tool by the researcher. The breakdown of cases according to the number of criteria met is shown in Figure 2-7. A total of 185 admissions met less than three criteria. Within this group, 167 admissions did not meet either of criterion one or two (the admission should meet at least one of criterion 1 or 2). Failure to meet these criteria showed that patients' complaints were not related to drugs they have taken prior to admission. Furthermore, seven admissions met only one of the five criteria and 11 admissions met only two criteria, indicating that there was not enough evidence to conclude that any of these admissions was related to a drug.

A total of 443 admissions met three or more criteria and therefore, were classified as ADE-related, giving a prevalence of 39%. Within these admissions, 34 (8%) met three criteria, 166 (30%) met four criteria, and more than 60% (n= 276, 62%) met all five criteria.

Figure 2-7: Breakdown of number of criteria met by potential ADE cases



The characteristics of patients whose admissions were ADE-related are shown in Table 2-5. Of the 443 patients, more than half were women (n= 239, 54%), almost 60% were aged between 40 to 64 years (n= 252, 57%) and 42% (n= 187) were from Malay ethnic group. The percentage of ADE-related admissions was the highest in patients aged between 40 to 64 years ($\chi^2 = 62.03$, $p < 0.001$). Men were less likely to have been admitted due to an ADE ($\chi^2 = 5.36$, $p = 0.02$) and there was no relationship found between ethnic group and ADE-related admissions ($\chi^2 = 21.7$, $p = 0.12$).

Table 2-5: Characteristics of patient admissions related and not related to ADEs (n= 1,124)

	Number (%) of patients			p-value*
	ADE-related admissions n= 443	Admissions not related to ADE n= 681	Total n= 1,124	
Age (year) (n= 1,124)				p <0.001
<15	-	16 (2.3)	16 (1.4)	
15-39	74 (16.7)	242 (35.5)	316 (28.1)	
40-64	252 (56.9)	300 (44.1)	552 (49.1)	
≥65	117 (26.4)	123 (18.1)	240 (21.4)	
Gender (n= 1,124)				p = 0.02
Male	204 (46.0)	361 (53.0)	565 (50.3)	
Female	239 (54.0)	320 (47.0)	559 (49.7)	
Ethnic group (n= 1,059[a])				p = 0.12
Malay	187 (43.3)	328 (52.3)	515 (48.6)	
Indian	181 (41.9)	222 (35.4)	403 (38.1)	
Chinese	64 (14.8)	77 (12.3)	141 (13.3)	

[a] this group does not total 1,124, due to exclusion of 'other' ethnic group (n= 65)
**based on chi-square tests*

There were a total of 483 ADEs identified in the 443 ADE-related admissions (patients could be assessed as having more than one ADE). Of the said 443 patients, 30 (7%) was admitted for TF and ADR, six for TF and ME, and four for ADR and ME. Almost three-quarters of ADE-related admissions (n= 351, 72%) were classified as resulting from TF (Table 2-6). ADRs were the next most common type of ADE classified as related to one-fifth of the admissions. The most common drug groups causing more than 80% of the admissions were cardiovascular drugs (n= 222, 50%) followed by anti-diabetics (n= 96, 22%), and anti-asthmatics (n= 65, 15%).

Table 2-6: Types of adverse drug events (n=483)

	Number of patients	Percentage (%)
Therapeutic failure	351	72.1
Adverse drug reaction	96	19.7
Drug overdose	21	4.3
Medication error	15	3.1

2.3.4 Therapeutic failure-related admissions

Three hundred and fifty one patient admissions were assessed as related to TF, a prevalence of 31%. Of these, half were men (n= 178, 51%)(Table 2-7). Patients from the Malay and Indian ethnic group were equally distributed. The mean age was 55.6 (SD 14.4), with a minimum age of 15 years and a maximum of 90 years. The percentage of TF was found the highest in patients aged 40 to 64 years. The occurrence of TF was higher in older age- group (χ^2 = 67.879, p <0.001). Those from Chinese ethnic group were less likely to be admitted due to a TF (χ^2 = 7.031, p= 0.03). There was no difference by gender in admissions due to TF (χ^2 = 0.196, p =0.658).

Table 2-7: Characteristics of patient admissions related and not related to TFs (n= 1,124)

	Number (%) of patients			
	TF-related admissions n= 351	**Admissions not related to TF n= 773**	**Total n= 1,124**	**p-value***
Age (year) (n= 1,124)				p <0.001
<15	-	16 (2.1)	16 (1.4)	
15-39	46 (13.1)	228 (34.9)	316 (28.1)	
40-64	215 (61.3)	323 (43.6)	552 (49.1)	
≥65	90 (25.6)	149 (19.4)	240 (21.4)	
Gender (n= 1,124)				p= 0.658
Male	178 (50.7)	367 (50.1)	565 (50.3)	
Female	173 (49.3)	349 (49.9)	559 (49.7)	
Ethnic group (n= 1,059[a])				p= 0.03
Malay	150 (43.7)	365 (51.0)	515 (48.6)	
Indian	150 (43.7)	253 (35.3)	403 (38.1)	
Chinese	43 (12.5)	98 (13.7)	141 (13.3)	

[a] this group does not total 1124, due to exclusion of 'other' ethnic group (n= 65)
**based on chi-square tests*

A total of 391 uncontrolled conditions were identified in the 351 patients with TF-related admissions. In 16% of these patients (n= 56), poor adherence was documented in the medical notes by attending physicians. . From the same notes, seven patients of these had poor to fair inhaler technique. On the other hand, the compliance status or medication-taking behaviour of the remaining patients was not documented. Hence, the likely cause of the TF for the rest of the patients is undetermined.

The drug groups most frequently associated with the four most common drug-related events are listed in Table 2-8. Despite being prescribed one or more antiplatelets, antianginals, and/ or statins prior to admission, 81 (23%) of the patients experienced chest pain resulting to their admission. This makes the aforementioned drugs the most common drug groups attributed to TF in this study, followed by corticosteroid inhaler, which was implicated in 17% of these TF-related admissions (n= 58).

Table 2-8: Drug group most commonly associated with TF-related admissions (n= 351)

Drug-related event (number of patients)	Drug group*	Number of patients (%) (n= 351)	Individual drug (number of patients)
Chest pain (n= 81[a])	Antiplatelet	70 (19.9)	aspirin (42), clopidogrel (18), ticlopidine (18), cardiprin (8)
	Antianginal	64 (18.2)	trimetazidime (35), glyceryl trinitrate (31), isosorbide dinitrate (29), isosorbide mononitrate (1)
	Statin	61 (17.4)	simvastatin (28), lovastatin (24), atorvastatin (8), rosuvastatin (1)
Hypertension (n= 80[a])	Calcium channel blocker	47 (13.4)	amlodipine (33), nifedipine (10), felodipine (4)
	Angiotension converting enzyme inhibitor	39 (11.1)	perindopril (25), captopril (12), enalapril (2)
	Beta-adrenoceptor blocker	35 (10.0)	metoprolol (21), atenolol (10), bisoprolol (3), propranolol (1)
Exacerbation of asthma (n= 65[a])	Corticosteroid inhaler	59 (16.8)	beclomethasone (25), budesonide (21)
	Beta-agonist inhaler	50 (14.2)	salbutamol (49), formoterol (1)
	Inhaler with combination of beta agonist + antimuscarinic bronchodilator	25 (7.1)	ipratropium bromide + albuterol (24), ipratropium bromide + fenoterol (1)
	Inhaler with combination of corticosteroid + beta-agonist	18 (5.1)	budesonide + formoterol (16), fluticasone + salmeterol (2),
Hyperglycemia (n= 55[a])	Biguanide	28 (8.0)	metformin (28)
	Sulphonylurea	24 (6.8)	glibenclamide (15), gliclazide (9)
	Insulin	20 (5.7)	intermediate to long acting insulin (29), short acting insulin (7)

[a] *more than one drug group can be associated with an admission*
**only the most frequent drug groups are listed in this table*

2.3.5 Adverse drug reaction-related admissions

Ninety-six patient admissions were assessed as ADR-related, a prevalence of 8.5%. The breakdown of causality assessments following the submission of all ADR cases to MADRAC are shown in Table 2-9. It was found that two out of 96 cases had insufficient information for causality assessment and were classified as 'unlikely' and 'unclassified'. They were excluded from further analysis. Of the remaining 94 cases, one was classified as 'certain' and the rest as 'possible'. The case with 'certain' causality had an event with plausible time relationship (patient had an oculogyric crisis upon administration of metoclopromide and the drug was withdrawn immediately). In all the remaining cases, patients were taking two or more drugs and it was not possible to attribute the reactions to specific drugs for they could be related to concurrent diseases, hence, resulting in 'possible' causality assessment. This particular result gives an adjusted prevalence rate of 8.4%.

Table 2-9: Causality assessment of suspected ADR cases by MADRAC (n= 96)

Causality Scale	Description	Number of patients (%)
C1: 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.	1 (1.0)
C2: 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.	-
C3: Possible	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration 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.	93 (97.0)
C4: 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 plausible explanations.	1 (1.0)
C5: 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 are under examination.	1 (1.0)
C6: Unassessible/ Unclassifiable	A report suggesting an adverse reaction which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified.	-

Source: WHO's ADR causality scale[98]

The characteristics of patients admitted due to ADRs are shown in Table 2-10. Of 94 patients, 60% were women (n= 56) and 40% were from Malay ethnic group (n= 38). About half of the patients were aged 40 to 64 years (n= 49, 52%). The mean age of the patients was 58.5 (SD 15.0) years, with minimum age of 18 years, and a maximum of 90 years. Older patients were more likely to have been admitted due to an ADR (χ^2 = 18.5, p < 0.001). Likewise, women also more likely to be admitted due to an ADR compared to men (χ^2 = 4.792, p= 0.03). Patient admissions related to ADR was higher in the Malay ethnic group than those from Chinese and Indian ethnic group (χ^2 = 13.3, p= 0.001).

Table 2-10 Characteristics of patient admissions related and not related to ADRs (n= 94)

	Number (%) of patients			p-value*
	ADR-related admissions n= 94	Admissions not related to ADR n= 1030	Total n= 1124	
Age (year) (n= 1124)				p < 0.001
<15	-	16 (1.6)	16 (1.4)	
15-39	10 (10.6)	306 (29.7)	316 (28.1)	
40-64	49 (52.1)	503 (48.8)	552 (49.1)	
≥65	35 (37.2)	205 (19.9)	240 (21.4)	
Gender (n= 1124)				p = 0.03
Male	38 (40.4)	527 (51.2)	565 (50.3)	
Female	56 (59.6)	503 (48.8)	559 (49.7)	
Ethnic group (n= 1059[a])				p= 0.001
Malay	38 (41.3)	477 (49.3)	515 (48.6)	
Indian	30 (32.6)	373 (38.6)	403 (38.1)	
Chinese	24 (26.1)	117 (12.1)	141 (13.3)	

[a] this group does not total 1124, due to exclusion of 'other' ethnic group (n= 65)
**based on chi-square tests*

The drug group most frequently responsible for ADR-related admissions was anti-diabetics (n= 36, 38%) (Table 2-11). Reactions affecting the endocrinology or metabolic system (n= 51, 54%) were responsible for more than half of the said admissions (Table 2-12). Among these, hypoglycaemia was found the most common adverse reaction (n= 34, 36%). The most common causative drugs associated with hypoglycaemia-related admissions were combination of glibenclamide and

metformin (n= 12). However, almost 80% (n= 26, 77%) of patients admitted due to hypoglycaemic reaction had poor oral intake prior to admission. This information was documented in patients' medical notes. In addition, one of the patients developed prolonged hypoglycaemic reaction (which was not immediately recognised by a family member) due to insulin. Subsequently, patient was hospitalised and diagnosed with neuroglycopenia coma.

Table 2-11: Drugs involved in admissions related to adverse drug reactions (n= 94)

Drug group	Number of patients (%) (n= 94[a])	Individual drug (number of patients)
Antidiabetic	36 (38.3)	metformin (21), glibenclamide (14), gliclazide (13), insulin (13), acarbose (1)
Antiplatelet	10 (10.6)	aspirin (9), ticlopidine (1)
Thiazide diuretic	10 (10.6)	chlorothiazide (10)
Angiotensin converting enzyme inhibitor	10 (10.6)	perindopril (7), captopril (2), enalapril (1)
Calcium channel blocker	10 (10.6)	amlodipine (4), nifedipine (4), felodipine (2)
Beta-adrenoceptor blocker	5 (5.3)	atenolol (3), metoprolol (2)
Analgesic	4 (4.3)	diclofenac (2), mefenamic acid (1), naproxen (1)
Other*	18 (19.1)	-

[a] *more than one drug group can be associated with an admission*
**'other' drug groups have frequencies of two or less*

Electrolyte imbalance was found the second most common reaction related to endocrinology or metabolic system (n= 11, 12%). Electrolyte imbalance means the serum electrolyte level is higher or lower than the normal level. The most common causative drug associated with electrolyte imbalance was hydrochlorothiazide (n= 5). Gastritis and peptic ulcer diseases were found to be the next common reaction related to admission (n= 6). Gastritis is inflammation of gastric lining and peptic ulcer disease is an ulcer of the gastric lining or duodenum. The most common causative drug associated with gastritis or peptic ulcer disease was aspirin (n= 5).

Table 2-12: The frequency of the types of adverse drug reactions (n= 94)

Type of adverse reaction	Number of patients (%) (n= 94)
Endocrinology or metabolic system	51 (54.3)
Hypoglycaemia	34 (36.2)
Electrolyte imbalances	11 (11.7)
Hyperglycaemia	3 (3.2)
Renal impairment	2 (2.1)
Neuroglycopenia	1 (1.1)
Central nervous system	16 (17.0)
Giddiness	5 (5.3)
Headache	4 (4.3)
Seizure	2 (2.1)
Dizziness	2 (2.1)
Vertigo	1 (1.1)
Fever	1 (1.1)
Oculogyric crisis	1 (1.1)
Cardiovascular system	13 (13.8)
Palpitation	4 (4.3)
Bradycardia	3 (3.2)
Hypotension	2 (2.1)
Exacerbation of angina	1 (1.1)
Tachycardia	1 (1.1)
Leg oedema	1 (1.1)
Gastrointestinal system	11 (11.7)
Gastritis or peptic ulcer disease	6 (6.4)
Nausea or vomiting	2 (2.1)
Diarrhoea	1 (1.1)
Constipation	1 (1.1)
Upper gastrointestinal bleed	1 (1.1)

table continued..

Table 2-12 continued: The frequency of the types of adverse drug reactions (n= 94)

Type of adverse reaction	Number of patients (%) (n= 94)
Dermatology	10 (10.6)
Rashes	4 (4.3)
Facial swell or oedema	3 (3.2)
Itchiness	2 (2.1)
Stevens-Johnson Syndrome	1 (1.1)
Haematology	6 (6.4)
Anaemia	2 (2.1)
Menorrhagia	1 (1.1)
Neutropenia	1 (1.1)
Jaundice	1 (1.1)
Respiratory system	5 (5.3)
Exacerbation of asthma	3 (3.2)
Shortness of breath	1 (1.1)
Cough	1 (1.1)

2.3.6 Drug overdose-related admissions

Twenty-one admissions were related to DO, a prevalence of 1.9%. The characteristics of patients admitted due to DO are shown in Table 2-13. Four-fifths of patients with overdose were women (n= 17, 81%) and all but one, were aged under 65 years (n= 20, 95%). The number of patients admitted for overdose was too small to be able to determine whether or not there were any relationships between patient characteristics and DO.

Table 2-13: Characteristics of patients admitted due to drug overdoses (n= 21)

	Number of patients	Percentage (%)
Gender		
Male	4	19.0
Female	17	81.0
Age (year)		
40-64	20	95.2
≥65	1	4.8
Ethnic group		
Malay	9	42.9
Indian	9	42.9
Chinese	1	4.8
Other	2	9.5

The drugs associated with patients admitted due to overdose are shown in Table 2-14. Single drugs caused the admissions of 10 patients suspected for overdose whilst multiple drugs were responsible for the remaining admissions. The drug group most frequently responsible for overdose-related admissions was analgesics either as a single drug (n= 5) or in combination with another analgesic or other drugs (n= 10). The most common analgesic responsible for overdose was paracetamol (n= 12), either alone or in combination with other drugs. All but one has intentionally ingested an overdose of drug.

Table 2-14: Drugs involved in admissions related to drug overdoses (n= 21)

Drug group	Number of patients (%) (n= 21)	Drugs (number of patients)
Analgesic	8 (38.1)	paracetamol (4)
		aspirin (1)
		paracetamol + mefenamic acid (1)
		paracetamol + mefenamic acid + diclofenac (1)
		paracetamol + bromhexine + naproxen + diclofenac + norethisterone + mefenamic acid (1)
Multiple drugs	7 (33.3)	paracetamol + methyl salicylate (1)
		paracetamol + oftalein (1)
		paracetamol + antidiarrhoea* (1)
		paracetamol + diclofenac + calcium lactate (1)
		cough mixture* + tablets for runny nose* (1)
		salbutamol inhaler + prednisolone + chlorpheniramine + cough mixture*, salbutamol + pain killer* (1)
		paracetamol + prednisolone + hyoscine butylbromide + pseudoephedrine/tripolidine + mefenamic acid + multi-vitamin* + frusemide (1)
Antidiabetic agent	3 (14.2)	glibenclamide (1)
		metformin (2)
Antidepressants	1 (4.8)	lorazepam + mirtazapine (1)
Beta-adrenoceptor blocker	1 (4.8)	metoprolol (1)
Calcium supplement	1 (4.8)	calcium carbonate (1)

**patient could not remember the drug name or did not bring the drug to the hospital*

2.3.7 Medication error-related admissions

Fifteen patients were admitted due to MEs. The characteristics of these patients are shown in Table 2-15. More than half of the patients were women (n= 9, 60%), two thirds were aged 40 to 64 years (n= 10, 67%), and around half were from Indian ethnic group (n= 8, 53%). However, the number of patients admitted for ME was too small to determine whether or not there were any relationships between patient characteristics and ME. The drug groups associated with ME are shown in Table 2-16. It was found that antiplatelets were the most common drug group which caused ME-related admissions. Three out of 15 patients were prescribed an antiplatelet without a prophylactic drug despite having history of gastritis or peptic ulcer disease.

Table 2-15: Characteristics of patients admitted due to drug medication errors (n= 15)

	Number of patients	Percentage (%)
Gender		
Male	6	40.0
Female	9	60.0
Age (year)		
15-39	1	6.7
40-64	10	66.7
≥65	4	26.7
Race		
Malay	4	26.7
Indian	8	53.3
Chinese	3	20.0

Table 2-16: Drug group most commonly associated with medication errors (n= 15)

Drug group	Drug-related event (number of patients)	Problem
Anti-platelet	Gastric pain (3)	Prescription in patients with history of gastritis without gastrointestinal protection
	Uraemic symptoms (2)	Prescription in patients with history of severe renal impairment
	Gout episode (1)	Prescription in patient with history of gouty arthritis
Angiotension converting enzyme inhibitor	Electrolyte imbalance (1)	Prescription in patient with history of hyponatremic and hypokalemic episodes
	Dizziness due to hypotension (2)	Unnecessary polypharmacy*
Hypoglycaemic agent	Hypoglycaemic attack (2)	Prescription in patient who is a chronic alcoholic
		Failure to reduce the dose of gliclazide in elderly patient with known renal failure
Beta-blockers	Hypoglycaemic attack (1)	Prescription in patient with frequent hypoglycaemic attacks (drug may mask the symptoms)
	Dizziness due to hypotension (1)	Unnecessary polypharmacy*
Statin	Chest pain (2)	Failure to prescribe in patient needing secondary prevention
Calcium channel blocker	Dizziness due to hypotension (1)	Unnecessary polypharmacy*
Alpha-adrenergic agonist	Worsening of systemic lupus erythematosus (1)	Prescription in patient with history of systemic lupus erythematosus

**more than one drug group associated with an admission*

2.3.8 Inter-assessor reliability

To assess the reliability of the researcher's categorisation, two additional health care professionals and a research supervisor classified a sample 10% of all potential ADEs. The results are shown in Table 2-17 and Table 2-18. Each assessor reviewed 65 cases and from these 75 types of ADEs were identified.

The overall agreement for presence of an ADE between all assessors ranged from 'slight agreement' to 'moderate agreement'. The agreement between all four assessors regarding classification of ADE types ranged from 'fair agreement' to 'substantial agreement'.

The agreement for classification of TF between the researcher and the physician indicated 'substantial agreement'. Likewise, the agreement for classification of ADR between the researcher and the pharmacists indicated 'substantial agreement'. The percentage and kappa agreement for classification of ME and DO were not conducted due to a small number of cases. There was only one ME and two DO cases assessed in 65 cases.

The percentage of ADE-related admissions identified by the researcher from the 10% of random cases was the highest (n= 46, 71%). The percentage was also higher for TF (n= 37, 57%) and ADR (n= 14, 22%) compared with other assessors. This showed that clinical judgement is based on individual interpretation and may vary between individuals. The pharmacists have identified few cases of TF (n= 17, 26%). However, no changes were made to the classification of ADEs by researcher but given the researcher's higher number of cases, it may be that the prevalence rates were overestimated.

Table 2-17: The agreement for ADEs classification (n= 75)

	Kappa value[a] (percentage agreement)		
	TF	ADR	ADE or not
researcher * academic	0.46 (73.3)	0.47 (86.7)	0.33 (58.7)
researcher * physician	0.71 (85.3)	0.55 (89.3)	0.47 (72.0)
researcher * pharmacist	0.36 (68.0)	0.75 (93.3)	0.34 (60.0)
academic * physician	0.31 (66.7)	0.21 (86.7)	0.05 (50.7)
academic * pharmacist	0.28 (70.7)	0.40 (88.0)	0.17 (0.25)
pharmacist * physician	0.30 (66.7)	0.63 (93.3)	0.13 (57.3)

[a]*kappa value; <0 indicates poor agreement, 0.01-0.20 indicates slight agreement, 0.21-0.40 indicates fair agreement, 0.41-0.60 indicates moderate agreement, 0.61- 0.80 indicates substantial agreement and 0.81-1.00 indicates perfect agreement*

Table 2-18: Classification of random cases by all four assessors (n= 65)

	Number of cases (%)		
	TF	ADR	ADE
Researcher	37 (56.9)	14 (21.5)	46 (70.8)
Academic	25 (38.5)	8 (12.3)	32 (49.2)
Physician	34 (52.3)	6 (9.2)	43 (66.2)
Pharmacist	17 (26.2)	9 (13.8)	27 (41.5)

2.4 Discussion

2.4.1 Key findings and comparison with other studies

2.4.1.1 Prevalence of adverse drug event-related admissions

Two-fifths (39%) of admissions to two medical wards in a government hospital in Malaysia were considered related to ADEs with almost 80% of it being due to TF. This was followed by ADR which accounted for 22% of ADE-related admissions. In other words, of 628 patients who were on medication prior to admissions, 70.5% admissions were related to ADE.

The prevalence of ADE-related admissions in this study is higher than previous studies, 0.5% to 30.4% [1, 8-11, 83, 119, 142]. The results from these published studies cannot, however, be directly comparable as the limitations in the current study's methodology could have influenced the differences in the findings. Furthermore, the study design, population, and criteria used in each study are different from one another and they make comparisons between the published studies and current study difficult. The latter was conducted only in two wards in one hospital compared with that by Bhalla et al., Ahmed et al., and Hallas et al., which were conducted in all medical wards of the study site (giving a prevalence of 10.1 to 11.4%), whilst Chan et al. conducted theirs (the highest prevalence of 30.4%) in acute medical units for elderly patients more than 75 years old. Despite these differences, the prevalence of ADE-related admissions found in the current study is alarming.

In common with previous studies [63, 143, 146], the present study found that admissions related to TF were highest compared to other types of ADE. Previous studies reported that TF accounted for 45% to 81% of ADE-related admissions. However, some studies have found ADRs the highest contributor to ADE-related admissions, accounting for 53% to 90% of it in these studies [9, 83, 140, 142]. This may be explained by a number of factors: First, the comprehensive assessment method using a classification tool may have increased the likelihood of all drug-related admissions as being identified. Second, a single assessor evaluated all the cases and the result heavily relied on individual interpretation. Individual interpretation may tend to have caused overestimation of the rate of ADE-related admissions as supported too, by the higher percentage in identified ADEs by the researcher herself compared with the other assessors. Third, the unavailability of patient medication adherence

information may have led to misclassification of some ADE cases and may have caused overestimation of the percentage of therapeutic failure. Finally, the types of ADEs investigated in the present study were comprehensive, whilst other studies have only investigated particular types such as ADR and TF [62], ADR and overdose [1, 11, 142] or ADR, TF, and overdose [9, 83, 143]. Thus, the differences in definitions resulted in a wide range of prevalences, making comparisons between and among studies difficult.

As previous studies have investigated different types of ADE (making comparisons difficult), the characteristics of each type are discussed individually and compared among ADE-related studies.

2.4.1.2 Prevalence of therapeutic failure-related admissions

The prevalence of TF-related admission was 31% and was higher than previous studies, where the prevalence ranged from 1.1% to 9.3% [8, 10, 62, 83, 143, 146, 147, 152]. The differences in the prevalence may be the result of differences in the criteria used to assess TF. Hallas et al. [62] proposed a classification tool (the symptoms are known to reappear at insufficient dosages, the symptoms were not likely to have been caused by progression of the disease, a reasonable temporal relationship exists between the start of inadequate or excessive dosage and the appearance of the symptoms, symptoms improved by dose adjustment, no other conditions could explain the symptoms and drug level below therapeutic range) to assess suspected TF and evaluate the causal relationship. This assessment method was also used in other studies [9, 63, 146, 147, 152]. The stringency of these criteria could have affected the evaluation and categorisation of suspected TFs. The criteria used in the present study, however, did include some of these criteria but they were less stringent (symptoms appear at insufficient doses, exacerbation of a medical condition, medication changes, lab and other findings associated with the symptoms, and diagnosis associated with symptoms). It did not include the criteria “temporal association” and “symptoms not caused by progression of the disease” as in the criteria by Hallas et al. This is because establishing and identifying these criteria are difficult for patients usually seek medical attention after the symptoms have already worsened and not in the early stages of such. Therefore, in this study, the use of less stringent criteria in identifying and classifying TF, is likely contributed to the detection of higher TF frequency.

Another possible reason for the higher prevalence in this study could be that there was no follow up or review on patients until they were discharged. In the study by Howard et al. [147], patients were followed up until their discharge. This gives the advantage of confirming the actual reasons for patients' admissions following further investigation. In their study, 29% of admissions which were initially classified as possible drug-related were excluded after further follow-up. Failure of this study to have done the same could have resulted in its probable overestimation of prevalence.

The third reason for higher prevalence in this study could be that a patient's adherence status was not assessed in this study. Patients complaining of chest pain, for example, although could be a result from the progression of their disease was classified under TF due to the lack of this crucial information. Thus, a number of limitations in the methodology could have overestimated the true prevalence of TF in this study.

2.4.1.3 Prevalence of adverse drug reaction-related admissions

The prevalence of ADR-related admissions was estimated to be 8.4%. Despite the differences in study methodology and population, the prevalence of ADR-related admissions found in this study was in common range with that of the previous studies, which was 7.5% to 8.5% [62, 83, 84, 134].

One of the strengths of the current study is that all suspected ADR cases were assessed for causality by MADRAC, a committee whose one routine among others, is to assess the causality of all the reports it receives. This is in contrast with other studies [62, 83, 84, 134] where two or more assessors were trained to evaluate all cases for causality, their judgment were then compared, and majority decision took into account in classifying cases as drug-related. There could be a potential weakness in their assessment method for they were subjected to individual clinical judgment of which may vary from person to person.

2.4.1.4 Prevalence of drug overdose-related admissions

DO was found to have caused 2% of medical admissions in this study, with an estimated prevalence higher than previous studies in Malaysia [164, 165]. However, it was within the range of prevalence reported in other countries – 0.1% to 17% [1, 9, 11, 63, 122, 143]. The higher prevalence in this study compared to the previous ones in Malaysia may be explained by the study design. The prospective design of the current research allowed collection of complete medical and medication histories and ensured that all information needed to correctly classify the events were gathered. Furthermore, chart review has been reported an effective method in identifying higher number of drug-related admissions [96, 117, 119, 120]. The previous studies conducted in Malaysia were retrospective, using computer records or discharge diagnoses [164, 165] to determine the rate of overdose. This method relies on the quality and accuracy of documentation, which, if not met, may result in underestimation of the actual rate. However, it should be criticised that the current study was conducted only in two medical wards in one hospital, compared with the previous studies in Malaysia, which have retrospectively examined the entire admissions in a specific hospital for more than two years. Thus, this current study in contrast, may have overestimated the true prevalence of DO-related admissions in the study site

2.4.1.5 Prevalence of medication error-related admissions

ME was responsible for 1.4% of admissions in this study. Although the prevalence was low it was still within the range of other studies, 1.2% to 10.6% [134, 139, 146-148]. Among these, only a small number of studies have investigated admissions related to ME *per se* [139, 148]. These studies reported a prevalence range of 1.2% to 4.3%. Other studies investigated drug related admissions and assessed the preventability of the event [134, 139, 146, 147]. The preventable event may include TF [8, 63, 83, 146], DO, [146, 147] and, in some studies, ADR [71, 134]. The prevalence reported by these studies was from 1.2% to 10.6%. Due to the differences in the definitions, comparisons of the prevalence rates among these studies are difficult.

2.4.2 Drug causes of ADE-related admissions

The most common drug groups, resulting in more than 80% of the ADE-related admissions were cardiovascular drugs, antidiabetics, and antiasthmatics. Within these groups, antiplatelets were the most frequently implicated. Similarly in other studies, cardiovascular drugs were reported as the most common drug group associated with ADE-related admissions in other studies [8-10, 63, 146].

Likewise, the highest proportion of admissions related to TF was seen in cardiovascular diseases (chest pain and hypertension), followed by respiratory diseases (exacerbation of asthma), and endocrinology and metabolic disorders (hyperglycaemia). TF was most frequently related to therapies with cardiovascular drugs (antiplatelets, antianginals, statins and antihypertensives), antiasthmatics and antidiabetics. TF in 16% of these patients was known to be related to poor adherence to medication whilst of 65 patients admitted for asthma 11% had poor to fair inhaler technique. In common with previous studies of drug-related admissions, TF was most frequently implicated with cardiovascular drugs [8, 83, 143, 146, 147, 152-154, 259], antiasthmatics [83, 147, 153], and antidiabetics [8, 83, 152], probably due to their widespread use in the medical practice. The Malaysian National Health and Morbidity Survey III which was conducted in 2006 reported that hypertension, diabetes mellitus, asthma and heart disease were the most prevalent conditions among the Malaysian population [260]. Thus, it is not suprising that TF in this study was frequently related to the same medical conditions. The prevalence of these medical conditions is reported to be increasing in Malaysia [33-36] – the reasons being poor dietary control and sedentary lifestyle [36]. In addition these studies reported that more than 70% of patients on drug therapy had poor control of their medical conditions [33, 34]. This shows that Malaysia has a serious problem with poor control of chronic medical conditions which may in part account for the higher TF prevalence found in this study. Non-adherence to medication was found the main cause of TF-related admissions in previous studies [62, 83, 143, 146, 152]. Although, patient medication adherence was not assessed in the present study, 16% of TF-related, admitted patients had a record of non-adherence in their notes.

The drugs which most commonly resulted in ADR-related admissions were antidiabetics. Hence, hypoglycaemic reaction was the most common event in these patients. This was in contrast with other studies Hallas et al. [83], Green et al. [134], and Rivkin et al. [84], which reported that gastrointestinal events due to NSAIDs and aspirin as most common ADR found in their studies.

Green et al. [134] in their study, reflected the possible for this: these drugs are most commonly prescribed drugs in the UK, thus, accounting for high incidence of ADRs relating to them. The study made by Rivkin et al. [84], on the other hand, used a population different from that of the current study: patients in an intensive care unit with severe ADRs such as bleeding.

The combination of glibenclamide and metformin was most frequently associated with hypoglycaemic reactions. However, almost 80% of patients admitted due to hypoglycaemia had poor oral intake prior to admission. A study and government statistics have shown metformin and glibenclamide to be the most utilised drugs in Malaysia [260, 261]. Furthermore, diabetes mellitus is one of the most prevalent medical conditions in Malaysia. In light of this, high utilisation of antidiabetics is expected. As indicated in the Malaysian Clinical Practice Guideline for the Management of Type 2 Diabetes Mellitus [262], metformin is the preferred choice of first line treatment. Patients who do not reach Hb1Ac (hemoglobin A1c) target of less than 6.5% after three to six months of metformin monotherapy or newly diagnosed patients who have Hb1Ac of 8-10% and fasting glucose level of 6-10 mmol/L, a combination is indicated [262]. In the guideline, metformin and glibenclamide are the suggested choice of combination therapy, probably due to cheaper price compared with other antidiabetics [263]. Thus, higher prevalence of hypoglycaemia in this study could also reflect high utilisation of these drugs.

Overdoses occurred due to ingestion of multiple drugs in one-thirds of the patients whilst paracetamol was most often, the drug ingested by more than half of the patients. All but one has ingested an overdose of drugs intentionally. The ingestion of multiple drugs as overdoses found in this study has also been reported in a study by Oguzturk et al. [166] in their research in Turkey. In common with previous studies [9, 122, 165], paracetamol was the most common drug associated with overdose-related admissions. Paracetamol is widely prescribed and available over-the-counter in Malaysia, and their predominance in overdose admissions could reflect their easy availability. Paracetamol is the second most commonly used substance in Malaysia in deliberate self- poisoning, the first being pesticides [165].

Antiplatelets (aspirin) were responsible for six out of 15 admissions related to ME, and three of the patients were prescribed aspirin without a gastro-protective drug (despite having history of gastritis or peptic ulcer). Similar with a previous study in the Netherlands, aspirin were found to have been prescribed to patients, who had high risk of developing GI bleeding without a prophylactic drug

[139]. However studies from Switzerland [148], the UK [134, 147] and Denmark [83] reported that NSAIDs were the most common drug group associated with MEs – resulting in GI bleeding.

2.4.3 Factors influencing the percentage of ADE-related admissions

2.4.3.1 Age

Seventy percent of 1200 screened patients were aged 40 years and above, with 21% aged over 64 years. The latter group of patients accounted for 26% of the ADE-related admissions. Older patients were more likely to be admitted due to an ADE. This has also been reported by previous studies [83, 146]. Similar results were found in admissions related to TF and ADR. The findings that older patients were more likely to be admitted for an ADR are similar with the results in previous studies of ADR-related admissions [11, 71, 83, 135, 264, 265]. It is possibly because elderly patients are likely to have a higher number of morbidities requiring prescription and are more sensitive to the adverse effects of drugs. Great care is essential when prescribing for this age group to avoid long-term adverse effects and TF.

2.4.3.2 Ethnic groups

Patients from Chinese ethnic group were less likely to be admitted for TF compared with patients from Malay and Indian ethnic groups. There is no study that allows comparisons of TF-related occurrences among different ethnic groups of Malaysia. However, a review of trends in cardiovascular diseases and risk factors in Malaysia revealed that Indians and Malay women were at higher risks of cardiovascular diseases due to high prevalence of high blood pressure, high blood cholesterol, glucose intolerance and being overweight [259]. Moreover, two studies have reported that the prevalence of diabetes was highest in the Indian ethnic group [33, 36]. Like Malaysia, Singapore is a multi-ethnic group with a majority of Chinese ethnic group (80%). A Singaporean study of multi-ethnic differences in diabetes found that Indians had higher prevalence of diabetes and poorer control of their condition [266]. Diabetes increases the risk of cardiovascular diseases, therefore, the high prevalence of cardiovascular diseases in Indians could be attributed to their said

high prevalence of diabetes [267]. Hence, this explains the higher proportion of TF-related, admitted patients from the Indian ethnic group.

Patients from Chinese ethnic group were more likely to be admitted due to ADRs. No studies have compared the occurences of ADR between Malaysian ethnic groups. However, pharmacogenetic differences between ethnic groups have been assumed the reason for susceptibility to different reactions [268, 269].

2.4.4 Methodological considerations

2.4.4.1 Patient screening method

This study was conducted prospectively (a major strength of this study), allowing the collection of complete and accurate information in evaluating and classifying ADEs. In the case of incomplete information on past medication, patients were interviewed for further information. Chart review method is known as a good method in identifying ADEs because it allows complete review of patient medical notes and charts [93, 94]. The most complete data, however, is collected through the use of multiple methodologies, such as computerised surveillance, incident reporting, intervention documentation, and patient and practitioner interviews. Since the study site did not have a computerised patient database, computerised surveillance or monitoring was not possible. However, if necessary, patients were interviewed to gain more information on their past medication history.

The prospective chart review method was piloted with the aim to ensure the highest possible number of patients screened in a day. The piloting meant that percentage of admissions screened in a day increased from less than half of the admissions to nearly all admissions, as patients were more likely available for review within 24 hours of admission, whilst the researcher was collecting data on that ward. However, half of the patients were still missed in both wards because the researcher visited the wards on alternate weeks. The basic information, such as, reason for admission, past medication and medical histories of these patients were not available. This would be necessary to ascertain in order to be confident that the patients screened by the researcher were indeed representative of all admissions to these two wards. Similarly, patients were missed when patient charts were not available for screening, for example when patients were attending to procedures such as scans and X-rays.

An attempt was made to include two pharmacists in screening all the cases in one ward while the researcher did the same in the other ward. However, although they were trained by the latter, the information collected by the two pharmacists were found insufficient to assess whether or not a patient was admitted due to an ADE. Thus, all the cases screened by the pharmacists were discarded. The data collection was restarted without the help of the two pharmacists because of changes in their work schedules, thus, making them no longer available to participate in the study.

Left single-handed with limited time, the researcher collected data from each ward on alternate weeks. As discussed in chapter 1 (section 1.5.1), chart review is labour intensive and a time-consuming method. A comprehensive study of all admissions would have required more researchers to collect data from the seven medical wards in the hospital.

Despite these criticisms, it seemed likely that the screening of ADE-related patients in this study was thorough. Data was collected systematically from two wards on alternate weeks, and a classification tool was used to systematically review all the cases in the same manner. Thus, the reported prevalence of admissions related to ADE is likely an accurate reflection of the true prevalence.

2.4.4.2 Case assessment and classification

The assessment of the admissions using a classification tool relied on the clinical experience and judgement of the researcher to classify ADE-related admissions. The reliability of the criteria assessed in 65 (10%) admissions showed a 'fair to moderate' agreement among the assessors. Furthermore, the percentage of ADE and types of ADE identified by the researcher was higher than the other assessors. This showed that different assessors have different clinical judgement which could be influenced by their different experiences. However, the enthusiasm and high interest of the researcher towards the study could have resulted in her identifying more ADEs compared with other assessors. Thus, the number of ADEs identified in this study may be an overestimate. Additionally, the information documented in the patient notes by attending physicians were assumed as accurate, thus, the assessments conducted were based on this information. Howard et al. [147] have included three assessors in their study to independently classify all the cases. After the independent classification, the three assessors met and majority decision was used to classify the cases where there were disagreements. The present study was not able to gather all the assessors to discuss and decide on the classification of the cases due to their different work schedules. Furthermore, the assessors were only able to assess 10% of the cases unlike the study by Howard et al. [147]. A lack of external validation may have caused an overestimate of the prevalence.

The main challenge in this study was to classify the ADEs into sub-types. As discussed in Chapter 1, all types of ADEs overlap and it can be difficult to distinguish one from another. Failure to appropriately classify cases may result in overestimation or underestimation of a sub-type. This problem is made

worse by a lack of standardisation in the terminologies. The pharmacist (assessor from the hospital) expressed that it was difficult to assess whether an admission was caused by TF without knowing the patient's adherence behaviour. Furthermore, the same pharmacist suggested that the assessment should be conducted whilst the patients were still on the ward so that further evaluation of an event could be done.

This study detected a high prevalence of TF-related admissions and highlights the areas for possible intervention. However, only a single assessor was responsible for detecting, assessing, and classifying all ADE-related cases. Thus, systematic misclassification of cases could have influenced the prevalence; in this case, the researcher identified a higher number of TF cases compared to other three assessors. Furthermore, patient adherence to medication was not assessed for all patients. Although likely to be a cause of TF, non-adherence was recorded in only 16% of the patients and the adherence status in the remaining patients is unknown. Due to this insufficient information, it was also challenging to differentiate whether or not an admission was due to therapeutic failure or progression of a disease. For example, the complaints of chest pain by patients classified under TF could be due to the progression of their disease. However, since the adherence status of each patient is not known, and whilst the patient complaints and medical interventions were suggestive of therapeutic failures, these cases were classified as TF. This highlights the importance of obtaining history of patient medication-taking behaviour to understand the underlying cause of uncontrolled diseases. Hence, the frequency of admissions due to TF is likely an overestimate.

The study was able to identify types of ADR and the drugs implicated in ADR-related admissions. Furthermore, all the ADR cases were sent to MADRAC for causality assessment and thus, have had an external validation. However, a lack of information of temporal relationship has resulted in 'possible' categorisation by MADRAC in almost all the cases.

Although 1.4% admissions were classified as ME, it is undeniable that a patient's medication behaviour could have influenced the occurrence of an error. For example, three patients were admitted due to GI bleeds but were not taking any prophylactic gastroprotective drug. However, it is unknown whether or not these patients have been prescribed a gastroprotective drug, as this was not reported by the patients and review of their medical and medication histories did not reveal such a prescription. Therefore, the prevalence of ME-related admissions is likely to be an overestimate or they could have been misclassified.

2.4.4.3 Choice of study setting

The overall aim of the study was to identify ADE-related admissions to a tertiary care hospital in Malaysia. The setting chosen was a typical government hospital suitable for identifying admissions associated with a broad range of medical conditions, and is likely to be representative of medical admissions to most government hospitals in Malaysia. However, the data from this study may not be representative of admissions to private hospitals because the characteristics of patients visiting these hospitals may be significantly different from those visiting the government hospitals. A study in Malaysia reported that a higher percentage of patients from Chinese ethnic group obtained treatment from private sectors compared to Indian and Malay ethnic groups [33]. This could explain the lower percentage of patients from Chinese ethnic group in this study. The generalisability of data from this study is further discussed in the next section.

Only two medical wards were selected for this study out of six. This selection was made by the head of medical department. These two medical wards serve as admissions wards (third class wards) and after further review and evaluation the patients may be transferred to a higher class ward (second class or first class wards) as explained in Chapter 1. Thus, the admissions to all medical wards are likely similar.

2.4.4.4 Generalisability of data

It is not known whether or not the admissions screened for this study are comparable with those not screened by the researcher and one of the major limitations was undersampling of cases each week (cases were missed alternately for one week in each ward as the researcher collected data in the other ward). Information on these cases such as age and reason for admissions are incomplete due to lack of documentation at the wards. Thus, a comparison cannot be made between the screened and unscreened admissions. However, since both wards were wards for general admission – one for males, the other, for females, the patients admitted to both wards are likely to be representative of the seven medical wards in the hospital. The results from this study, however, will not be generalisable to other types of departments such as intensive care unit, orthopaedic, or surgical because these population of patients in such will be very different to medical admissions.

The results of this study broadly reflect the health care practice in tertiary care. Therefore, the important factor in wider generalisability of this study is how representative this sample population is to the rest of Malaysia. Malaysia is represented by multiple ethnic groups. Malay ethnic group makes up 54% of the population, followed by Chinese (25%), and Indian (7%) ethnic groups [24]. In this study, 47% of patients were from Malay ethnic group followed by Indian (36%), and Chinese (13%). The population in this study does not reflect the ethnic group distribution of the Malaysian because patient attendance at the public hospitals differs by ethnic groups [33]. However, it is likely to be representative of the Malaysian patient-population attending government hospitals as compared to private hospitals.

2.4.4.5 Ways in which this chart review study could have been strengthened

The study would have been strengthened if all admissions to the medical wards had been prospectively screened and followed up throughout their admission. The medical wards in the study site received 10 to 20 admissions each day. Therefore it was not feasible to screen all these admissions with only one researcher collecting the data. Appointing a research assistant to collect data on one of the wards could have solved this problem. Although two pharmacists were recruited to assist with data collection, initial problems and changes in their professional work patterns hindered this from happening through the study. A thorough training of at least one month would need to be given to a research assistant so that he or she becomes familiar with the patient record system and data collection form. Additionally, an inter-rater test would need to be conducted to ensure data has been collected and assessed in the same manner.

Each patient was screened on admission and data were checked so that the next day any queries could be followed-up. However, charts for each patient were not checked daily for their entire hospital stay. It was not feasible to do this because, for instance, if a patient's duration of hospital stay was for three days, it would have meant screening as many as 40 to 60 charts in a day.

The study would have been also strengthened if all patients were interviewed to determine their adherence status. However it was not feasible to interview 10 to 20 patients a day, in addition to screening 10 to 20 charts with only one researcher. It was likely that not all patients would be well

enough for an interview, particularly on the first day of admission. However, gaining data on each patient's adherence status would have allowed easier classification of events.

Therefore, the methodology used in this study was the most appropriate given the available resources.

2.4.5 Implications

Health care system and health care professionals

This study revealed that 70.5% of patients on medication were admitted due to ADEs and based on the results from the current and previous studies, ADEs continues to be a considerable burden on health care systems. This warrants for a continuous monitoring of patients on medication. It is important that prescribers determine the need for a particular drug in patients and whether or not it is appropriate for them. Additionally, prescribers should continuously monitor or follow-up on patients and the progress in their medical conditions, to ensure that the therapy given is adequate or appropriate.

One of the important issues observed in this study was the lack of information on patients' past medical and medication histories which could result in inadequate monitoring of progress of the patients. If a patient followed-up with physicians in government hospitals, they were given a 'small book' where the details of their past medical and medication were documented. Patients are to carry the book every time they visit the hospital. However, some patients in this study were found to have lost the book or forgotten it, giving limited information about their past treatment. Furthermore, medical treatments received in private institutions are usually not documented in a 'small book'. Perhaps, there is a need for a better system for recording patient medical and medication histories, as well as, information linkage between the government and private institutions to ensure that progress of patients are monitored continuously.

Cardiovascular diseases are the principal cause of admissions and death in Malaysian public hospitals [25]. Poor control of these medical conditions could worsen the situation. Furthermore, hypertension and diabetes mellitus are the major predisposing risk factors for many cardiac complications. Poor control of these medical conditions could increase the risk of cardiovascular events. Thus, it is important to recognise patients with established cardiovascular disease or those at high risk of it to prevent the recurrence of the event, and provide advice to patients regarding the importance of adherence, the impact and risk of an uncontrolled medical condition. With the current situation in public hospitals in Malaysia which are always crowded, it is not possible for physicians to provide a one-to-one care for patients, let alone a counselling service. These provide opportunities for

pharmacists to play their role, and their involvement in educating patients with regular, follow-up check-ups have been shown to improve disease management and medication adherence of patients [270, 271]. The implementation of MTAC services in certain public hospitals in Malaysia is one of the strategies provided by pharmacists to improve patient medication adherence behaviour. This service has been reported to increase the medication adherence and better disease control in patients who have attended eight counselling sessions with a pharmacist [211]. More MTAC services should be encouraged in all hospitals – public and private sectors, and at community level – community pharmacy. In educating patients on adherence to medication, pharmacists should be trained to recognise patients at high risk of disease complications to ensure they are referred to such services or reminded about adherence regularly. Patients who were admitted for recurrent or poor control of their medical conditions should be enrolled to the MTAC service and regularly monitored. To guarantee the quality of the services provided in the clinic, it is important to have a protocol or guideline to ensure minimum standards of all hospitals.

Malhotra et al. [153] reported in their study that a greater number of physicians regularly consulted by patients was one of the factors associated with increased risk of hospitalisation related to non-adherence. In view of the current health care system in Malaysia, this poses a great danger to patients. A lack of coordination in the primary care level may have contributed to poor control of medical conditions. Steps need to be taken to minimise the 'physician-hopping' habits of Malaysian people so that the care they receive is consistent and adequately monitored. The mixed treatment in the private and public sectors could create confusion to patients and thus increase the risk of ADEs. There should be a system that allows practitioners to have access to complete patient information – past medical and medication histories, drug allergies, and OTC drugs, and this should be made available to all the practitioners a patient consults with. Primary care practitioners also play crucial role in educating patients about the safe and effective use of prescription and non-prescription drugs. Thus, providers must allow sufficient time for consultations with patients about medication management. Primary care practitioners, particularly in the private sector should work closely with MOH to ensure that their disease management practice is according to the guideline and protocols developed by MOH.

Although, MOH has taken steps to increase the number of public clinics and hospitals in Malaysia, the overcrowding of patients is still a problem. This may have forced the public to seek treatment from the private sector. However, some patients without the insurance coverage may find the costs too high and thus may not receive a comprehensive care. It would be a good strategy to introduce a national insurance scheme available for all Malaysians so that patients can receive treatment in any health institutes without the concern about costs and waiting in long queues.

In this study, most ADRs were predictable from the known pharmacology of the drugs and therefore, likely to be preventable (especially hypoglycaemic reactions found in most patients). The main reason for admission related to hypoglycaemic reaction was poor oral intake prior to admission. This indicates lack of knowledge about disease management and drug therapy among patients. Since the physicians and pharmacists are responsible for providing adequate information about drug effects, the blame falls on the health care system. As hypoglycaemia is a prominent problem in diabetic patients, prescribers should be vigilant when prescribing antidiabetics and ensure that patients have adequate knowledge about their medicines. It is important that primary care practitioners provide information about side effects, contraindications, and how to recognise and handle adverse reactions, as well as where to obtain high quality information.

Many countries such as the UK and France have restricted the sale of paracetamol [168]. Other than the habit of selling paracetamol in individual blister rather than tablets, there is no sale restriction on its amount that can be sold in Malaysia. Furthermore, other than obtaining paracetamol from a pharmacy, paracetamol-contained products can also be purchased from convenience stores. This explains the popularity of this pharmaceutical agent in intentional self-poisoning. Restricting the amount of paracetamol or paracetamol-contained products sold at one time may be a good strategy to reduce the rate of overdose related to it. Studies in some countries show reduction in the rates of overdose since the introduction of such restriction [272, 273].

Although the product packaging of OTC drugs always comes with an overdose warning, OTC drugs sold in blister strips do not include information about the appropriate dose or warning about the dangers of overdose. This places the health care professionals in the best position to warn patients,

or counsel them about OTC drugs, to reduce the potential risk of misusing them, especially, taking more than the required dose.

The fact that Malaysians are able to get treatment from any GP or pharmacist could be detrimental to their health. This, not only encourages 'doctor- or pharmacy-hopping' by patients, it could also pose danger of possessing multiple drugs obtained from visits to different practitioners, which may be ingested by anyone with suicidal intention. The 'freedom' of obtaining treatment from different practitioners is in part, due to primary care being a private transaction and without system of registration with doctors. The current system needs improvement especially in sharing of patient information among hospitals, general practitioners (GPs), and pharmacies.

It is reported that previous ulcer history, aspirin, NSAID and *Helicobacter pylori* are the risk factors for GI bleed [274, 275]. The strategies to reduce the risk of drug-induced GI bleed should, therefore, include minimising the use of aspirin in patients with known history of GI bleed, or who are at high risk of such (for example, one who was already prescribed a drug which can cause it). Thus, it is the responsibility of health care professionals to obtain accurate and thorough medical and medication histories of patients before prescribing a drug. When use of aspirin is unavoidable, patients should be prescribed a gastroprotection drug (such as proton pump inhibitor or misoprostol) to reduce the risk of GI bleed [276]. The risk factors for GI bleed have been published in a local guideline [274] and practitioners should be encouraged to adhere to it during the prescribing process.

Patients and society

The drugs implicated with TF-related admissions (cardiovascular drugs, anti-asthmatics, and anti-diabetics) confirm their key role in TF. Treatment with such drugs may have a high risk of poor adherence due to being used for long-term therapies. Patients with cardiovascular diseases were found at higher risk for TF-related admissions. Cardiovascular disease itself is a complex medical condition, therefore, patient should be educated about the disease, complications, and consequences of poor control of their condition. While emphasising the importance of disease control, it is important to also identify the risk factors and causes of poor control to implement

preventative strategies. Many studies have identified poor adherence to medication as the most common cause of TF [9, 83, 146, 152]. However, poor adherence does not only relate to medication-taking behaviour but also to lifestyle changes, such as dietary control. Thus, educational programs for patients should emphasise the importance of adherence, dietary control and other lifestyle changes.

Hypoglycaemic reactions are a known side effect of anti-diabetic drugs. Patients' lack of awareness of their condition and poor oral intake after these drugs could precipitate a hypoglycaemic reaction. In this study, a female patient developed prolonged hypoglycaemic reaction and this was not recognised by her family members. She was hospitalised and diagnosed with neuroglycopenia coma. Neuroglycopenia is caused by deprivation of glucose in the brain resulting from chronic hypoglycaemia [277]. The early symptoms which develop in response to a low blood glucose level such as, sweating, tachycardia, and tremor could alert patients and their families to take necessary actions (ingestion of sugar by the patient) [278, 279]. However, failure to recognise these symptoms can lead to development of neuroglycopenia, and ultimately, death. This illustrates the importance of recognising hypoglycaemic symptoms, and how lack of information can be detrimental to patients. Therefore, it is vital for patients and their family members to be well informed about the effects, monitoring steps, and management of any side effects at an early stage.

One of the strategies of preventing hypoglycaemia as suggested by NHS is regular self-blood glucose monitoring for early identification [280]. Self-monitoring of blood glucose provides the possibility of collecting information on blood glucose level at different time points, which could allow adjustment of therapy in response to blood glucose level [281]. This has been associated with improved outcomes [282, 283]. Thus, blood glucose self-monitoring should be recommended to all patients with diabetes. However, the self-monitoring program should be individualised and the program should take into account the patient's disease control level and type of therapy [284].

Educational interventions for the public should be provided to increase their awareness about the impact and risks of DOs. They should also be advised on the proper storage of their drugs. Patients should be encouraged to return their unused medication either to nearby hospitals, clinics or pharmacies. This may help in preventing intentional drug overdoses using multiple drugs. Women particularly, should be encouraged to reach out for help, such as from 'Befrienders'[285] a non-

profit organisation run by volunteers that provide emotional support and telephone counselling to its caller, or family, and friends in case of emotional distress.

It is important that patients are advised on the importance of adhering to medication that reduces the risk of GI bleed. Furthermore, patients should be made aware that concomitant use of OTC drugs such as NSAID, together with aspirin, increase the risk of GI bleed. A patient's medical and medication histories are important in evaluating his or her suitability for the drug. Thus, patients should be encouraged to disclose their medication-taking behaviour to the health care professionals, so that an appropriate therapy is planned for him or her.

Future research

- The prevalence of ADEs identified through this study is high compared to other published studies. This figure is rather alarming and creates speculation on ADEs being supposedly, a really big problem in Malaysia. Since this study was conducted only in two wards of only one hospital, it may not be able to give a bigger and clearer picture of the actual burden of ADEs in Malaysia, thus, a larger study involving more than one hospital is needed. Additional to this, due to differences in the characteristics of the population visiting the government and private healthcare institutions, it would be practical to involve the private institutions as well in the proposed future study. This large study should involve more manpower to collect data to avoid missing cases and data, and inter-rater reliability test should be conducted to ascertain the reliability of the data collected.
- The present study showed that TF was major cause of admission but was not able to identify the causes or risk factors of TF. This should be investigated to provide an insight into the problem and highlight areas for intervention. As patient adherence behaviour is an important determinant for TF, further investigation on this should highlight the factors associated with non-adherence and suggest ways to improve the opposite. This can be done through patient interviews.
- Similarly, patient interviews can be conducted to understand the underlying reasons for admissions related to hypoglycaemia. Patients' understanding about disease management and drug therapy should be evaluated to identify the root cause of hypoglycaemia-related admissions. This would provide information whether a better patient education is needed to overcome this problem.
- This research revealed that the rate of admissions due to overdose is actually higher than the reported results in previous studies [164, 165]. However, a larger, prospective, multi-centred study is needed to provide an insight of the demographic profiles of DO-related admissions and therefore, determine the area for interventions. A number of studies have already been conducted in public hospitals, therefore, overdose cases should also be investigated in the private sector. Furthermore, research on the type of drugs used in these cases and where they are obtained could as well suggest areas for prevention strategies.

- The restriction of the amount of paracetamol sale was found to have reduced overdose cases in a few countries [272, 273]. Perhaps, this approach should be proposed and a study could be designed to evaluate whether or not similar outcomes can be achieved in Malaysia.
- Antiplatelet has been found to be the main cause of admissions related to ME. However, it is not known whether or not errors resulting from this drug group are attributable to lack of knowledge about patients or poor prescribing by doctors. Thus, further investigation is needed in this area to understand the underlying cause resulting in ME-related admissions. This will suggest ways to minimise or prevent future errors.

2.5 Summary

This study found that 39% of admissions in two medical wards were related to drugs. TF was the highest contributor to these admissions with poor control of cardiovascular conditions being the most frequent reason for such admissions. The prevalence of ADRs was 8.4% and hypoglycaemia associated with the use of anti-diabetics was the most common symptom that led to these admissions. The prevalence of admissions due to overdoses and MEs were small (2.0% and 1.4% respectively) but comparable with other studies.

CHAPTER 3

SURVEY STUDY

A questionnaire was designed using new questions and previously published questions to explore the experiences of health care professional of ADEs. The questionnaire was tested by piloting during a pharmacy seminar. A population survey was conducted using the piloted questionnaire to investigate the experiences of pharmacists about ADE – its types, the drugs involved, and actions taken in response to ADEs. In addition, the experiences of hospital and clinic pharmacists were compared with those of the community pharmacists'.

3.1 Objectives

The objectives of this survey were:

i) To investigate whether or not pharmacists were able to observe occurrences of ADEs during their daily work activities

ii) To identify the strategies taken by pharmacists to solve the ADEs observed

iii) To evaluate whether or not the pharmacists are aware of the role of MADRAC and ADR reporting system

3.2 Method

3.2.1 Development of the questionnaire

A questionnaire was designed following a literature search and discussions with supervisors (Appendix 7). It included previously validated questions [216, 219, 232] and alongside, new questions to determine the experiences of Malaysian health care professionals of adverse drug events.

The questionnaire contained 52 items with six sections: (i) awareness of ADR, (ii) attitudes towards ADR reporting, (iii) awareness of TF, (iv) awareness of other ADEs, (v) demographic information, and (vi) feedback about the questionnaire. Majority of the questions were closed questions with categorical answers, and 10 to 15 minutes were given to complete the questionnaire. Respondents were requested to recall the ADEs they had observed in the last six months and answer the questions based on that. A summary of the questionnaire contents follows.

Experience of observing ADRs

3.2.1.1 Percentages of ADRs occurring in Malaysia- all respondents

Respondents were asked to estimate the percentage of suspected ADRs and severe ADRs that occur in Malaysia. Respondents were expected to answer these questions based on their experiences, rather than based on the previously reported levels.

3.2.1.2 Experience of observing ADRs and actions taken- respondents who have observed ADRs

Respondents were asked if they have observed ADRs in their daily activities in the last six months and if so, were asked for descriptions of such in terms of frequency and its type they have encountered most recently. Additionally, they were asked to report the specific actions they took upon encountering one.

3.2.1.3 Experiences of patients reporting ADRs and actions taken- all respondents

Respondents were asked whether or not they have received any ADR-related reports from patients and if so, were asked for descriptions of the group of patients who reported ADRs most frequently, and the type of ADRs most frequently and recently reported. Additionally, they were asked to recount the specific actions they took after receiving a report.

3.2.1.4 Attitudes or awareness on spontaneous reporting- all respondents

Respondents were asked to select from a list the factors that encourage and discourage them from reporting a suspected ADR. They were also asked about their awareness of the following: reporting system in Malaysia, the existence of a reporting system, availability of report forms, places or areas where to obtain them, and purpose of collating the reports from across Malaysia. Furthermore, respondents were asked their manner of preference in reporting ADRs (online, fax, phone, email, or post) and type of ADRs they think should be reported.

Experiences of observing therapeutic failures

3.2.1.5 Percentages of TF occurring in Malaysia- all respondents

Respondents were asked to estimate the percentage of TFs that occur in Malaysia. They were expected to answer based on their experiences rather than their knowledge of its prevalence based on previous studies.

3.2.1.6 Experiences of observing TFs and actions taken- respondents who have observed TFs

Respondents were asked whether or not they have observed TFs in their daily activities and if so, were asked for descriptions of the observed TFs in terms of frequency, the disease or therapy associated with the observed TFs, and the type of TFs they have encountered most commonly and

recently. Additionally, they were asked to report the actions they took in response to an observed TF and describe the group of patients they usually encounter with TFs.

Experiences of observing medication errors, adverse drug withdrawal syndromes and drug overdoses – respondents who observed medication errors, adverse drug withdrawal syndromes and drug overdoses

Respondents were asked whether or not they have observed MEs, ADWS, and DOs during their daily activities and if so, were asked to describe the frequency of encounter with them. Respondents were also asked about the type of DOs they experienced and the drug involved in the most recent case.

Demographics – all respondents

All respondents were asked to answer this section which includes gender, state of residence, highest level of education, work area, and number of years of practice as a pharmacist. Additionally, respondents were asked their educational and professional specialisations.

Comments about the questionnaire- all respondents

Respondents were asked whether or not all the questions were clear and easy to understand and if not, state which questions were unclear and answer why. They were also asked of the time span it took them to completely answer the questionnaire and the manner they prefer to answer a similar questionnaire in the future. Respondent were also given space to write their comments about the questionnaire.

3.2.2 Piloting and testing the questionnaire

Ethical approval was obtained from the Division of Social Research in Medicines and Health, School of Pharmacy, University of Nottingham, and UK and permission for conducting the survey, from the President of MPS.

The questionnaires were handed out to pharmacists attending a three-day pharmacy seminar organised by MPS. The seminar was held in conjunction with the MPS annual general meeting and was targeted at pharmacists from all sectors of the profession.

Pharmacists were approached during the seminar registration, tea or meal break by the researcher and details of the survey were briefly explained. An information sheet (Appendix 8), together with the questionnaire (Appendix 7) was provided to prospective participants. The questionnaires were distributed to the pharmacists over all three days of the seminar which was attended by around 400 pharmacists. Announcements between the talks were made by the organiser to encourage pharmacists to complete the questionnaire. Respondents were asked to drop off the completed questionnaire in a box placed at the registration counter.

The testing of the questionnaire addressed the following:

i) Response rate

- The proportion of completed questionnaire returned out of the quantities distributed [286]

ii) Internal consistency

- Refer to different items which aim to measure the same or similar things

iii) Completion rate

- Percentage of respondents responding to all questions

3.2.2.1 Results from piloting and testing the questionnaire

3.2.3 Response rate

Two hundred and nine (n= 209) questionnaires were distributed and 122 completed questionnaires were returned giving a response rate of 58%. Demographic details of pharmacists are shown in Table 3-1. Most of the respondents were female (n=97, 80%), while almost 80% of them have been practicing pharmacy for five or less years (n= 92, 76%). Furthermore, almost four-fifths (n= 95, 78%) of the respondents worked in the hospital setting.

Table 3-1: Characteristics of the respondents (n= 122)

	Number of respondents (%)		
	Hospital (n= 95)	**Community (n= 12)**	**Other[a] (n= 14)**
Gender (n= 121[b])			
Male (n= 24)	17 (17.9)	5 (41.7)	2 (14.3)
Female (n= 97)	78 (82.1)	7 (58.3)	12 (85.7)
Years of work experience (n= 121[b])			
More than 5years (n= 29)	24 (82.8)	5 (17.2)	-
5years or less (n= 92)	71 (74.7)	7 (58.3)	14 (100.0)
Level of education (n= 121[b])			
Bachelor's degree (n= 114)	88 (92.6)	12 (100.0)	14 (100.0)
Master's degree (n= 7)	7 (7.4)	-	-

[a] *other includes respondents working at a pharmacy enforcement (n= 8), government health clinic (n= 4), state health department (n= 1) and industrial sector (n= 1).*
[b] *these groupings do not total 122 due to missing data*

3.2.4 Completion rate

Completion rate for the 52 items in the questionnaire ranged from 1 to 100% (Table 3-2). Majority of the items had completion rates of 90% or more. High completion rates were seen in sections on ADRs, where all items had more than 90% completion rates. Questions related to ADWS had completion rates of 80 to 86%, and a question about drug groups associated with DO had completion rate of 81%. Furthermore, questions related to the type of patients associated with TF and its most common type had completion rate of less than 90%. The lowest completion rates were obtained from open questions that ask respondents to state their 'education specialisation', 'profession specialisation', and 'comments about the questionnaire' (completion rate, less than 20%).

Table 3-2: **Completion rates of the 52 items in the questionnaire (n= 122 respondents)**

Question (question number)	Number of respondents expected to answer	Number of respondents answered	Completion rate
Percentage of ADRs in Malaysia (Q1a & Q1b)	122	121	99.2%
Observed a suspected ADR (Q2)	122	122	100.0%
Frequency of ADR (Q3)	107	107	100.0%
Frequency of recent ADR (Q4)	107	106	99.1%
Symptoms of recent ADR (Q5) - multiple choice	107	107	100.0%
Actions taken in response to observed ADR (Q6) - multiple choice	107	107	100.0%
Patient reported ADR (Q7)	122	122	100.0%
Group of patient who report (Q8)	104	100	96.2%
Most frequent patient-reported ADR (Q9)	104	90	86.5%
Most recent patient-reported ADR (Q10) - multiple choice	104	103	99.0%
Actions taken in response to patient-reported ADR (Q11) - multiple choice	104	104	100.0%
Factor encouraging ADR reporting (Q12)- multiple response	122	120	98.4%
Factor discouraging ADR reporting (Q13)- multiple response	122	113	92.6%
Preference to report ADR (Q14)- multiple choice	122	120	98.4%
Aware of a form to report ADR (Q15)	122	120	98.4%
Aware of where to obtain the form to report ADR (Q16)	117	117	100.0%
Where to obtain the form (Q17)- multiple choice	117	115	98.3%

table continued.....

Table 3-2 continued: Completion rates of the 52 items in the questionnaire (n= 122 respondents)

Question (question number)	Number of respondents expected to answer	Number of respondents answered	Completion rate
Aims of monitoring ADR reports (Q18)- multiple choice	122	122	100.0%
Which ADR should be reported (Q19)- multiple choice	122	122	100.0%
Percentage of therapeutic failures in Malaysia (Q20)	122	121	99.2%
Observed a therapeutic failure (Q21)	122	120	98.4%
Types of therapeutic failure encountered (Q22)- multiple choice	84	84	100.0%
Most common therapeutic failure (Q23)	84	73	86.9%
Frequency of observed therapeutic failure (Q24)	84	84	100.0%
Frequency of recent therapeutic failure (Q25)	84	77	91.7%
Actions taken in response to observed therapeutic failre (Q26) - multiple choice	84	84	100.0%
Types of disease/ therapy associated with therapeutic failure (Q27)- multiple choice	84	84	100.0%
Group of patient therapeutic failure observed - age (Q29)	84	84	100.0%
Group of patient therapeutic failure observed - gender (Q29)	84	75	89.3%
Group of patient therapeutic failure observed - race (Q29)	84	74	88.1%
Observed a medication error (Q30a)	122	119	97.5%
Observed a adverse drug withdrawal syndrome (Q30b)	122	105	86.1%
Observed a drug overdose (Q30c)	122	110	90.2%

table continued...

Table 3-2 continued: Completion rates of the 52 items in the questionnaire (n= 122 respondents)

Question (question number)	Number of respondents expected to answer	Number of respondents answered	Completion rate
Frequency of observed medication error (Q31a)	122	113	92.6%
Frequency of observed adverse drug withdrawal syndrome (Q31b)	122	98	80.3%
Frequency of observed drug overdose (Q31c)	122	102	83.6%
Cause of drug overdose (Q32)	122	114	93.4%
Drug group associated with drug overdose (Q33)	84	68	81.0%
Gender (Q34)	122	122	100.0%
State of residence (Q35)	122	112	91.8%
Highest level of education (Q36)	122	121	99.2%
Specialization in education (Q36a)- open question	122	1	0.8%
Profession (Q37)	122	121	99.2%
Specialisation within profession (Q37a)- open question	122	7	5.7%
Number of years working as pharmacist (Q38)	122	122	100.0%
Questionnaire clear and easy (Q39)	122	116	95.1%
Comments on the clarity and level of difficulty of the questions (Q39a)- open question	9	9	100.0%
Time taken to answer all questions (Q40)	122	116	95.1%
Preference to answer future questionnaire (Q41)	122	112	91.8%
Other comments (Q42)- open question	122	18	14.8%

3.2.5 Internal consistency

Consistency was expected between responses of two pairs of items in the questionnaire. These items were compared. The consistency was 95% and 100% (Table 3-3).

Table 3-3: Test of internal consistency of questionnaire responses

First-question response	Number of respondents	Second-question response	Number of respondents	Consistency
Involvement of a new drug encourage reporting	84	Reactions to new drug should be reported	80	95.2%
Unusual/ unexpected reactions encourage reporting	74	Unusual/ unexpected reactions should be reported	74	100.0%

3.2.6 Comments of respondents about the questionnaire

Almost all respondents (n= 112, 92%) reported that the questionnaire was clear and easy to understand. The comments given by the respondents who disagreed are summarised in few points (Figure 3-1). Respondents reported that some of the questions using the phrase 'most common,' 'most recent,' 'most frequent,' and 'ever' were confusing. They have also stated that some questions were not clear (question about the cause of DO – question number 32), repetitive (questions about factors encouraging and discouraging ADR-reporting – question numbers 12 and 13), and too general (questions about the percentage of ADR and TF occurring in Malaysia) and lengthy.

The respondents reported that the average time taken to answer the questionnaire was 16 minutes (SD 8.7), a minimum of 5 minutes, and a maximum of 60 minutes. When asked about the preferred mode of answering similar questionnaire in the future, almost 60% (n= 68, 56%) preferred email over post (n= 25, 20%). Second preference is face-to-face (n= 20, 16%), and third is telephone (n= 1, 1%).

Figure 3-1: Comments of respondents about the questionnaire

1) Confusing
a) the use of "most common", "most recent" and "most frequent"
b) the phrase sub-optimal dosage and inadequate dosage
c) the use of "ever"

2) Not clear
a) question regarding the cause of drug overdoses
b) some questions were ambiguous

3) Repetitive questions
a) questions regarding factors encouraging and discouraging ADR reporting were overlapping

4) Questionnaire is too lengthy

5) Too simple and general
a) questions regarding the percentage of occurrence of events were too general

3.2.7 Discussion of results from piloting and testing of the questionnaire

The completion rates for questions were generally good with majority being more than 90%. A few questions generated a completion rate less than 90%. Questions about ADWS fell into this group. The reasons could be that the respondents may be unfamiliar with the term ADWS, or have poor knowledge of ADWS and therefore, are more likely to find the questions hard to answer. Open questions had the lowest completion rates, especially about the educational specialisation and professional specialisation. The reason could be that pharmacists' specialisations are yet to be established in Malaysia. In connection, only a small number of respondents reported having achieved a higher degree and would be more likely to specialise in certain fields. Thus, pharmacists with bachelor's degree, who were the majority of the respondents, may be generalists rather than specialists.

As about internal consistency, very few respondents were found with inconsistent answers. However this was only done for four questions. Four respondents who have reported that reaction involving new drug encouraged them to report ADR (question number 12), but in another question (question number 19), did not state that reactions involving such should be reported.. Possible reason could be that respondents were not sure what type of reactions should be reported.

3.2.8 Strengths and limitations

The mode of distributing the questionnaire allowed the researcher to personally explain the purpose of the survey to the respondents. It also allowed the respondents to interact with the researcher when they had questions. This is likely to increase the response rate.

In this survey, respondents were asked to report their preferred mode of answering future questionnaire, allowing planning for the main study.

However, there is no gold standard to identify or detect an ADE, and observing one is subject to individual interpretation and clinical judgement. The ADE definitions given in the questionnaire may not be the same as the ones known and used by the pharmacists. Furthermore, the questions did not

mention about time frames of an observed ADE (e.g., six months ago or three months ago). Hence, the observed ADE reported by the pharmacists could be, for example, of one observed one year ago – a time frame obsolete enough to make the reported event significantly irrelevant to the research. Therefore, in the main study, a time frame will be asked in the questions.

3.2.9 Review of pilot questionnaire and amendments prior to the main survey

The questions with low completion rate were reviewed for changes prior to the main study. Some new questions were added to have a common pattern of questions in all the sections. The following amendments were made to the questionnaire:

1) Percentages of ADR and TF occurring in Malaysia

   Questions that asked about the percentage of ADR and TF occurrences (question numbers 1a, 1b, and 20) were deleted. There is no data on the occurrences of ADR and TF in Malaysia, and these questions will be answered by the respondents based only on their experiences. Furthermore, the researcher was not able to compare the answers given with any data. These questions were added based on a study conducted in Italy [216], and may not be suitable for one that is conducted in Malaysia due to lack of available data for comparison.

2) Symptoms of the most recent observed ADR

   Initially, the symptoms of ADRs in question 5 (section A) were derived from the literature [216, 232]. Following the pilot study, a longer list was created based on the answers given by respondents and the common ADR symptoms listed by MADRAC [287].

3) Drug associated with recently observed ADR

   In the pilot study, pharmacists were asked whether or not they have observed any ADR and to list down the types of reactions they have observed. However, the drug(s) that were associated with the reaction(s) were not asked. It would be useful to know what types of

drugs are associated with the reactions observed by the respondents, and whether or not respondents working in different settings observe reactions to different types of drugs. Thus a new question was added to identify the type of drug(s) associated with the ADR observed by respondents. The list of drugs was obtained from MADRAC annual report which has listed the type of drugs most commonly reported to them [287].

4) Patients reporting ADRs

Questions about patients reporting ADRs were deleted (question number 7 to 11). Upon discussion with supervisors, it was decided so because it was found that they may overlap with questions about the pharmacists' experiences of observing ADRs.

5) Therapeutic failure

Questions that asked about the types of observed TF (question number 22, 23 and 26) were deleted. All three questions had similar answers and in order to identify the reason or cause of TF, further investigation need to be done. It is not known whether or not the respondents would have been able to conduct further investigations and correctly classify the TF observed according to the list. Furthermore, the completion rate for question 23 was less than 90%, and this may indicate that respondents were unsure how to answer. Thus, based on discussions with supervisors, these questions were deleted.

The question about the patient group most commonly associated with TF was deleted (question number 29). This question was found to be too general as reported by some of the respondents. The group of patients most commonly encountered with TF cannot after all, be generalised based on the respondents' experiences or observation.

6) Medication error

As discussed in chapter 1, ME overlaps with other types of ADEs. The question on whether or not respondents have recently observed ME will not be able to provide details on what the respondents have actually observed – it could be a TF or an ADR. For this reason, a list of

types of ME was added. This means that not only the different types of MEs observed by them may be identified, but this also allows comparisons of types of MEs observed by hospital and community pharmacists. Additional questions about the actions taken in response to the observed ME were incorporated to be consistent with other sections. Since the questionnaire is designed for both hospital and community pharmacists, all types of ME were included in questions about types of MEs observed in the last six months. Thus, the types of MEs identified during the chart review study (Chapter 2) are only a small part of this list.

7) Adverse drug withdrawal syndrome

Questions asking about ADWS were deleted (question number 30b and 31b). The chart review discussed in Chapter 2 did not identify any ADWS and studies found that it is difficult to identify and are rare [175, 178]. In addition, the completion rates for these questions in the pilot study were less than 90%. Considering all these factors, these questions were deleted.

8) Drug overdose

Additional questions about the actions taken as responses to the observed DO were incorporated. This is to ensure consistent and similar questions in all sections.

9) Time frame

A time frame was indicated in some questions (question numbers 2, 21 and 30), thus, questions about the time frame of recently observed ADEs were deleted (question numbers 4 and 25).

10) Demographic

Questions about educational and professional specialisations were deleted (question numbers 36a and 37a). Pharmacist specialisation is still new in Malaysia and this was evident in the completion rates for these questions which were less than 10%.

Additional questions were numbered 4, 6, 21, 22, and 26 in the revised questionnaire (Appendix 9). The deleted questions were numbered 1a, 1b, 7 to 11, 20 to 25, 29, 36a, and 37a in the pilot questionnaire (Appendix 7).

3.2.9.1 Methodological issues

The content of survey for other health care professionals was also validated by a few doctors, nurses, and research supervisors after the pilot study (Appendix 10). Approval was obtained from National Institutes of Health, Malaysia to distribute the questionnaire to all health care professionals working in the medical wards of the study site where the chart review study took place (Appendix 11). The survey was planned to be distributed during a few internal hospital meetings. However, due to lack of willingness from the head of department on the day of distribution, it could not be conducted (before this day he had given his support for the survey and approved of the said distribution during meetings). Approaching health care professionals individually was suggested by the head of department, but this was not possible due to time constraints. Thus, the survey was only conducted among Malaysian pharmacists.

3.2.10 Main survey population sample

There are more than 6,000 pharmacists in Malaysia. There are about 2,000 pharmacists registered as members of Malaysian Pharmaceutical Society (MPS). MPS stores the contact details of all its

members. They consist of 750 (38%) hospital and health clinic pharmacists, 727 (36%) community pharmacists, and 523 (26%) working in other sectors such as industrial and education institutions.

Since this study aims to explore their experiences of ADEs during their daily work activities, pharmacists needed to have patient contact to be able to identify or detect it. Industrial pharmacists and academics do not usually have direct patient contact in their daily work activities. These categories of pharmacists were not included in this study. Thus, all 1477 (74%) hospital, health clinic, and community pharmacists were included in the main survey study.

Based on the findings from the pilot survey, most of the respondents preferred email over post as a method of receiving and responding to questionnaires. However, confidentiality constraint meant the MPS was not able to provide the researcher with email addresses of all its members. After further discussion, the MPS agreed to post the questionnaires on behalf of the researcher. The home or office addresses of its members were not given to the researcher but the researcher prepared envelopes containing all the documents for the survey. Thereafter, MPS addressed the envelopes and posted the survey.

3.2.11 Mailing method

The questionnaires were given serial numbers matching those of the pharmacists' records at MPS database. The survey packs contained a cover letter explaining the survey (Appendix 12), the questionnaire (Appendix 9), and a post-paid return envelope.

On return of the completed questionnaires, the serial numbers of the questionnaires were entered in a mailing database. The serial numbers of non-respondents were then given to the staff at MPS, together with a second survey pack which contained the same questionnaire, an edited cover letter, (Appendix 13) and a post-paid return envelope.

3.3 Data analysis

Statistical analysis was performed in Predictive Analytics SoftWare (PASW) Statistics 18.0 (© SPSS, Inc., 2009, Chicago, IL).

3.3.1 Data cleaning and checking

The survey questions were coded and all data were entered in PASW. In order to ensure the data were entered accurately and completely, frequencies of variables were computed and checked for values outside possible ranges. A random five percent of cases (n= 24) were selected and data entry for these cases was compared with the data in the questionnaires. Data entry errors were found in four questionnaires and cleaned.

3.3.2 Descriptive analysis

Frequency and percentage tables were used to describe the demographic data of respondents, their experiences of ADEs, types of ADEs or drugs, and their ADR-reporting attitudes, and the experiences were compared across work setting. Drugs were classified into therapeutic classes and ADR symptoms, according to organ systems. The frequency of observing ADEs was categorised into two groups: i) observation of one or more ADEs per month (which included ADE-observation of at least one per day, per week, or per month) and ii) observation of less than one ADE per month or its absence.

3.3.3 Difference between groups

The chi-square was used to assess whether or not there was a difference in the response rates of pharmacists according to years of work experience and work setting, where appropriate. Differences were considered statistically significant when p-value was less than 0.05.

3.4 Results - Survey response

A total of 1477 questionnaires were mailed. Of these, 271 completed questionnaires were returned after the first mailing and an additional 202 after the second, giving a total of 472 (32% response) returned questionnaires. Response rate was higher in hospital/ clinic pharmacists compared with community pharmacists with 35% and 25% returning the completed questionnaires respectively (Table 3-4). No other details about the non-respondents were available.

Table 3-4 : Response rate according to work settings (n= 1,477)

	Number of respondents (%)		
	Respondents n = 472	**Non-respondents n = 1,036**	**Total n = 1,477**
Hospital/ clinic pharmacists	259 (34.5)	491 (65.5)	750
Community pharmacists	182 (25.0)	545 (75.0)	727

The characteristics of the respondents are shown in Table 3-5. Most respondents (74%, n= 208) were women. Most of the hospital or clinic pharmacists (n= 186, 72%) had been in practice for five years or less compared with the community pharmacists where majority (n= 162, 89%) had been in practice for more than five years (χ^2 = 12.384, p <0.001). This is attributed to the implementation of a three-year compulsory service in the public sector for newly graduated pharmacists in 2005. Due to shortage of pharmacists at the public sector, freshly graduated pharmacists are placed in public hospitals or clinics and must serve the government for three years upon completing a one-year pre-registration. This approach has led to an influx of young pharmacists to the government hospitals or clinics.

All community pharmacists (n= 180, 100%) reported direct contact with patients compared to hospital or clinic pharmacists where 12% (n= 32) reported no direct patient contact (χ^2 = 24.829, p <0.001). The nature of work of hospital or clinic pharmacists is diversified. Unlike the community pharmacists, not all of them have direct contact with patients. Some are located in departments

where little patient contact is possible, for example, the pharmacy stores and department of extemporaneous preparation. These pharmacists' job schedules change regularly (within three to six months), and although the current department is restricted from direct patient contact, they would have had patient contacts in their previous department – thus, these pharmacists were included in the analysis. For the purpose of this study, views of only pharmacists who currently have direct patient contact were deemed needed and therefore, the 'other' group was excluded from further analysis.

Table 3-5: Characteristics of the respondents (n= 472)

Characteristics	Number of respondents (%)			
	Hospital/ clinic n= 259	Community n= 182	Other n= 29	Total n= 472
Gender (n= 468[a])				
Male	50 (19.4)	62 (34.3)	9 (31.0)	121 (25.9)
Female	208 (80.6)	119 (65.7)	20 (69.0)	347 (74.1)
Years of work experience (n= 468[a])				
5 years or less	186 (72.1)	19 (10.5)	9 (31.0)	214 (45.7)
More than 5 years	72 (27.9)	162 (89.5)	20 (69.0)	254 (54.3)
Level of education (n= 468[a])				
Bachelor's degree	218 (84.5)	163 (90.1)	28 (96.6)	409 (87.4)
Master's degree	38 (14.7)	17 (9.4)	1 (3.4)	56 (12.0)
Doctorate degree	2 (0.8)	1 (0.6)	-	3 (0.6)
Have direct patient contact (n= 438[b])				
Yes	226 (87.3)	180[c] (100.0)	-	406 (92.7)
No	32 (12.4)	-	-	32 (7.3)

[a] *these groupings do not total 472 due to missing data*
[b] *respondents from 'other' group skipped this question, however, this group does not total 439 due to missing data*
[c] *this group does not total 181 due to missing data*

3.5 Results - Experiences about adverse drug reactions

3.5.1 The pharmacists experiences of observing an adverse drug reactions

Pharmacists were asked to state their experiences of observing ADRs in the last six months (Table 3-6). About 70% of respondents reported observing ADRs in the said time frame (n= 293, 68%). Seven out of ten combined hospital and clinic pharmacists (n= 186, 73%), and six out of ten community pharmacists (n= 107, 60%) reported they had observed ADRs in the last six months. Additionally, more than 50% of all pharmacists reported to have observed one or more ADR cases per month (n= 152, 53%) (Table 3-7).

Table 3-6: Experiences of pharmacists observing ADRs in the last 6 months (n = 439)

	Number of respondents (%)	
	Observed n= 293	**Did not observe any n= 141**
Work setting (n= 434[a])		
Hospital/clinic (n= 255)	186 (72.9)	69 (27.1)
Community (n= 179)	107 (59.8)	72 (40.2)
Years of work experience (n= 431[a])		
5 years or less (n= 204)	154 (75.5)	50 (24.5)
More than 5 years (n= 227)	136 (59.9)	91 (40.1)
Level of education (n= 432[a])		
Bachelor's degree (n= 375)	250 (66.7)	125 (33.3)
Postgraduate degree (n= 57)	41 (71.9)	16 (28.1)

[a] *these groups do not total 439 due to missing data*

Table 3-7: Frequency of observing ADRs (n = 293)

	Number of respondents (%)	
	One or more ADR(s) n= 152	Less than one ADR n= 135
Work setting (n= 287[a])		
Hospital/clinic (n= 183)	102 (55.7)	81 (44.3)
Community (n= 104)	50 (48.1)	54 (51.9)
Years of work experience (n= 285[a])		
5 years or less (n= 153)	81 (52.9)	72 (47.1)
More than 5 years (n= 132)	69 (52.3)	63 (47.7)
Level of education (n= 285[a])		
Bachelor's degree (n= 246)	130 (52.8)	132 (53.7)
Postgraduate degree (n= 39)	24 (61.5)	15 (38.5)

[a] *these groups do not total 293 due to missing data*

3.5.2 Characteristics of adverse drug reactions observed by the pharmacists

The types of ADRs observed by pharmacists are listed in Table 3-8. The characteristics of the most common ADRs they have observed involved dermatology (rash and itchiness), gastrointestinal (gastritis and diarrhoea), and central nervous systems (dizziness, headache and giddiness). ADRs related to gastrointestinal systems were reported most often by community pharmacists. The specific symptoms all responding pharmacists reported observing most often was rash (n= 160, 55%), followed by itchiness (n= 138, 47%).

Table 3-8: Most recent ADRs observed by the pharmacists (n = 293)

Symptoms or complications according to organ systems*	Number of respondents (%)		
	Hospital/ clinic (n = 186)	Community (n = 107)	Total (n= 293[a])
Dermatology			
Rash	96 (51.6)	64 (59.8)	160 (54.6)
Itchiness	80 (43.0)	58 (54.2)	138 (47.1)
Oedema periorbital	16 (8.6)	18 (16.8)	34 (11.6)
Erythema	13 (7.0)	12 (11.2)	25 (8.5)
Steven Johnson Syndrome	18 (9.7)	6 (5.6)	24 (8.2)
Pemphigus	1 (0.5)	-	1 (0.3)
Gastrointestinal system			
Gastritis	30 (16.1)	40 (37.4)	70 (23.9)
Diarrhoea	30 (16.1)	31 (29.0)	61 (20.8)
Nausea	24 (12.9)	26 (24.3)	50 (17.1)
Heartburn	12 (6.5)	34 (31.8)	46 (15.7)
Flatulence	16 (8.6)	27 (25.2)	43 (14.7)
Vomiting	22 (11.8)	14 (13.1)	36 (12.3)
Constipation	11 (5.9)	19 (17.8)	30 (10.2)
Other	2 (1.1)	-	2 (0.7)
Central nervous system			
Dizziness	59 (31.7)	37 (34.6)	96 (32.8)
Headache	58 (31.2)	26 (24.3)	84 (28.7)
Giddiness	55 (29.6)	25 (23.4)	80 (27.3)
Other	7 (3.8)	4 (3.7)	11 (3.8)
Respiratory system			
Dry cough	57 (30.6)	49 (45.8)	106 (36.2)
Cough	16 (8.6)	20 (18.7)	36 (12.3)
Other	2 (1.1)	1 (0.3)	3 (1.0)
Cardiovascular system			
Oedema	31 (16.7)	25 (23.4)	56 (19.1)
Palpitation	12 (6.5)	22 (20.6)	34 (11.6)
Other	6 (3.2)	1 (0.9)	7 (2.3)

[a] the total is based on the number of pharmacists who have reported observing an ADRs in the last six months (n=293)

**respondents had the choice to select more than one answer – as an ADR may present with more than one symptom*

table continued.....

Table 3-8 continued: Most recent ADRs observed by the pharmacists (n= 293)

Symptoms or complications according to organ systems*	Number of respondents (%)		
	Hospital/ clinic (n = 186)	Community (n = 107)	Total (n= 293[a])
Bones, joints and muscles			
Myalgia	19 (10.2)	20 (18.7)	39 (13.3)
Muscle cramps/ rigidity/ weakness	2 (1.1)	1 (0.3)	3 (1.0)
Haematology			
Thrombocytopenia	18 (9.7)	-	18 (6.1)
Jaundice	8 (4.3)	1 (0.9)	9 (3.1)
Other	2 (1.1)	-	2 (0.6)
Endocrinology or metabolic system			
Renal failure	15 (8.1)	1 (0.9)	16 (5.5)
Other	5 (2.7)	-	5 (1.7)
Liver			
Acute hepatitis	13 (7.0)	-	13 (4.4)
Elevated liver enzymes	4 (2.2)	-	4 (1.4)
Other	**6**	**-**	**6**

[a] *the total is based on the number of pharmacists who have reported observing an ADRs in the last six months (n=293)*

**respondents had the choice to select more than one answer– as an ADR may present with more than one symptom*

3.5.3 Drugs associated with the observed adverse drug reaction

Pharmacists were asked to state the drug(s) associated with the most recent ADR they have observed and these drugs are listed in Table 3-9. Overall, cardiovascular drugs were the most often reported drug group followed by NSAIDs. More than half of the community pharmacists (n= 58, 54%) reported perindopril as one of the drugs associated with most recent ADRs whilst less than half of the hospital or clinic pharmacists (n= 68, 37%) reported so. Furthermore, four out of ten community pharmacists reported observing ADRs associated with diclofenac (n= 46, 43%). A correlation between the drugs with suspected ADRs could not be done because both questions were multiple choice questions.

Table 3-9: Drugs associated with the most recent suspected ADRs (n = 293)

Drugs associated with the most recent ADRs*	Number of respondents (%)		
	Hospital/ clinic (n= 186)	Community (n =107)	Total (n= 293[a])
Angiotensin-converting ezyme inhibitor (ACEI)			
Perindopril	68 (36.6)	58 (54.2)	126 (43.0)
Captopril	10 (5.4)	11 (10.3)	21 (7.2)
Other[b]	1 (0.5)	3 (2.8)	4 (1.4)
Nonsteroidal Anti-inflammatory Drug (NSAID)			
Diclofenac	22 (11.8)	46 (43.0)	68 (23.2)
Mefenamic acid	13 (7.0)	30 (28.0)	43 (14.7)
Paracetamol	8 (4.3)	7 (6.5)	15 (5.1)
Other[b]	6 (3.2)	10 (9.3)	16 (5.5)
Antibiotics			
Co-trimoxazole	15 (8.1)	10 (9.3)	25 (8.5)
Erythromycin	7 (3.8)	15 (14.0)	22 (7.5)
Amoxicillin	7 (3.8)	13 (12.1)	20 (6.8)
Cloxacillin	8 (4.3)	7 (6.5)	15 (5.1)
Other[b]	36 (19.4)	5 (4.7)	41 (14.0)
Calcium channel blocker			
Amlodipine	38 (20.4)	38 (35.5)	76 (25.9)
Nifedipine	15 (8.1)	11 (10.3)	26 (8.9)
Felodipine	1 (0.5)	-	1 (0.3)
Antiplatelet			
Aspirin	31 (16.7)	38 (35.5)	69 (23.5)
Ticlopidine	12 (6.5)	7 (6.5)	19 (6.5)

[a] *the total is based on the number of pharmacists who have reported observing ADRs in the last six months (n=293)*

[b] *the number of respondents was less than ten for each 'other' drugs*

**respondents had the choice to select more than one answer*

table continued.....

Table 3-9 continued: Drugs associated with the most recent suspected ADRs (n = 293)

Drugs associated with the most recent ADRs*	Number of respondents (%)		
	Hospital/ clinic (n= 186)	Community (n =107)	Total (n= 293[a])
Hypoglycaemic agent			
Metformin	30 (16.1)	34 (31.8)	64 (21.8)
Other[b]	6 (3.2)	-	6 (2.0)
Traditional medicine			
Traditional medicine	25 (13.4)	16 (15.0)	41 (14.0)
Statin			
Lovastatin	17 (9.1)	11 (10.3)	28 (9.6)
Other[b]	3 (1.6)	5 (4.7)	8 (2.7)
Antigout			
Colchicine	-	1 (0.9)	
Allopurinol	18 (9.7)	13 (12.1)	31 (10.6)
Nitrate			
Isosorbide dinitrate	15 (8.1)	5 (4.7)	20 (6.8)
Beta-adrenergic blocker			
Atenolol	4 (2.2)	10 (9.3)	14 (4.8)
Metoprolol	1 (0.5)	-	1 (0.3)
Biphosphonate			
Alendronate	4 (2.2)	10 (9.3)	14 (4.8)
Thiazide			
Chlorothiazide	8 (4.3)	3 (2.8)	11 (3.8)
Vaccine			
H1N1[i] vaccine	9 (4.8)	-	9 (3.1)
Vaccine[c]	1 (0.5)	-	1 (0.3)
Other[b]	**66**	**28**	**94**

[a] the total is based on the number of pharmacists who have reported observing an ADR during the last six months (n=293)
[b] the number of respondents was less than ten for each 'other' drugs
[c] respondent did not specify the name of the vaccine
**respondents had the choice to select more than one answer*
[i] H1N1- influenza A virus

3.5.4 Actions taken in response to observed adverse drug reactions

While more than 50% (n= 96, 52%) of combined hospital and clinic pharmacists reported sending ADR reports to MADRAC in response to most recently observed ADRs, only 3% (n= 3) of community pharmacists reported doing so (Table 3-10). Furthermore, more than 40% of the first mentioned group of pharmacists (n= 81, 44%) reported sending ADR reporting forms to drug information centres of hospitals. Almost half of the same group (n= 89, 48%) have also reported taking the initiative to explain to patients about the reactions. However, about eight out of ten community pharmacists (n= 88, 82%) claimed referring the patients back to their doctors, or explaining to the patients about the reactions (n= 83, 78%). They have also reported suggesting to patients to stop taking the drug (n= 59, 55%), introduced another to relieve the reaction (n= 49, 46%), or suggesting an alternative drug (n= 41, 38%). In contrast, only a small number of combined hospital and clinic pharmacists have reported taking these actions.

Table 3-10: Actions taken in response to observed ADRs (n = 293)

Actions taken*	Number of respondents (%) n =293[a]
Explained to patient about the reaction	172 (58.7)
Suggested patient to inform doctor	170 (58.0)
Sent ADR form to MADRAC	99 (33.8)
Suggested patient to stop the medicine	96 (32.8)
Noted in patient's chart/record	94 (32.1)
Did further evaluation	88 (30.0)
Sent ADR form to hospital DIC[b]	81 (27.6)
Informed the physician in-charge	77 (26.3)
Suggested patient a medicine to relieve the reaction	66 (22.5)
Suggested patient a different medicine	54 (18.4)
Informed the pharmacist in hospital DIC[b]	27 (9.2)
Informed the associated pharmaceutical company	11 (3.8)
Issued an allergy card to patient	13 (4.4)
No action	4 (1.4)
Other action	3 (1.0)

[a] the total is based on the number of pharmacists who have reported observing ADRs in the last six months (n=293)
[b] DIC – drug information centre
**respondents had the choice to select more than one answer*

The actions taken by pharmacists were further evaluated according to work setting and years of experience and are shown in Table 3-11 (only the actions with more than 20% response were evaluated). The education level was not cross-tabulated in this evaluation because the number of pharmacists under the postgraduate group is small and therefore comparison would not be meaningful.

About 80% of community pharmacists reported suggesting patients to inform their doctors (n=88, 82%) and/or explained to patient about the reaction (n= 83, 78%), but less than 50% of combined hospital and clinic pharmacists reported taking these actions. Additionally, about 50% of community pharmacists suggested patient to stop taking the medicine (n= 59, 55%) and/or suggested another

drug to relieve the reaction (n= 49, 46%), whilst less than 30% of the other group of pharmacists did so. About half of the hospital and clinic pharmacists reported to have sent an ADR form to MADRAC (n=96, 52%) but only three community pharmacists (3%) had done the same.

More than 50% (n= 79, 51%) of pharmacists who have been in practice for 5 years or less claimed to have submitted an ADR form to MADRAC but only 14% (n= 19) of pharmacists who have been in practice for more than 5 years reported to have done the same task. Around two-thirds of pharmacists who have been in practice for more than 5 years reported explaining to patient about the reaction (n= 92, 68%) and/or suggesting patients to inform their doctors about the ADRs (n= 90, 66%) compared with around half of those who have been qualified for less time.

Table 3-11: Actions taken in response to observed ADRs according to work setting and years of experience (n= 293)

Actions	Number of respondents (%)			
	Work setting		Years of experience	
	Hospital/clinic (n= 186)	Community (n= 107)	5 years or less (n= 155)	More than 5 years (n= 136)
Explained to patient about the reaction	89 (47.8)	83 (77.6)	79 (51.0)	92 (67.6)
Suggested patients to inform their	82 (44.1)	88 (82.2)	78 (50.3)	90 (66.2)
Sent ADR form to MADRAC	96 (51.6)	3 (2.8)	79 (51.0)	19 (14.0)
Suggested patient to stop the medicine	37 (19.9)	59 (55.1)	33 (21.3)	62 (45.6)
Noted in patient's chart/record	60 (32.3)	34 (31.8)	45 (29.0)	47 (34.6)
Did further evaluation	61 (32.8)	27 (25.2)	49 (31.6)	37 (27.2)
Sent ADR form to hospital DIC	81 (43.5)	-	63 (40.6)	17 (12.5)
Suggested patient a medicine to relieve the reaction	17 (9.1)	49 (45.8)	18 (11.6)	48 (35.3)

3.6 Results – Spontaneous adverse drug reaction reporting

3.6.1 The pharmacists' awareness about the adverse drug reaction reporting system

Pharmacists were asked about their experiences of reporting ADRs. More than 80% (n= 220, 86%) of combined hospital and clinic pharmacists claimed reporting ADRs but only 14% (n= 36) of community pharmacists have ever reported one (Table 3-12). In terms of work experience, more than 80% of pharmacists with 5 years or less of this have claimed reporting ADRs, whilst about 70% of pharmacists with more than 5 years of experience have claimed to have done otherwise.

Reporting online was the preferred method for almost 70% of combined hospital and clinic pharmacists (n=170, 66%) and 60% of community pharmacists (n= 103, 57%).

Table 3-12: The pharmacists experiences about reporting ADRs (n = 439)

Characteristics	Number of respondents (%)	
	Reported	Never reported
Working setting (n= 437[a])		
Hospital/ clinic (n = 256)	220 (85.9)	36 (14.1)
Community (n = 181)	25 (13.8)	156 (86.2)
Years of work experience (n= 434[a])		
5 years or less (n = 202)	169 (83.7)	33 (16.3)
More than 5 years (n= 232)	74 (31.9)	158 (68.1)
Level of education (n= 435[a])		
Bachelor's degree (n = 378)	205 (54.2)	173 (45.8)
Postgraduate degree (n =57)	39 (68.5)	18 (31.5)

[a] *these groupings do not total 439 due to missing data*

Almost all the combined hospital and clinic pharmacists (n= 250, 97%) were aware of ADR report forms and of these, only 5% (n= 12) were not aware of where to obtain them. Majority obtained the forms from a drug information centre at hospitals (n=192, 81%).

Seven out of ten community pharmacists (n= 131, 72%) were aware of the existence of the said report forms, although 36% (n= 46) of these did not know where to obtain them. The remaining said population reported to have obtained such from drug information books (n=59, 73%).

3.6.2 Factors that encourage and discourage pharmacists to report an ADR

Almost all the pharmacists claimed that they are more likely to report ADRs if the reactions are severe (n= 418, 95%) (Table 3-13). Moreover, they are more likely to report one if the reaction is related to a new drug (n= 345, 79%), unusual or unexpected (n= 331, 75%), not widely known (n= 320, 73%), or they are certain that the drug had caused the reaction (n= 301, 69%). Similar traits were found in factors that discourage ADR reporting: if the reaction is widely known (n= 265, 60%), if pharmacists are unsure if the drug indeed had caused the reaction (n= 273, 62%), or if they are unsure of the types of reactions that need to be reported (n= 265, 60%). However, almost 80% stated that the most common factor discouraging them from reporting an event was the lack of information from patients (n= 333, 76%). Additionally, the following reasons were found to discourage four out of ten community pharmacists in reporting ADRs: lack of information regarding the regulations and procedure for such action (n= 79, 43%), finding it difficult to obtain report forms (n= 77, 42%), and that the form was complex to accomplish (n= 83, 46%). However, only two out of ten combined hospital and clinic pharmacists reported facing these difficulties.

Table 3-13: Factors that encourage or discourage ADR reporting (n= 439)

Factors*	Number of respondents (%)		
	Hospital/ clinic (n= 258)	Community (n =181)	Total (n= 439)
Factors encouraging ADR reporting (n= 439)			
The high degree of severity of a clinical reaction	249 (96.5)	169 (93.4)	418 (95.2)
The involvement of a newly licensed drug	221 (85.7)	124 (68.5)	345 (78.6)
The specific typology of the reaction (unusual/ unexpected)	216 (83.7)	115 (63.5)	331 (75.4)
The reaction is not widely known	211 (81.8)	109 (60.2)	320 (72.9)
An obvious causal relationship with the administration of the drug	197 (76.4)	104 (57.5)	301 (68.6)
The explicit request of a pharmaceutical company	65 (25.2)	78 (43.1)	143 (32.6)
Factors discouraging ADR reporting (n= 439)			
A lack of information from the affected patient	194 (74.9)	139 (76.4)	333 (75.9)
The uncertainty of a causal relationship with the administration of the drug	150 (57.9)	123 (67.6)	273 (62.2)
Uncertainty regarding the type of reactions to be reported	147 (56.8)	118 (64.8)	265 (60.4)
The reaction is widely known	141 (54.4)	124 (68.1)	265 (60.4)
The low degree of severity of a clinical reaction	121 (46.7)	115 (63.2)	236 (53.8)
A lack of time due to heavy responsibilities	94 (36.3)	67 (36.8)	161 (36.7)
The complexity of the form	69 (26.6)	83 (45.6)	152 (34.6)
A lack of knowledge regarding the regulations and procedure for reporting	57 (22.0)	79 (43.4)	136 (31.0)
The difficulty in obtaining a form	52 (20.1)	77 (42.3)	129 (29.4)
Reporting does not seem worthwhile	55 (21.2)	62 (34.1)	117 (26.7)
The fear of medical legal consequences	43 (16.6)	66 (36.3)	109 (24.8)
A lack of support from organisation/ head of department/ colleagues	61 (23.6)	47 (25.8)	108 (24.6)

**respondents had the choice to select more than one answer*

3.6.3 Types of adverse drug reactions the pharmacists believe should be reported

In full agreement with MADRAC's requirement (which state that all suspected ADRs should be reported), almost 80% of combined hospital and clinic pharmacists (n= 203, 79%) believe that suspected reactions should be reported. However, only half of the community pharmacists believe so (n= 90, 50%) (Table 3-14). Similar to the factors that encourage ADR reporting, more than 80% of the pharmacists stated that severe reactions (n= 425, 97%), reactions to new drugs (n= 393, 90%), and unexpected or unusual reactions (n= 389, 89%) should be reported.

Table 3-14: The types of ADRs that the pharmacists believe should be reported (n= 439)

Type of ADRs*	Number of respondents (%)		
	Hospital/ clinic (n= 258)	Community (n =181)	Total (n= 439)
Severe reactions	252 (97.7)	173 (95.6)	425 (96.8)
Reactions to new drugs	244 (94.6)	149 (82.3)	393 (89.5)
Unexpected/ unusual reactions	240 (93.0)	149 (82.3)	389 (88.6)
Certain reactions	218 (84.5)	131 (72.4)	349 (79.5)
Teratogenicity phenomena	218 (84.5)	128 (70.7)	346 (78.8)
Reactions to vaccinations	220 (85.3)	103 (56.9)	323 (73.6)
Suspected reactions	203 (78.7)	90 (49.7)	293 (66.7)
Interactions between drugs	144 (55.8)	106 (58.6)	250 (56.9)
Reactions to drugs that have been in use for a long time	131 (50.8)	83 (45.9)	214 (48.7)
Mild reactions	139 (53.9)	32 (17.7)	171 (39.0)
Known reactions	111 (43.0)	42 (23.2)	153 (34.9)
Lack of efficacy of a drug due to development of newly resistant strain	83 (32.2)	62 (34.3)	145 (33.0)

**respondents had the choice to select more than one answer*

3.6.4 The pharmacists' perception about the aims of monitoring ADR reports

Almost all pharmacists believe that the purpose of ADR spontaneous reporting system is to measure incidence of ADRs (n= 412, 94%) and identify uncommon ADRs (n= 412, 94%) (Table 3-15). Furthermore, 80% of them believe that the system is able to identify predisposing factors to ADRs (n= 350). More than 30% of the pharmacists believe that the reporting system is able to identify the indication for which the drugs are prescribed, which is not an aim of monitoring ADR reports.

Table 3-15: The pharmacists opinion about the aims of monitoring ADRs (n = 439)

Aims*	Number of respondents (%)		
	Hospital/ clinic (n= 258)	Community (n =181)	Total (n= 439)
To measure the incidence of ADR	242 (93.8)	170 (93.9)	412 (93.8)
To identify uncommon ADR (allergic, idiosyncratic, etc)	252 (97.7)	160 (88.4)	412 (93.8)
To identify previously unknown ADR	241 (93.4)	156 (86.2)	397 (90.4)
To maintain a database of ADR	227 (88.0)	152 (84.0)	379 (86.3)
To identify factors predisposing patients to ADR	210 (81.4)	140 (77.3)	350 (79.7)
To identify safe drugs	194 (75.2)	130 (71.8)	324 (73.8)
To identify the indication for which the drugs are prescribed	78 (30.2)	61 (33.7)	139 (31.7)

**respondents had the choice to select more than one answer*

3.7 Results – Experiences about therapeutic failure

3.7.1 The pharmacists experiences of observing therapeutic failures

When asked about their experiences of observing TFs, about half of the pharmacists from hospitals or clinics (n= 132, 52%) and community (n= 101, 56%) reported observing TF-related patients in the last six months (Table 3-16). The same is to be said for more than 50% of pharmacists with five years or less of work experience, as well as those in practice for more than five years. Similar results were also found in the groups of different education levels (those with bachelor's degree and postgraduate degree).

Table 3-16: Experiences of pharmacists observing TFs in the last 6 months (n = 439)

	Number of respondents (%)	
	Observed n= 233	**Did not observe any n= 202**
Work setting (n= 435[a])		
Hospital/ clinic (n= 256)	132 (51.6)	124 (48.4)
Community (n= 179)	101 (56.4)	78 (43.6)
Years of work experience (n= 429[a])		
5 years or less (n= 202)	108 (53.5)	94 (46.5)
More than 5 years (n= 227)	120 (52.9)	107 (47.1)
Level of education (n= 433[a])		
Bachelor's degree (n= 376)	198 (52.7)	178 (47.3)
Postgraduate degree (n= 57)	34 (59.6)	23 (40.4)

[a] *these groups do not total 439 due to missing data*

More than 70% of pharmacists who observed TF reported observing one or more TF-related patients each month (combined hospital and clinic pharmacists, n=94, 74%, community pharmacists, n=73, 74%).

Table 3-17: Frequency of observing TF cases (n= 233)

	Number of respondents (%)	
	One or more case(s)	Less than one case
	n= 161	n= 66
Work setting (n= 226[a])		
Hospital/ clinic (n= 132)	96 (72.7)	36 (27.3)
Community (n= 105)	75 (71.4)	30 (28.6)
Years of work experience (n= 231[a])		
5 years or less (n= 107)	78 (72.9)	29 (27.1)
More than 5 years (n= 129)	92 (71.3)	37 (28.7)
Level of education (n= 233)		
Bachelor's degree (n= 203)	146 (71.9)	57 (28.1)
Postgraduate degree (n= 33)	24 (72.7)	9 (27.3)

[a] *these groups do not total 233 due to missing data*

3.7.2 Characteristics of therapeutic failures as observed by pharmacists

Seven out of ten pharmacists from hospitals or clinics and community setting reported observing cases of TF in patients with diabetes mellitus (n= 180, 77%) and hypertension (n= 159, 68%). Almost 90% (n= 90, 89%) of the community pharmacists reported observing TFs in patients with diabetes mellitus (Table 3-18). The same group have observed TF in pain management (n=63, 62%) more often than pharmacists from either hospitals or clinics.

Table 3-18: Most recent therapeutic failures observed by pharmacists (n = 233)

Medical condition or therapy*	Number of respondents (%)		
	Hospital/ clinic (n= 132)	Community (n= 101)	Total (n= 233[a])
Diabetes mellitus	90 (68.2)	90 (89.1)	180 (77.3)
Hypertension	82 (62.1)	77 (76.2)	159 (68.2)
Asthma	66 (50.0)	42 (41.6)	108 (46.4)
Antibiotic therapy	50 (37.9)	46 (45.5)	96 (41.2)
Pain management	29 (22.0)	63 (62.4)	92 (39.5)
Other cardiovascular disease	36 (27.3)	17 (16.8)	53 (22.7)
Epilepsy	20 (15.2)	5 (5.0)	25 (10.7)
Renal failure	17 (12.9)	2 (2.0)	19 (8.2)
Cancer	11 (8.3)	4 (4.0)	15 (6.4)
HIV[i]/ AIDS[ii] therapy	11 (8.3)	-	11 (4.7)
Tuberculosis	8 (6.1)	-	8 (3.4)
Weight management	-	2 (2.0)	2 (0.9)
Antiplatelet/ anticoagulant therapy	2 (1.5)	-	2 (0.9)
Psychiatric disorder	2 (1.5)	-	2 (0.9)
Cough and cold management	1 (0.8)	1 (1.0)	2 (0.9)
Antifungal therapy	-	1 (1.0)	1 (0.4)
Gastritis	1 (0.8)	-	1 (0.4)
Hormone replacement therapy	1 (0.8)	-	1 (0.4)
Migraine	-	1 (1.0)	1 (0.4)
Ear, nose and throat disorder	-	1 (1.0)	1 (0.4)
Skin disease	-	1 (1.0)	1 (0.4)
Disease-modifying antirheumatic drug therapy	1 (0.8)	-	1 (0.4)

[a] the total is based on the number of pharmacists who have observed a patient with therapeutic failures in the last six months (n= 233)

**respondents had the choice to select more than one answer*

[i] HIV- Human Immunodeficiency Virus; AIDS- Acquired Immunodeficiency Syndrome

3.7.3 Actions taken in response to observed therapeutic failures

Counselling patients on how to consume or use their drugs (n= 199, 85%) and/or the importance of adherence (n= 180, 77%) were the actions reported taken by more than 70% of the pharmacists in response to observed cases of TF (Table 3-19).

Table 3-19: Actions taken by pharmacists in response therapeutic failures (n = 233)

Actions taken*	Number of respondents (n= 233[a])
Counsel the patient the right way to use/ consume their medicines	199 (85.4)
Explained to patient/ family member about the importance of adherence to medicines	180 (77.3)
Did further evaluation	136 (58.4)
Suggested patients to inform their physicians	133 (57.1)
Informed the physician in-charge	87 (37.3)
Noted in patient's chart/record	79 (33.9)
Suggested patient a different medicine	46 (19.7)
No action	2 (0.9)
Counsel the patient about diet and lifesytle modification	1 (0.4)
Follow-up patient through medicines reconcilation	1 (0.4)

[a] *the total is based on the number of pharmacists who have observed a patient with therapeutic failures in the last six months (n= 233)*
**respondents had the choice to select more than one answer*

Further evaluation was conducted according on the questions which gathered more than 20% response, according to work setting and years of experience. Cross-tabulation of level of education with the actions taken was not conducted because of small number of respondents in the postgraduate group (Table 3-20). The table shows that more than 70% of the pharmacists,

regardless of their number of years of practice or work setting have counselled their patients on the right way to use or consume their medicines and/or explained to them and their family members the importance of adherence. Meanwhile, nine out of ten community pharmacists reported referring the patients back to their physicians (n= 87, 86%), whilst 60% of the combined pharmacists from either clinic or hospital reported communicating to the physicians-in-charge about the patient (n= 79, 60%). Of pharmacist who have been in practice for 5 year or more 76% reported suggesting to patients that they inform their physicians about the ADE compared with 38% of those with less experience. More than half of the latter group of pharmacists reported informing the physicians-in-charge of the observed TF cases while only 23% of those with more than 5 years of practice reported taking the same action.

Table 3-20: Actions taken in response to observed TFs according to years of work experience and work setting (n= 233)

Actions taken	Number of respondents (%)			
	Work setting		Years of experience	
	Hospital/ clinic (n= 127)	Community (n= 101)	5 years or less (n= 108)	More than 5 (n= 120)
Counsel the patient the right way to use/ consume their medicines	109 (82.6)	90 (89.1)	94 (87.0)	105 (87.5)
Explained to patient/ family member about the importance of adherence to medicines	98 (74.2)	82 (81.2)	87 (80.6)	93 (77.5)
Did further evaluation	82 (62.1)	54 (53.5)	62 (57.4)	71 (59.2)
Suggested patients to inform their physicians	46 (34.8)	87 (86.1)	41 (38.0)	91 (75.8)
Informed the physician in-charge	79 (59.8)	8 (7.9)	60 (55.6)	27 (22.5)
Noted in patient's chart/record	52 (39.4)	27 (26.7)	38 (35.2)	40 (33.3)

[a] *this group does not total 199 due to missing data*
[b] *this group does not total 136 due to missing data*
[c] *this group does not total 133 due to missing data*

3.8 Results – Experiences about medication errors

3.8.1 The pharmacists experiences of observing medication errors

More than 60% of pharmacists reported having observed medication errors in the last six months (Table 3-21). Of these, eight out of ten were hospital or clinic pharmacists (n= 204, 71%). Whilst 75% (n= 152) of the hospital or clinic pharmacists reported observing more than one ME in a month, only 36% (n= 30) of community pharmacists reported the same (Table 3-22).

Table 3-21: Experiences of pharmacists observing ME cases in the last six months (n = 439)

	Number of respondents (%)	
	Observed n= 289	Did not observe any n= 147
Work setting (n= 435[a])		
Hospital/ clinic (n= 258)	204 (79.1)	54 (20.9)
Community (n= 178)	85 (47.8)	93 (52.2)
Years of work experience (n= 433[a])		
5 years or less (n= 230)	132 (57.4)	98 (42.6)
More than 5 years (n= 203)	155 (76.4)	48 (23.6)
Level of education (n= 434[a])		
Bachelor's degree (n= 377)	246 (65.3)	131 (34.7)
Postgraduate degree (n= 57)	42 (73.7)	15 (26.3)

[a] *these groups do not total 439 due to missing data*

About 80% of pharmacists with more than 5 years of experience reported observing MEs in the last six months (n= 155, 76%), with more than half of these pharmacists observing less than one ME in a month (n= 71, 54%). Conversely, 78% of 132 pharmacists with 5 years or less experience (who reported to have observed MEs in the last 6 months), observed more than one ME in each month.

Table 3-22: Frequency of observing MEs (n= 289)

	Number of respondents (%)	
	One or more ME(s) n= 183	Less than one ME n= 106
Work setting (n= 286[a])		
Hospital/ clinic (n= 202)	152 (75.2)	50 (24.8)
Community (n= 84)	30 (35.7)	54 (64.3)
Years of work experience (n= 287[a])		
5 years or less (n= 155)	121 (78.1)	34 (21.9)
More than 5 years (n= 132)	61 (46.2)	71 (53.8)
Level of education (n= 288[a])		
Bachelor's degree (n= 246)	151 (61.4)	95 (38.6)
Postgraduate degree (n= 42)	31 (73.8)	11 (26.2)

[a] *these groups do not total 289 due to missing data*

3.8.2 Characteristics of medication errors observed by the pharmacists

Prescribing errors (n= 241, 83%) was reported as being the most recent error observed by more than 80% of pharmacists followed by dosage error (n= 183, 63%) (Table 3-23). A higher percentage of hospital or clinic pharmacists than community pharmacists reported observing errors related to dosage form (n= 48, 24%), administration technique (n= 44, 22%), drug preparation (n= 36, 18%), and route of administration (n= 27, 13%).

Table 3-23: Most recent types of errors observed by the pharmacists (n = 289)

Types of error*	Number of respondents (%)		
	Hospital/ clinic (n = 204)	Community (n = 85)	Total (n = 289[a])
Prescribing error	185 (90.7)	56 (65.9)	241 (83.4)
Dosage error	136 (66.7)	47 (55.3)	183 (63.3)
Omission error	94 (46.1)	14 (16.5)	108 (37.4)
Wrong time error	68 (33.3)	31 (36.5)	99 (34.3)
Monitoring error	60 (29.4)	23 (27.1)	83 (28.7)
Unauthorised drug error	50 (24.5)	16 (18.8)	66 (22.8)
Dosage form error	48 (23.5)	14 (16.5)	62 (21.5)
Administration technique	44 (21.6)	15 (17.6)	59 (20.4)
Drug preparation error	36 (17.6)	4 (4.7)	40 (13.8)
Route of administration error	27 (13.2)	8 (9.4)	35 (12.1)
Deteriorated drug error	19 (9.3)	12 (14.1)	31 (10.7)
Compliance error	1 (0.5)	-	1 (0.3)
Labelling error	1 (0.5)	-	1 (0.3)
Storage error	1 (0.5)	-	1 (0.3)

[a] *the total is based on the number of pharmacists reported observing MEs in the last six months (n =289)*
**respondents had the choice to select more than one answer*

3.8.3 Actions taken in response to observed medication errors

The most common actions taken by pharmacists in response to MEs were correcting the error (n= 190, 66%) and/or informing the physicians-in-charge (n= 189, 65%) (Table 3-24). Only 30% of the pharmacists made incident reports or records of observed MEs (n= 88, 30%).

Table 3-24: Actions taken by the pharmacists in response to observed medication errors (n = 289)

Actions taken*	Number of respondents (%) (n =289[a])
Corrected the error	190 (65.7)
Informed the physician in-charge	189 (65.4)
Explained to patient about the error	124 (42.9)
Suggested ways to minimise the error	115 (39.8)
Suggested patient to inform their doctors	105 (36.3)
Made an incident report/ record	88 (30.4)
Informed the nurse in-charge	77 (26.6)
Noted in patient's chart/record	72(24.9)
No action	3 (1.0)
Inform all staff involved	1 (0.3)
Further evaluation	1 (0.3)
Change to a different drug	1 (0.3)

[a] the total is based on the number of pharmacists who reported observing MEs in the last six months (n= 289)
**respondents had the choice to select more than one answer*

While most of the hospital and clinic pharmacists reported communicating with physicians-in-charge about the error (n= 170, 83%) and/or correcting the error (n= 137, 67%), most of the community pharmacists reported explaining to patients about the error (n= 70, 82%) and/or suggesting that patients inform their doctor (n= 61, 72%) (Table 3-25). Only 27% (n= 54) of hospital and clinic pharmacists reported explaining to patients about the error. Meanwhile, more than 40% (n= 86, 42%) of hospital and clinic pharmacist reported making incident reports or recording the observed MEs compared with only 2% (n=2) of community pharmacists who did the same.

Most of the pharmacists with 5 years or less work experience reported communicating with physicians-in-charge about the error (n= 130, 84%), compared with only 43% of those with more than 5 years of work experience. Conversely, 60% of pharmacists with more than 5 years of experience claimed explaining to patients about the error (n= 79, 60%), while only 29% of those with 5 years or less work experience reported so (n= 45, 29).

Table 3-25: Actions taken in response to observed MEs according to work setting and years of work experiences (n= 289)

Actions taken	Number of respondents (%)			
	Work setting		Years of experience	
	Hospital/ clinic (n= 204)	Community (n= 85)	5 years or less (n= 155)	More than 5 (n= 132)
Corrected the error	137 (67.2)	53 (62.4)	103 (66.5)	87 (65.9)
Informed the physician in-charge	170 (83.3)	19 (22.4)	130 (83.9)	57 (43.2)
Explained to patient about the error	54 (26.5)	70 (82.4)	45 (29.0)	79 (59.8)
Suggested ways to minimise the error	82 (40.2)	33 (38.8)	56 (36.1)	57 (43.2)
Suggested patient to inform their doctors	44 (21.6)	61 (71.8)	43 (27.7)	61 (46.2)
Made an incident report/ record	86 (42.2)	2 (2.4)	51 (32.9)	34 (25.8)
Informed the nurse in-charge	75 (36.8)	2 (2.4)	54 (34.8)	24 (18.2)
Noted in patient's chart/record	61 (29.9)	11 (12.9)	43 (27.7)	28 (21.2)

3.9 Results – Experiences about drug overdoses

3.9.1 The pharmacists' experiences of observing drug overdoses

Of 439 pharmacists who responded to the survey, only 32% (n= 138, 31.4%) reported having observed patients with drug overdose in the last six months (Table 3-26). This was lower than the percentages of pharmacists who reported having observed ADRs, TFs or MEs.

Table 3-26: Experiences of pharmacists observing DOs in the last six months (n = 439)

	Number of respondents (%)	
	Observed n= 139	**Did not observe any n= 295**
Work setting (n= 434[a])		
Hospital/ clinic (n= 254)	87 (34.3)	167 (65.7)
Community (n= 180)	52 (28.9)	128 (71.1)
Years of work experience (n= 433[a])		
5 years or less (n= 200)	67 (33.5)	133 (66.5)
More than 5 years (n= 231)	71 (30.7)	160 (69.3)
Level of education (n= 434[a])		
Bachelor's degree (n= 376)	122 (32.4)	254 (67.6)
Postgraduate degree (n= 56)	17 (30.4)	39 (69.6)

[a] *these groups do not total 439 due to missing data*

About 60% of the hospital and clinic pharmacists (n= 52, 61%) and almost 60% of community pharmacists (n= 30, 58%), who reported having observed DOs reported encountering less than one patient with DO in a month (Table 3-27). Whilst more than 50% of pharmacists with 5 years or less work experience reported observing one or more patient with DO in a month (n= 44, 54.3%), 53% of pharmacists with more than 5 years of work experience reported observing less than one patient with DO in a month (n= 30, 52.6%).

Table 3-27: Frequency of observing DO cases

	Number of respondents (%)	
	One or more case(s) n= 57	Less than one case n= 82
Work setting (n= 138[a])		
Hospital/ clinic (n= 86)	34(39.5)	52 (60.5)
Community (n= 52)	22 (42.3)	30 (57.7)
Years of work experience (n= 138[a])		
5 years or less (n= 81)	44 (54.3)	37 (45.7)
More than 5 years (n= 57)	27 (47.4)	30 (52.6)
Level of education (n= 139)		
Bachelor's degree (n= 122)	51 (41.8)	71 (58.2)
Postgraduate degree (n= 17)	6 (35.3)	11 (64.7)

[a] *these groups do not total 139 due to missing data*

3.9.2 Drugs associated with observed drug overdoses

Almost 70% of community pharmacists reported having observed cases of DO associated with analgesics (n= 36, 69%) (Table 3-28). This was followed by cough and cold drugs (n= 52, 37%) and vitamin, mineral, or food supplement (n= 38, 27%). In contrast, only 36% (n= 31) of hospital or clinic pharmacists reported having observed events of DO associated with analgesics, followed by cough and cold drugs (n= 23, 26%), and anti-infectives (n= 23, 26%).

Table 3-28: Types of drugs associated with DOs as observed by the pharmacists (n = 139)

Drug group*	Number of respondents (%)		
	Hospital/ clinic (n= 87)	Community (n =52)	Total (n= 139[a])
Analgesic	31 (35.6)	36 (69.2)	67 (48.2)
Cough and cold medication	23 (26.4)	29 (55.8)	52 (37.4)
Anti-infective	23 (26.4)	15 (28.8)	38 (27.3)
Cardiovascular drug	20 (23.0)	4 (7.7)	24 (17.3)
Vitamin/ mineral/ food supplement	7 (8.0)	17 (32.7)	24 (17.3)
Respiratory drug	13 (14.9)	8 (15.4)	21 (15.1)
Psychiatric drug	14 (16.1)	3 (5.8)	17 (12.2)
Topical agent	1 (1.1)	14 (26.9)	15 (10.8)
Gastrointestinal drug	5 (5.7)	10 (19.2)	15 (10.8)
Anti-epileptics	13 (14.9)	-	13 (9.4)
Mixed drugs[i]	9 (10.3)	2 (3.8)	11 (7.9)
Herbal remedies	2 (2.3)	4 (7.7)	6 (4.3)
Hormones	-	3 (5.8)	3 (2.2)
Anti-diabetic	2 (2.3)	1 (1.9)	3 (2.2)
Central nervous system drug	2 (2.3)	-	2 (1.4)
Vaccines	2 (2.3)	-	2 (1.4)
Cytotoxic drugs	1 (1.1)	-	1 (0.7)
Recreational drugs	1 (1.1)	-	1 (0.7)
Bisphosphonate	1 (1.1)	-	1 (0.7)
Steroid	1 (1.1)	-	1 (0.7)

[a] the total is based on the number of pharmacists who reported observing patients with drug overdose in the last six months (n= 139)

**respondents had the choice to select more than one answer*

[i] mixed drugs – a combination of more than one drug from different drug classes

3.9.3 Actions taken in response to observed DOs

The most common action taken by pharmacists in response to the observed DOs was informing the physicians- in-charge (n= 79, 56.8%) (Table 3-29). In terms of work setting, most of the hospital or clinic pharmacists (n= 70, 80%) reported informing the physicians-in-charge regarding the DO, whilst 40% (n= 21) of community pharmacists reported referring the patients to hospitals. While 30% (n= 24, 28%) of hospital or clinic pharmacists claimed making incident reports or records, only two (4%) community pharmacists reported making such. However, only a small number of pharmacists reported counselling the patient on the correct dose and proper use of drug (n= 12, 9%), or contacting the national poison centre for clarification (n= 6, 4%). Comparisons between levels of education and years of work experience were not done because of small number of respondents in each group.

Table 3-29: Actions taken by pharmacists in response to observed DOs (n = 139)

Actions taken*	Number of respondents (%)		
	Hospital/ clinic (n= 87)	Community (n =52)	Total (n= 139[a])
Informed the physician in-charge	70 (80.5)	9 (17.3)	79 (56.8)
Noted in patient's chart/record	22 (25.3)	16 (30.8)	38 (27.3)
Referred patient to a hospital	7 (8.0)	21 (40.4)	28 (20.1)
Made an incident report/ record	24 (27.6)	2 (3.8)	26 (18.7)
Suggested an antidote	17 (19.5)	2 (3.8)	19 (13.7)
Counselled patient on the correct dose/ proper use of a drug	3 (3.4)	9 (17.3)	12 (8.6)
No action	4 (4.6)	8 (15.4)	12 (8.6)
Call national poison centre to clarify about the effects of drug overdoses	5 (5.7)	1 (1.9)	6 (4.3)
Suggest patient to inform doctor	-	4 (7.7)	4 (2.9)
Monitor patient through therapeutic drug monitoring	2 (2.3)	-	2 (1.4)
Suggest patient to stop medication	-	2 (3.8)	2 (1.4)
Suggest to doctor to reduce the dose	1 (1.1)	-	1 (0.7)
Treat symptoms	-	1 (1.9)	1 (0.7)

[a] *the total is based on the number of pharmacists who reported having observed DOs in the last six months (n= 139)*

**respondents had the choice to select more than one answer*

3.10 Discussion

3.10.1 Key findings and comparisons with other studies

At least half of the pharmacists reported having observed ADRs, MEs, and/or TFs in the last 6 months but less than half reported having observed DOs. Further evaluation showed that different groups of pharmacists (depending on work setting and/ or years of practice) reported having observed different types of ADEs. These are discussed in the following paragraphs.

More than 70% of hospital and clinic pharmacists reported having observed ADRs and MEs in the last 6 months where, 80% of those who observed ADRs and 73% of those who observed MEs, have practised for 5 years or fewer. Thus, a logical explanation for the high percentage of pharmacists from this group could be due to the implementation of the three-year compulsory service in the public sector for newly graduated pharmacists (where they work in either a hospital or a clinic). This has increased the number of pharmacists in the public sector, and one of the requirements for their training during these three years is to identify and report at least 10 ADR cases each year. Parallel to these findings, the number of reports received by MADRAC has also increased since the implementation of this three-year compulsory service – an almost 200% increase in reports between 2006 to 2011 [20]. Discussion with a pharmacist from MADRAC revealed this compulsory service as one of the main reasons for the increase in reports and this was evident in this survey, where almost 90% of the pharmacists who have practised for five years or less, claimed to have reported ADRs to MADRAC. A high percentage of hospital and clinic pharmacists observing MEs is expected, as it is one of their routines to receive and screen prescriptions before dispensing medication to patients. While screening, it is their responsibility to identify and rectify the prescribing and legal errors.

Out of 182 community pharmacists who have responded to this survey, 60% reported having observed ADRs whilst 56% reported observing TFs in the last 6 months. Additionally, almost 50% reported having observed MEs. It is an interesting finding as community pharmacists do not receive as many prescriptions as pharmacists in other countries. A study in Malaysia found that community pharmacists fill an average of 1.8 prescriptions per day [288]. This is because community pharmacists in Malaysia do not have dispensing rights – the traditional 'dispensing prescribers' are still in practice and community pharmacists have little involvement with dispensing of prescription medicines. The

events claimed seen by these pharmacists could have been patients' complaints about their medication, or perhaps the small numbers of prescriptions that they receive do come with errors. Furthermore the errors could also been due to OTC medicines. It is a limitation of this survey that the number of prescriptions received by the pharmacists responding to this survey was not identified to justify this finding. However, 54% of these pharmacists reported that the ADRs observed were associated with perindopril and 43%, with diclofenac. These indicate that ADRs seen by community pharmacists not only were associated with prescribed medicines but also over-the-counter (OTC) medicines which could explain the high percentage of them observing ADRs. Unlike other countries, most community pharmacists in Malaysia provide disease monitoring services such as screening patients' blood pressure, blood glucose and blood cholesterol levels. Whilst providing these services to patients, it is likely that they encounter patients with poor control of their medical conditions and thus, report on observing TF cases.

At least 30% of the pharmacists reported having observed cases of DO in the last 6 months. It is acceptable that hospital and clinic pharmacists are able to observe events of DO since these cases are regularly admitted to hospitals for medical attention. It was anticipated that community pharmacists would observe less DO compared with those working in the hospital setting, however a similar percentage of community pharmacists reported observing DOs. These DOs are likely to be less severe that those seen in the hospital. Perhaps, one limitation of the survey was that it did not ask about the severity of cases the respondents have witnessed. Although DO was defined in the questionnaire, it was still subject to individual interpretation of the pharmacists, thereby, affecting the way they classify the cases.

The following sections discuss experiences of pharmacists with different types of ADEs and the actions taken in response to these observed events.

3.10.1.1 Adverse drug reaction

More than half of the pharmacists who imparted having had observed ADRs in the last six months did so one or more times in each one month. This finding is similar with that of Vessal et al. [215] in a study of knowledge, attitude, and perceptions of pharmacists to ADRs in Iran. In this study, 73% of pharmacists reported that they have noticed an ADR during their daily work routines. However, majority of the pharmacists (90%) were community pharmacists. Similarly, another study by Irujo et al., [220] in Spain reported almost all pharmacists in their study have detected ADRs at least once in their professional life. These two studies did not state how frequently they noticed ADRs, however, the findings do suggest that pharmacists are capable of recognising and identifying ADRs in their work setting.

In response to the observed ADRs, most hospital or clinic pharmacist in this study claimed they made ADR reports. Community pharmacists, on the other hand, tend to refer the patients to their physicians which was also reported in a Spanish study of factors influencing ADR-reporting among community pharmacists [220]. The number of prescriptions received by community pharmacists in Malaysia is small [288] However, when patients report symptoms that the pharmacists attribute to potential ADRs and they think the patients need to take action, referring them to their physician is a reasonable course of action if there is no immediate need for medical intervention. It is reassuring that the results show that more than 70% of community pharmacists discussed the reaction with their patients. Similarly, a German survey of drug-related problems identified by community pharmacists cited that 37% of the community pharmacists solve these problems by consulting with patients [194].

In common with the report from MADRAC, it was found that reactions involving dermatological, gastrointestinal, and central nervous systems were the most often reported ADRs [241]. Furthermore, in both 2007 and 2008, perindopril was the drug with the highest number of ADR reports sent to MADRAC [287]. Incidentally, this was the drug most often reported by pharmacists in this survey as associated with ADRs. Furthermore, in common with other studies, cardiovascular drugs [72, 135, 136] and NSAIDs [71, 85, 124, 135, 140] were also frequently associated with ADRs. This is in contrast with the finding from the chart review study (Chapter 5) where antidiabetics were found instead, to be the most common drug associated with ADRs. However, the chart review study

had only identified ADR-related admissions whilst the ADRs in the survey were gathered from pharmacists working in various departments and work settings.

3.10.1.2 Spontaneous ADR reporting

Findings from the survey show that majority of the hospital or clinic pharmacists are actively involved in reporting ADRs. This is evident in the MADRAC bulletin where majority of reports received by MADRAC in 2010 were from hospital pharmacists working in the public sectors [20]. Only a small percentage of community pharmacists in this survey claimed to have ever reported ADRs even though many were aware of the existence of report forms and where to obtain them. Similar findings were also found in other studies [215, 220, 222, 229]. However, more than 40% of community pharmacists reported difficulty in obtaining the forms and its complexity. They have also reported that they lack knowledge regarding the regulations and procedure for reporting. These setbacks they expressed were also reported in a qualitative Malaysian study of barriers and facilitators to reporting of ADRs among community pharmacists [226]. Compared with community pharmacists, the ones in the hospitals or clinics in Malaysia have the advantage of receiving up-to-date information on ADR-reporting and obtaining report forms from the drug information centre located in almost all the public hospitals.

Pharmacists reported that they were more likely report a reaction if such was severe, not widely known, unusual, involved a newly marketed drug, or that there was an obvious causal relationship with the drug. Lack of information from affected patients was the major barrier to reporting ADRs. Widely known reactions and uncertainty about a causal relationship or the types of ADRs to be reported have discouraged pharmacists from reporting ADRs. The findings 'reaction is well known' and 'uncertain of the association between the reaction and the drug' as barriers to reporting ADRs were similar with other studies [215, 220, 221, 223, 225, 228]. This shows that pharmacists are still not confident and sure of what need to be reported, indicating the need for education on these aspects.

It is a matter of concern that more than 90% of the pharmacists believe that the purpose of monitoring ADR reports is to measure incidence of ADRs. The ADR reporting system is unsuitable for measuring the incidence due to incomplete numerators (number of ADR reports) and denominators

(number of patients exposed to a drug). A few studies have reported this misunderstanding by health care professionals [215, 216]. However, the main purposes of monitoring ADRs are also correctly reported by more than 80% of the pharmacists: to identify 'uncommon ADRs' and previously unknown ones and 'maintain a database of ADRs. More than 30% of the pharmacists believe that ADR reports are able to identify the indication for which the drugs are prescribed. This shows that either these pharmacists lack knowledge on the process of pharmacovigilance or they have misinterpreted the statement. However, this highlights the need for more education in ADR reporting systems and pharmacovigilance for pharmacists.

3.10.1.3 Therapeutic failure

More than 70% of the pharmacists who reported to have observed TFs in the last six months, revealed monthly encounters with one or more of its patients. This shows that the occurrence of TF was high. Its prevalence was also found to be high in the chart review study (Chapter 2 – Section 2.3.4). Other studies have also quoted that cases of TF was very common [63, 146].

The finding from this specific survey revealed that TF was common in patients with diabetes mellitus and hypertension. Studies in Malaysia have also highlighted that prevalence of hypertension and diabetes are on the rise, and 80% of the patients have poor control of their medical conditions [33, 34]. Adding to this, the National Health and Morbidity Survey III cited that hypertension and diabetes mellitus were two of the top four chronic medical conditions in Malaysia [260].

The actions reported taken by almost all pharmacists (counselling the patients as to the use of their drugs and the importance of medication adherence) indicated that most of these TFs are caused by patients' poor adherence to drugs and lack of knowledge of them. Similar causes were also reported by other studies [143, 146, 152, 153, 289]. This finding also showed that the pharmacists were actively involved in patient counselling and in connection, a study by Westerlund et al. [115] showed that interventions by community pharmacists were able to reduce or prevent the occurrence of adverse drug events [6, 290].

Almost 90% of the community pharmacists reported suggesting to patients with suspected TF to inform their physician. Where the pharmacists think the patient needs their treatment reviewed to

address the TF, this would be an appropriate course of action for the patient (where there is not an immediate need for medical intervention).

3.10.1.4 Medication error

About 80% of the hospital or clinic pharmacists reported having observed MEs in last six months and of these, 75% claimed encountering one or more MEs in a month. In contrast, only less than half of the community pharmacists reported having observed one. A high percentage of both groups of pharmacists reported of having observed prescribing errors most recently. In response to these observed errors, 83% of the hospital or clinic pharmacists claimed to have informed the physicians-in-charge, whilst 82% of the community pharmacists explained the errors to the patients. While 22% of community pharmacists contacted their physicians, more than 70% on the other hand, resorted to suggesting that patients inform their doctors. Furthermore, less than half of the hospital or clinic pharmacists and less than 10% of the community pharmacists claimed to have reported or recorded the incidences.

The specific finding of community pharmacists having observed MEs less commonly was similar with a UK-based investigation of prescribing errors and other problems reported by pharmacists [291]. Howver, studies conducted in Germany and Sweden [115, 194] revealed otherwise.

In common with other studies [147, 292, 293], prescribing error was the cited as the most common error. The error could be due to incorrect drug product selection, dose, dosage form, quantity, route of administration, concentration, rate of administration, or instructions for use of a drug [49].

Similar with other studies, the intervention hospital or clinic pharmacists mostly took in response to a medication error was contacting physicians [113]. In contrast, a few studies found that community pharmacists corrected most of the errors without contacting doing so [115, 195, 291]. However in studies by Hammerlein et al. [194] and Doucette et al. [191] physicians were contacted by community pharmacists in more than 60% of ME cases. In the present study, on the other hand, community pharmacists discussed with patients about the error and corrected them.

3.10.1.5 Drug overdose

The percentage of pharmacists observing patients with DOs was low (32%) and of these, about 60% have observed lesser cases of overdose in each month. Overdose related to analgesics (69%), and cough and cold medicines (56%) were reported more often by community pharmacists. In response to an overdose, more than 80% of the hospital or clinic pharmacists informed the physicians- in-charge, whilst about 40% of community pharmacists referred patients to hospitals. Only a small number of pharmacists reported counselling patients the correct dosage or proper use of drugs (9%).

The low percentage of pharmacists who have observed DOs may be attributed to low prevalence of the occurrence. Other studies in Malaysia have reported the prevalence of overdose to be 0.2% to 0.4% [164, 165], and overdoses were found in 1.9% of admissions in the in chart review study (Chapter 2 – Section 2.3.6). Analgesics were the drug group most often reported responsible for overdose cases. This was similar to the findings from other studies in Malaysia [165, 172] and in other countries [9, 11, 122, 171].

3.10.2 Methodological considerations

3.10.2.1 Selection of respondents

The survey aimed to determine the experiences of health care professionals relating to ADEs. This survey was to complement the chart review study by determining the extent of burden of ADEs in Malaysia. The initial plan was to survey all health care professionals where the chart review study was conducted but due to poor cooperation from the head of medical department, the plan was abandoned (see Section 3.2.9.1), and the survey was carried out with pharmacists who are members of MPS in Malaysia.

There are more than 6000 pharmacists registered in Malaysia. However, their complete details (names and addresses) were not available due to confidentiality restrictions of the Malaysian Board of Pharmacists. The only option was to obtain the information from Malaysian Pharmaceutical Society (MPS) where the names, addresses and/or work setting of its members are recorded. These details were not provided to the researcher. Staff from MPS agreed to post the questionnaires. Furthermore, MPS has experience of regularly sending conference invitations and pamphlets to its members. At the time of the study, there were 2000 members registered in MPS. Of these, 750 were hospital and health clinic pharmacists, 727 were community pharmacists, and 523 were working in other sectors such as industrial and education institutions. In view of poor response rates in other surveys conducted among health care professionals in Malaysia which is typically less than 30% [294, 295], it was decided that all 1477 pharmacists directly providing patient services (750 hospital or clinic pharmacists and 727 community pharmacists) should be included in the study. For this reason, a sample size calculation was not conducted.

Of the 472 respondents, 29 (6%) were working in other sectors. This shows that the information recorded in the MPS database was not up-to-date. The MPS database relies on pharmacists to update any changes in details and this is one of the limitations of this study. Some pharmacists may not have responded because their work setting does not involve direct interaction with patients. However, the questionnaire did include questions about work setting and whether or not the respondents have direct contact with patients. Pharmacists who worked in other sectors were requested to skip all the questions and proceed to the last section of the questionnaire which asked for demographic data. Perhaps, not being able to answer any of the questions discouraged these

respondents from returning the questionnaire. Another limitation may be that, those who have observed ADEs and have interaction with patients were more likely to be interested in the subject of the survey and therefore, have returned the questionnaires.

3.10.2.2 Questionnaire design and piloting

The pilot questionnaire was designed based on previously published questionnaire and discussion with research supervisors. Upon completion of the pilot study, many changes were made to the questionnaire – addition and/or deletion of questions. Due to time constraints, another pilot study was not conducted to test the reliability and validity of the new questionnaire and this is another limitation of this study. However the majority of questions remained the same and those that were changed or added were due to feedback in the pilot study requesting clarification or indicating confusion in the answers.

Correlation between variables could not be conducted. For example, a suspected ADR could not be correlated with a drug because both questions allowed more than one answers. Similarly, the actions taken in response to an ADE could not be correlated with an ADE or the drug(s) involved. However, the data from the survey was able to identify the types of ADEs pharmacists observed, the types of drugs, and the actions taken by pharmacists, giving an overview of practice in Malaysia and areas for possible interventions.

The respondents were asked to recall the types of ADEs, causative drugs, and actions taken in response to the ADEs observed in the last six months. There are possibilities that pharmacists had difficulty recalling the ADEs and tried to please the researcher in their answers. This meant that details may be recalled incorrectly or the events may not have actually taken place within the six-month-timeframe. Furthermore, pharmacists in the hospitals or specific wards (such as medical wards or ICU) may have observed a higher number of ADEs compared with others and it was not possible to identify this from the survey.

Although this survey was done to complement the chart review study (Chapter 2), the type of MEs identified through this survey is comprehensive compared with those identified through chart review. The list of MEs in the survey question covers all types of MEs (those which have caused harm

and those identified and prevented before causing harm), unlike the chart review study where only MEs that caused harm and led to hospital admissions were identified. This is due to the survey being aimed at both hospital and community pharmacists, and the types of MEs identified by both groups may have differed. Thus, the findings gathered on MEs from the chart review study may not be directly comparable with that of the survey.

3.10.2.3 Distribution of questionnaires and the response rate

Based on the results from the pilot study, almost 60% of the respondents preferred email to postal survey. The initial plan was to obtain the email addresses of all MPS-registered pharmacists from MPS and use an electronic survey program such as Survey Monkey®, in sending the questionnaires to the pharmacists. This may have increased the survey response rate. However, due to confidentiality constraints, MPS was not able to provide the email addresses and upon further discussion, it was decided to conduct a postal survey.

The low response rate (32%) to this survey means the results may not be generalisable to the pharmacist members of MPS. Nevertheless, this is typical of surveys in Malaysia that involve health care professionals whose response rates to questionnaires since 2000 vary between 30 to 88% [294] Moreover, a survey response rate of 37% [295] was reported in a 2010 publication involving community pharmacists. A number of reasons could have affected the low response from pharmacists in this survey. The distribution of first mailing was close to the Chinese New Year and thus, pharmacists may have been very busy preparing for the long break or on holiday. Other possible reasons for the low response include outdated address details found on the MPS database, absence of interest in the survey, or low knowledge about the subject by pharmacists.

3.10.2.4 Generalisability of data

A strength of this survey is that it collected information from pharmacists who were members of MPS. They receive constant updates from the society, thus, keeping them updated of the latest events or news. The pharmacist population in this survey may not be representative of all pharmacists in Malaysia because the experiences of non-MPS members were not explored. Members

of MPS may differ from other Malaysian pharmacists in that they chose to join the professional body, and thus, may be more up-to-date with clinical or legal issues affecting the profession. However, the extent to which being members of the MPS would have affected pharmacists' responses is unknown.

3.10.2.5 Ways in which this survey study could have been strengthened

The study would have been strengthened if all health care professionals were surveyed using the questionnaire. This would have given a better overview of the situation in Malaysia. However as detailed in Section 3.2.9.1, an attempt to do this was not successful. Perhaps, using professional bodies to survey other health care professionals rather than attempting one in a hospital setting might have been more successful.

The study could have also been strengthened if all Malaysian pharmacists were surveyed instead of only the MPS members. Unfortunately, this was not possible and the survey was conducted with the next most comprehensive group of pharmacists.

The questions in the questionnaire did not allow for further analysis of correlation between the types of ADEs and the causative drugs, or the actions taken in response to ADEs. This information would have given a better overview of the situation and practice in Malaysia. This limitation could potentially have been identified and rectified if a second pilot study was conducted, following the changes to the questionnaire after the pilot study. Although this would have strengthened this research, the information collected from the main study was still able to provide reliable information of the types of ADEs the pharmacists observed and their actions in response to them.

3.10.3 Implications

Health care system and health care professionals

The most common ADRs observed by the pharmacists were related to the dermatological, gastrointestinal, and central nervous systems. Pharmacists should be aware of this and suspect it in patients complaining of complications such as rash, itchiness, gastritis, diarrhoea, nausea, and dizziness, and thereafter, initiate further investigations. Furthermore, the drug most often reported observed by all the responding pharmacists was perindopril. This may be attributable to the increased usage of perindopril (almost 70% of increase between year 2006 and 2009) in Malaysia [260]. Knowing that ADRs associated with an ACEI are common, pharmacists can play an important role in regularly monitoring patients prescribed an ACEI. They have the opportunity to reduce the frequency and impact of ADRs through offering more advice on the possible causes of ADRs and appropriate therapies. This has been shown in a study of pharmacists' interventions through patient education and follow-up [6].

Whilst ADRs were reported as being observed by a high number of the sample pharmacists, there were differences in the management of the reactions between the two different groups. The hospital or clinic pharmacists have the habit of reporting ADRs while the community pharmacists referred the patients to their physicians and discussed the reactions with the patients. One reason for these differences could be the types of ADRs observed by both groups of pharmacists. Minor reactions such as gastritis, diarrhoea, nausea, and heartburn were more often reported by community pharmacists and therefore, may not be reported to MADRAC. These pharmacists solve the problems themselves by discussing them with the patients. Another reason could be that the hospital or clinic pharmacists are well informed about the procedure and process of reporting ADRs compared with community pharmacists. Thus, the latter group is prompted to refer the patients to their physicians instead, anticipating that the physicians themselves will be able to solve and report about the ADRs.

Although the current practice of reporting ADRs by hospital pharmacists is reassuring, they should be regularly updated and reminded of the importance of reporting ADRs to ensure that this practice is continued throughout their professional life. Community pharmacists on the other hand, should be

educated about the ADR report system and understand that reporting ADRs is the responsibility of all health care professionals.

It was previously known that knowledge and attitudes exerted strong influence on ADR reporting [229]. Thus, the low rate of reporting among community pharmacists in this study may be secondary to poor knowledge of it and its procedures. Training by MADRAC are mainly conducted in hospitals [241, 287] and are usually held within office hours. Such arrangements may have deterred community pharmacists from participating. This places the hospital or clinic pharmacists in a better position for good information on ADR report system. Furthermore, the existence of a drug information centre within each government hospital has made ADR reporting effortless for the said group of pharmacists. A study by Granas et al. [232] have shown that an educational program can change reporting attitudes of pharmacists in a positive manner. Attitudes are potentially modifiable, thus, MADRAC needs to improve and expand the promotion of ADR reporting to community pharmacists. MADRAC should understand the nature of work of the said pharmacists and tailor their training accordingly.

MADRAC has urged health care professionals to report all suspected reactions and this approach is taken to encourage the reporting culture among them. However, pharmacists in this study believe only certain types of ADRs (serious, unusual, or involving a new drug) should be reported. Perhaps, better and regular communication between MADRAC and pharmacists would change this misconception. Training and workshops should emphasize the expectation from MADRAC and the types of ADRs that need to be reported.

The high number of pharmacists observing patients with therapeutic failure places them in best position to provide patient counselling services. The pharmacists' involvement in patient counselling in this study showed that they understand its importance in improving patient healthcare. The introduction of MTAC in Malaysia has provided a platform for pharmacists to educate patients on their drugs and monitor its outcomes. MTAC has been running since 2004 in various public hospitals and is provided for medical conditions such as diabetes, hypertension, and renal failure. This service was found to have increased patients' adherence to medicines [211]. Similar approaches, if introduced in community pharmacies, would benefit the public. Additionally, pharmacists should be well-trained in educating patients and identifying ADEs.

Hospital pharmacists have the advantage of working in a multi-disciplined institution which allows them to have direct communication with other health care professionals. However, community pharmacists do not have the opportunity to directly interact with any general practitioners or physicians. A two-way communication will be useful in exchanging information and although the current health care system does not allow this between community pharmacists and GPs, the former should take the initiatives to contact GPs via telephone using the information provided by patients. It is not known whether or not patients who were asked to contact their physicians have actually contacted them. Thus, to ensure that patients receive adequate care and avoid further risk of ADEs, community pharmacists should be encouraged to communicate with GPs. Furthermore, effective communication between health care professionals and patients is important. This is essential so patients learn to build trust, be constantly motivated to adhere to medicine and understand problems that might influence their medication-taking behaviour.

The first step in preventing medication error is to design a system that accurately identifies errors and their causes. For example – pharmacist-led interventions or participation in the rounds was proven to reduce the occurrence of an error [78] and the use of CPOE [201] was found to detect and intercept an error before it reaches a patient. However, no single approach can be identified as the best method and each institute should evaluate which combination strategies will work best. For example; a medication error reporting system (MERS) in Malaysia was established in 2009 [21]. A total of 2,572 medication error reports were received since the system was started [242]. Probably due to its being a new system, most of the pharmacists do not have the habit of reporting MEs, or may not be aware of, or familiar with the system. Hence, there should be continuous evaluation of the system for improvement. Information and reminders should be disseminated regularly so that health care professionals are aware of the availability of an active system. If any such system is to make a substantial impact on patient care, a no-blame report system and allowance of anonymous reporting are needed to encourage self-reporting of errors. Additionally, regular training or workshops should be conducted to guide health care professionals as to how to report an incident and community pharmacists should be included. Once a system is in place, interventions can be targeted at places where high numbers of medication errors occur to improve the medication use process and the health care system.

Community pharmacists in Malaysia were found to be filling an average of 1.8 prescriptions per day [288]. A qualitative study in Malaysia also revealed that 10 out of 16 community pharmacists fill less than ten prescriptions per day [226]. Malaysia still practices the traditional "dispensing prescribers." Thus, community pharmacists have little involvement with dispensing of prescription medicines. Owing to this, the occurrence of medication errors related to prescribed drugs observed in community pharmacies may be lower compared to other countries. Furthermore, a low proportion of pharmacists reported documenting or reporting an error. Documentation of errors and the interventions taken to solve the errors should be encouraged. This practice could serve as a surveillance of the current health care system and an opportunity to evaluate and improve the system.

The most common errors observed by pharmacists were prescribing errors. The physician-pharmacist collaboration has been reported to have the potential to improve a patient's health [296]. This indicates that there is an opportunity for pharmacists to collaborate with physicians to make decisions about the appropriate drug therapy for a patient. Pharmacists can provide information on a suitable drug choice and dosage to physicians. The health care system in Malaysia is such that community pharmacists are not linked to any general practitioners or patient records. Hence, the decisions they make are based on the knowledge and information provided by patients. It is important to optimise communication among health care professionals to improve patient safety. Thus, community pharmacists should be encouraged to communicate and build good professional relationships with physicians whose patients regularly visit their pharmacy.

A retrospective study in Malaysia revealed that 24% of poisoning patients have already received treatment before admission to hospital [172] and most of them received treatment at private hospitals or private clinics. Thus, pharmacists may not be the first-line professionals who patients seek medical attention from. Nevertheless, despite the low prevalence, pharmacists do observe overdose cases during their daily work activity and thus, it is important for them to know what actions should be taken. Pharmacists should be educated about assessing overdose patients as prompt actions can save lives. A guideline for the pharmacists about overdose-patient management could be the first step. Such guideline is currently available for clinicians in the UK [297, 298]. This guideline assists them on the steps that need to be taken once a patient reports of taking an overdose of a drug.

In cases of DO, the current practice by the hospital or clinic pharmacists of informing the physicians-in-charge should be enhanced with their involvement in the team for better management. The pharmacists' role as provider of drug information to other health care professionals has been reported in a few studies [114, 192]. Hence, there are opportunities for them to provide information about antidotes that can be used and their availability in the hospitals.

The types of drugs associated with the cases of overdose observed by community pharmacists (analgesics, and cold and cough drugs) are easily available OTC. Community pharmacists have the opportunity to reduce the frequency and the impact of drug overdoses through offering more advice about its possibilities and on appropriate actions in cases of overdose. Pharmacists should provide advice on the proper use of medicines while emphasising safety to the patient. Furthermore, warning labels should be affixed on products or product information materials can be given out to the patients. As OTC drugs which are usually sold as blister strips do not have warning labels, pharmacists should supply them in boxes rather than individual strips.

Patients and society

Providing better advice to patients about their drugs and the expected ADRs has the potential to reduce the impact of ADRs for individuals and society. Patients should be given good counselling when medicines are dispensed, so they know what an ADR is and the actions that should be taken in response to such, for example, seeing a pharmacist or a doctor. Furthermore, practitioners should reassure patients of keeping their personal details confidential. Patients should also be educated on the importance of knowing their drugs and disclosing the drugs they have been consuming (prescribed, OTC, or herbal remedies) to their health care professionals.

The high percentage of therapeutic failure observed by the pharmacists is a matter of concern. The fact that many patients may lack knowledge on the proper use of their medicines and may have poor adherence problems shows that there is potential for an intervention strategy. A patient-centred strategy aimed at patients at risk should focus on improving their insights of their medical conditions, adherence to medicine, and also encouraging patients to lead a healthy lifestyle. The practice of 'doctor or pharmacist-hopping' by Malaysians makes monitoring of disease outcomes difficult. Perhaps, patients or their families should carry a list of all prescription drugs, OTC drugs, herbal

remedies and supplements, the indications for each drug, and any known drug allergies with them all the time. Every health care professional involved in patient care should have access to this list.

Although this study did not identify who was responsible for the occurrences of errors, patients can do a great deal to decrease their chances of experiencing a ME. Patients should know what questions to ask their health care professionals, how to insist on answers, and how to recognise situations that could result in MEs. Furthermore, patients should be involved in the process of decision making with regard to management of their medical conditions. Their participation could ensure that they understand why certain medicines are prescribed to them.

As discussed in Chapter 2 – Section 2.4.5, patients should be advised about the consequences of DO and to reach out for help in case of emotional distress. Patients should be advised on purchasing OTC drugs – only the amount required should be bought. Any unused drug should be appropriately disposed of, returning them to pharmacists or to physicians. In addition, it is important to educate patients about what actions to take in response to overdoses. Prompt actions may help in minimising the impacts of the events.

Research

- This study found that ADRs associated with perindopril was observed by most of the pharmacists. This may be the result of its increased usage. However, further investigation is needed especially on the types of reactions associated with the drug, so that appropriate measurement can be taken to reduce the frequency of these reactions.

- The findings from this study could provide a good source in designing an educational program aimed at promoting the reporting culture among community pharmacists. Further studies could be conducted in the future to evaluate the impacts of interventional strategies.

- The factors that encourage and discourage ADR reporting identified in this study were correlated with the questions asked in the questionnaire. Other factors which might have influenced the pharmacists' decision to report ADRs may be identified using qualitative studies.

- Further research to determine the causes of TFs could determine the areas for prevention strategies. The study should investigate medication-taking behaviour of patients and their beliefs about their medical conditions and medication.

- The high percentage of pharmacists who have observed TFs means that there is opportunity for an intervention study to advice patients on the best use of medicines. Despite the implementation of MTAC for diabetic and hypertension patients, a high percentage of pharmacists still have observed TFs in patients with diabetes mellitus and hypertension. Therefore, effectiveness of these services should be evaluated to ensure they deliver what they are expected to deliver and that further investigation could provide insights on improving the services.

- This survey was able to identify the most common MEs observed by the pharmacists. However, further investigation on the types of MEs and their causes is needed to identify the areas in need of attention.

- A study of the awareness of health care professionals of the existence of the current ME-report system and the barriers to report the events could provide information on improving the system.

- Further research is needed to provide more insights into the types of drugs involved in overdoses. The common modes and types of overdoses (accidental or intentional), and the group of consumers involved in such events should also be identified and explored before any intervention or prevention strategies are initiated.

- Analgesics have been found to be the common drug group used in overdoses, thus, further investigation on where these drugs are obtained and the actions that should be taken to overcome this problem should be made to provide a better view of the actual problem.

3.11 Summary

This study shows that pharmacists in Malaysia encounter patients with adverse drug events in their daily work activities. There were differences in the management of ADE patients by hospital or clinic pharmacists and community pharmacists. The role of pharmacists in identifying, resolving and preventing adverse drug events can be further enhanced through education and training, and better communication with physicians. Pharmacists also play an important role in educating patient about their drug therapy.

CHAPTER 4

SUMMARY DISCUSSION

This chapter collates the main findings from the chart review study and survey study. It provides a discussion of the important issues which have emerged from both studies and presents the implications of the findings for policy, practice, and future research.

The first aim of this thesis was to measure the prevalence of ADE-related admissions so that the extent of this problem and the drugs which are largest target for potential interventions can be identified. The second aim was to obtain the opinions of health care professionals in Malaysia and understand the current practices in their professions, so appropriate actions or interventions could be suggested to resolve any problems. The following key issues emerged from the two studies:

1) The occurrence of ADEs in a Malaysian hospital was high.

2) The most common drug classes associated with ADEs were cardiovascular drugs, anti-diabetics, anti-asthmatic drugs and analgesics.

3) Community pharmacists were not actively involved in ADR reporting.

4) Given the high levels of ADEs, the use of analgesics should be monitored carefully.

5) Prescribing errors were major contributor to medication error

The occurrence of ADEs in a Malaysian hospital

The findings of chart review and survey studies suggest that ADEs continue to be an important health care problem. The chart review study identified that 39% of admissions to two medical wards were related to ADEs, which is high compared with studies in other countries. Additionally, at least half of the respondents to the survey reported having observed ADRs, MEs, and/or TFs in the last six months. These suggest that ADEs may result in a large burden to the Malaysian health care system and that the extent of this may not be widely known. Thus, these studies (chart review and survey) may be the starting point in determining the actual situation in Malaysia.

It is important that the current emphasis on patient safety in Malaysia – the establishment of patient safety council, continuous efforts from MADRAC to promote the ADR reporting culture, and introduction of MERS – continues to receive support to ensure that the high proportion of ADEs is addressed.

Patient safety can be maximised and the optimal effects of drug treatment can be achieved by identifying, preventing, and solving potential complications – the core processes of pharmaceutical care [42]. Considering more than half of the pharmacists who responded to the questionnaire were able to identify ADEs in their daily work activities, it would be useful to include them in any prevention programs. As reported in the survey study, pharmacists perform a valuable role in supporting the patients in safely managing their medicines: communicating with them about ADEs, counselling them on the right way to consume medicines, and emphasising the importance of adherence. Although these roles are laudable, it is important that they are clearly defined and recognised within the health care system.

Pharmacists were able to identify ADEs during their daily work activities, so documenting them and the actions taken to resolve them should become part of routine practice for pharmacists. These data will be useful in monitoring the occurrence of ADEs, and sharing the documented information with MADRAC and other health care providers could improve awareness and therefore, improve ADE prevention.

The findings from both studies although useful, are limited in that they do not give a full picture of the prevalence of ADEs and the practices of all health care professionals in preventing ADEs in Malaysia. In order to fully understand the frequency of ADEs, a larger and multi-centred chart review

study involving public and private hospitals in Malaysia should be conducted. Although time-consuming and resource intensive, it would be able to provide a better picture. Furthermore, the practices of other health care professionals should be identified and evaluated in order to suggest educational interventions for efficient prevention strategies.

Drug classes associated with ADEs

The chart review and survey studies both identified some group of drugs which were responsible for the majority of ADEs. Both studies identified the following drug groups as major contributors: cardiovascular drugs, antidiabetics, anti-asthmatic drugs and analgesics. The four main medical conditions (hypertension, diabetes mellitus, asthma, and heart disease) that are prevalent in the Malaysian population [260], were implicated in the ADEs found in the chart review study and reported by pharmacists in the survey. The widespread use of these drugs may reflect the medical conditions that are highly prevalent in Malaysia, and probably explains the high ADE rate.

Targeting interventions at the prescription, administration and monitoring of these drugs could substantially reduce the prevalence of ADEs. This would result in better quality of life for patients and cost savings for Malaysian health care system. Some useful strategies for prevention could include targeted education about the main causes of ADEs (updates on the most common drugs causing ADEs and strategies to identify ADEs), targeted patient monitoring (patients prescribed drugs most likely to result in ADEs should be carefully monitored) and targeted computer alerts (using computerised databases for records and prescribing could help reduce ADEs both in preventing and identifying problems).

Due to the increasing number of drugs available, regimen complexity, changing drug interactions and adverse events, health care professionals need to be kept up to date. Thus, education on main causes of ADEs whether it be as bulletin posts, online alerts, seminars, or workshops should be available to health care professionals to both help prevent ADEs and identify them where they do occur.

Cardiovascular drugs, antidiabetics, anti-asthmatic drugs and analgesics were the major causes of ADEs in the present studies and patients prescribed these drugs are likely to be at higher risk of

experiencing an ADE. Thus, these patients should be monitored for ADEs by all the health care professionals involved in their care. Health care professionals also have a responsibility to ensure that patients are aware of the risks with the medicines they are taking and what to do if they experience any unwanted effects.

Computerized systems at hospitals perform many different functions. The essential functions in relation to ADEs are in their identification, monitoring, and prevention [111, 131, 201]. Computer alerts could be targeted at the drugs most likely to cause ADEs. These may aid in both the prevention of ADEs and in decreasing the harm resulting from ADEs. Many hospitals in Malaysia are not yet equipped with computerised systems, although some do have such systems, computer ADE alerts may play an important role in preventing future ADEs in these hospitals. Nevertheless, further research is needed to assess the effectiveness of any system in producing alerts and minimising ADEs.

Community pharmacists and ADR reporting

The role of community pharmacists in spontaneous ADR reporting is crucial since it enables monitoring of patient treatment in real-life conditions. The majority of community pharmacists who responded to the survey had not reported an ADR. This may be attributable to a lack of awareness of the reporting system in Malaysia or that any reactions they see may be mild or moderate, something the pharmacists felt they were able to resolve and therefore were not important enough to report.

The literature shows that knowledge and attitudes towards ADR reporting exerts a strong influence on actual reporting [229]. However, knowledge and attitudes are modifiable and therefore educational programmes targeted at community pharmacists could increase reporting. Such programmes have been shown to significantly modify pharmacists' reporting-related attitudes, and influence the ADR reporting behaviour in a positive way[232]. MADRAC should encourage community pharmacists to report ADRs by involving them in their training which should be tailored to the nature of community pharmacists' work. MADRAC should also facilitate the process of reporting by making reporting forms easily available and easy to complete. It is also important to improve communication between MADRAC and community pharmacists if reporting rates are to increase. The proposed training should be assessed by evaluating the pharmacists' attitudes towards

ADR reporting before and after such programmes. This will provide an insight whether these educational interventions are successful or need further improvement.

The use of analgesics should be carefully monitored

Analgesics were found to be the most common drugs associated with overdose in the chart review and survey studies. These drugs were also found to be one of the most common drugs implicated in ADRs in the survey study. As these drugs are known to be associated with ADEs and are widely used [299] careful monitoring of patients using such medicines is essential.

The most common analgesic associated with overdose in the chart review study was paracetamol. Pharmacists reported diclofenac, mefenamic acid and paracetamol were associated with ADRs in the survey study. A survey in Malaysia reported that analgesics were the most commonly used nonprescription medications with paracetamol as the most common active ingredient [299]. Although a high number of pharmacists, especially community pharmacists in the survey, reported having observed overdoses associated with analgesics, it was not possible to identify the type of analgesics from the questionnaire. It is not known where the drugs were obtained by patients but in Malaysia it was reported that many patients purchase these medications from pharmacies, and less than 30% obtained them from non-pharmacy outlets such as doctors' clinics, grocery shops, Chinese medical halls, supermarkets, and convenient stores [299].

Because of the widespread availability of analgesics, self-medication with these drugs has become commonplace. Patients may not realise the potential toxicity and adverse effects associated with the long-term or inappropriate use of analgesics. They may use the drugs at higher than recommended doses or in combinations that magnify the risk of adverse effects. Pharmacists who responded to the survey were able to identify ADRs and overdoses related to analgesics and therefore have a significant role in providing good quality information about analgesics, including warning consumers of their potential side effects. Furthermore, pharmacists could also play an important role in the selection and safe use of these drugs. The maximum doses of paracetamol for adults should not exceed 4 grams (usually 8 tablets) per day, and pharmacists must emphasize such precautions to the general public to prevent misuse and to minimize the occurrence of side effects.

Better monitoring by health care professionals is needed in terms of adverse reactions and overdose to analgesics. Increased collaboration among poison centres, pharmacists and other health care professionals is needed, together with better databases for recording information to identify problems and allow appropriate remedial actions. Where analgesics are supplied, health care professionals should be aware of potential adverse effects of these drugs when prescribing. Additionally, patients should be properly counselled on the appropriate and safe use of analgesics.

Prescribing errors are major contributor to medication error

At every stage of the medication-use process there is a risk of error and the stages most frequently associated with errors are prescribing and administration [3] and are important targets for prevention. In the chart review study there were 15 ME cases - all of them were due to prescribing error. Additionally in the survey study, the most common MEs reported by pharmacists were prescribing errors.

Pharmacists play a key role in preventing and resolving prescribing errors. The survey showed that pharmacists were able to identify and classify medication errors. They had also tried to resolve the errors by correcting them, contacting or informing the prescribers and discussing with the patient about the error. There are several other ways pharmacists can play their part in reducing prescribing errors such as: checking for errors as prescriptions are received; contacting prescribers for clarification or amendment before filling prescriptions; visiting the wards to review patient charts; providing suggestion to the prescribers; conducting medicine reconciliation and medication review [300]. These roles should be maintained and developed as a part of a strategy to reduce prescribing errors. Pharmacists need to equip themselves with sufficient skills and spend adequate time on clinical duties. Interventions made by pharmacists should be documented as analysing those interventions is a useful method to investigate prescribing errors and therefore devising ways to prevent or reduce them. Although this study was able to give an overview of the type of errors observed in the hospital and community settings, it was not able to provide the cause or source of the errors nor was it able to determine whether or not the actions taken or suggested by pharmacists were accepted by prescribers or resulted in positive outcomes for patients. Further research would provide details about strategies that work best to prevent or reduce ME in the Malaysian context.

Inappropriate prescribing involves the use of medicines that pose more risk than benefit, misuse of medicines (inappropriate dose or duration), the prescription of medicines with clinically significant drug-drug and drug-disease interactions and the underuse of potentially beneficial medications [185]. Education is the main strategy to ensure that prescribers are equipped to prescribe appropriately and safely [208]. This strategy should focus on stopping the errors before they occur. For example, prescribers should be educated in how to determine the dose of a drug and its frequency of administration, including how the medicine should be monitored and any adjustments made. In any attempt to prevent errors, it is important that prescribers are aware the patterns of error and the most common medications involved. These patterns may change over time as new medicines come to market and changes in disease patterns. Thus, such information should be disseminated to the prescribers, accompanied by education on appropriate prescribing. Prescribers should actively interact with pharmacists to obtain drug information and work together to minimise medication errors. In a health care system where patients can consult more than one physician and may use multiple pharmacies, communication between health care professionals is essential in providing care that is in the interest of patients. The survey study investigated the types of MEs observed and the actions taken by pharmacists but little is known about the experiences and practices of other health care professionals. Expanding the survey to other health care professionals would provide a wider picture of the situation in Malaysia.

Recently the Malaysian Ministry of Health (MOH) established a Medication Error Reporting System (MERS) to encourage ME reporting and documentation [21]. The system was launched during the survey and so the survey was not able to obtain information about the utilisation of the system by pharmacists. This move by MOH is commendable and all health care professionals should be trained and encouraged to report MEs in order to move towards safer practice. The details of reports received by MERS should be made public, whilst maintaining the confidentiality of the reporters. By reviewing the errors and sharing them openly, health care professionals can learn safer methods of practice which will benefit patients. Future studies should focus on investigating the reports received by MERS in terms of the types of errors and reporters.

4.1 Summary

The occurrence of ADEs in a hospital in Malaysia was found to be high with cardiovascular drugs as the major contributor. Pharmacists play an important role in preventing ADEs by providing education and counselling to patients. Educational interventions on the main causes of adverse drug events, patient monitoring and appropriate prescribing should be developed to both prevent ADEs and minimise their impact, where they do occur. Adverse drug events and interventions taken in relation to them should be documented as this will be useful in monitoring such events. Dissemination of ADE information to both health care professionals and patients has the potential to improve awareness and reduce harm.

REFERENCES

1. Hurwitz, N, *Admissions to hospital due to drugs.* Br Med J, 1969. **1**: p. 539-540.

2. Seidl, LG, Thornton, GF, and Cluff, LE, *Epidemiological studies of adverse drug reactions.* Am J Public Health, 1965. **55**(8): p. 1170-1175.

3. Hepler, CD, *Understanding Adverse Drug Therapy Outcomes*, in *Preventing Medication Errors and Improving Drug Therapy Outcomes: A Management Systems Approach.*, Hepler, C.D. and Segal, R., Editors. 2003, CRC Press: Boca Raton, Florida.

4. Knudsen, P, Herborg, H, Mortensen, AR*, et al.*, *Preventing medication errors in community pharmacy: frequency and seriousness of medication errors.* Qual Saf Health Care, 2007. **16**: p. 291-296.

5. Morris, CJ and Cantrill, JA, *Preventing drug-related morbidity – the development of quality indicators.* J Clin Pharm Ther, 2003. **28**(4): p. 295-305.

6. Schnipper, JL, Kirwin, JL, Cotugno, MC*, et al.*, *Role of Pharmacist Counseling in Preventing Adverse Drug Events After Hospitalization.* Archive of Internal Medicine, 2006. **166**: p. 565-571.

7. Kohn, L, Corrigan, J, and Donaldson, M. 2000: Institute of Medicine: Washington DC.

8. Raschetti, R, Morgutti, M, Menniti-Ippolito, F*, et al.*, *Suspected adverse drug events requiring emergency department visits or hospital admissions.* Eur J Clin Pharmacol, 1999. **54**: p. 959-963.

9. Bhalla, N, Duggan, C, and Dhillon, S, *The incidence and nature of drug-related admissions to hospital.* Pharmaceutical Journal, 2003. **270**(7246): p. 583-586.

10. Chan, M, Nicklason, F, and Vial, JH, *Adverse drug events as a cause of hospital admission in the elderly.* Int Med J, 2001. **31**: p. 199-205.

11. Schwake, L, Wollenschläger, I, Stremmel, W*, et al.*, *Adverse drug reactions and deliberate self-poisoning as cause of admission to the intensive care unit: a 1-year prospective observational cohort study.* Intensive Care Med, 2009. **35**(2): p. 266-274.

12. Lazarou, J, Pomeranz, BH, and Corey, PN, *Incidence of Adverse Drug Reactions in Hospitalized Patients: A Meta-analysis of Prospective Studies.* JAMA, 1998. **279**(15): p. 1200-1205.

13. Bates, DW, Cullen, DJ, Laird, N*, et al.*, *Incidence of Adverse Drug Events and Potential Adverse Drug Events: Implications for Prevention.* Journal of the American Medical Association, 1995. **274**(1): p. 29-34.

14. Classen, DC, Pestotnik, SL, Evans, RS*, et al.*, *Adverse Drug Events in Hospitalized Patients: Excess Length of Stay, Extra Costs, and Attributable Mortality.* JAMA, 1997. **277**(4): p. 301-306.

15. Leape, LL, Brennan, TA, Laird, N*, et al.*, *The Nature of Adverse Events in Hospitalized Patients.* N Engl J Med, 1991. **324**(6): p. 377-384.

16. Bates, D, Spell, N, Cullen, D*, et al.*, *The costs of adverse drug events in hospitalized patients.* Adverse Drug Events Prevention Study Group, 1997. **277**(4): p. 307 - 311.

17. MOH. *Patient Safety Council of Malaysia*. [cited 2012 20 Jan]; Available from: http://patientsafety.moh.gov.my/modules/mastop_publish/?tac=Introduction.

18. *Malaysian Guidelines for the Reporting and Monitoring of Adverse drug Reactions*. 2002 [cited 2008 10 Jan]; Available from: http://www.bpfk.gov.my/madrac.

19. Syed, A, *Pharmacovigilance Initiatives in Malaysia.* Drug Inf J, 2003. **37**: p. 143(S)-148(S).

20. MADRAC (April 2011) *MADRAC Newsletter*.

21. (June 2010) *Medication Safety Newsletter*. **2**.

22. Farooqui, M, Noorizan, AA, Hassan, Y*, et al.*, *Drug related problems as a cause of admission to the medical wards of hospital Pulau Pinang. Abstracts Of The 5th Asian Conference On Clinical Pharmacy, 23–26 July 2005, Penang, Malaysia.* Malaysian Journal of Pharmaceutical Sciences, 2005. **3**(2): p. 65-66.

23. Loganadan, NK, Ab Rahman, NS, and Mokhtar, F, *A Study On The Management Of Uncontrolled Diabetes In Medical Wards Of Hospital Kuala Lumpur. Abstracts Of The 5th Asian Conference On Clinical Pharmacy, 23–26 July 2005, Penang, Malaysia.* Malaysian Journal of Pharmaceutical Sciences, 2005. **3**(2): p. 43-114.

24. *The Source of Malaysia's Official Statistics*. 20 June 2011 [cited 2011 20 June]; Available from: http://www.statistics.gov.my.

25. MOH. *Health Facts*. 2009 [cited 2011 14 Feb]; Available from: http://www.moh.gov.my/images/gallery/stats/heal_fact/healthfact-P_2009.pdf.

26. *Malaysian Ministry of Health*. [cited 2010 4 Jan]; Available from: http://www.moh.gov.my/.

27. MOH (2010) *Health Facts*.

28. *Pharmaceutical Services Division*. [cited 2011 11 Jan]; Available from: http://www.pharmacy.gov.my.

29. Hasan, SS, Chong, DWK, Ahmadi, K*, et al.*, *Influences on Malaysian Pharmacy Students' Career Preferences.* Am J Pharm Educ, 2010. **74**(9): p. Article166.

30. *Pharmacists' three-year stint with Govt reduced to one*, in *The Star Online*. 2011.

31. *Malaysian Pharmaceutical Society*. [cited 2011 20 Dec]; Available from: http://www.mps.org.my.

32. Amal, N, Paramesarvathy, R, Tee, G*, et al.*, *Prevalence of Chronic Illness and Health Seeking Behaviour in Malaysian Population: Results from the Third National Health Morbidity Survey (NHMS III) 2006.* Med J Malaysia, 2011. **66**(1).

33. Rampal, S, Rampal, L, Rahmat, R*, et al.*, *Variation in the Prevalence, Awareness, and Control of Diabetes in a Multiethnic Population: A Nationwide Population Study in Malaysia.* Asia Pac J Public Health, 2010. **22**(2): p. 194-202.

34. Rampal, L, Rampal, S, Azhar, MZ*, et al.*, *Prevalence, awareness, treatment and control of hypertension in Malaysia: A national study of 16,440 subjects.* Public Health, 2008. **122**: p. 11-18.

35. Wan Ahmad, WA and Sim, KH, *Annual Report of the National Cardiovascular Disease-Acute Coronary Syndrome Registry Malaysia 2006.* Kuala Lumpur, 2006.

36. Letchuman, GR, Wan Nazaimoon, WM, Wan Mohamad, WB*, et al.*, *Prevalence of Diabetes in the Malaysian National Health Morbidity Survey III 2006.* Med J Malaysia, 2010. **65**(3): p. 173-179.

37. Tan, MY and Magarey, J, *Self-care practices of Malaysian adults with diabetes and sub-optimal glycaemic control.* Patient Educ Couns, 2008. **72**: p. 252-267.

38. ASHP, *Suggested definitions and relationships among medication misadventures, medication errors, adverse drug events, and adverse drug reactions*, in *Am J Health Syst Pharm*. 1998. p. 165-166.

39. Nebeker, JR, Samore, MH, and Barach, P, *Clarifying Terminology for Adverse Drug Events.* Ann Intern Med, 2005. **142**(1): p. 77-78.

40. Aronson, JK, Ferner, R. E., *Clarification of terminology in drug safety.* Drug Saf, 2005. **28**(10): p. 851-870.

41. Strand, L, Morley, P, Cipolle, R*, et al.*, *Drug-related problems: their structure and function.* Ann Pharmacother, 1990. **24**(11): p. 1093-1097.

42. Hepler, C and Strand, L, *Opportunities and responsibilities in pharmaceutical care.* Am J Health Syst Pharm, 1990. **47**(3): p. 533-543.

43. Ackroyd-Stolarz, S, Hartnell, N, and MacKinnon, NJ, *Demystifying medication safety: Making sense of the terminology.* Res Soc Adm Pharm, 2006. **2**(2): p. 280-289.

44. Gurwitz, JH, Field, TS, Avorn, J*, et al.*, *Incidence and preventability of adverse drug events in nursing homes.* The American Journal of Medicine, 2000. **109**(2): p. 87-94.

45. WHO. *Safety Monitoring of Medicinal Product: Guidelines for setting up and running a pharmacovigilance centre*. 2000 [cited 2009 25 May]; Available from: http://www.who-umc.org/graphics/4807.pdf.

46. Nebeker, JR, Barach, P, and Samore, MH, *Clarifying Adverse Drug Events: A Clinician's Guide to Terminology, Documentation, and Reporting.* Ann Intern Med, 2004. **140**: p. 795-801.

47. Handler, SM, Wright, RM, Ruby, CM*, et al.*, *Epidemiology of Medication-Related Adverse Events in Nursing Homes.* The American Journal of Geriatric Pharmacotherapy, 2006. **4**: p. 264-272.

48. Karuppannan, M, Mohd Ali, S, Wong, KT, KN*, et al.*, *Adverse drug events related medical admission in Malaysia: A pilot study.* Pharm World Sci, 2009. **31**(4): p. 502-503.

49. *The NCC MERP Taxonomy of Medication Errors*. [cited 2009 15 September]; Available from: http://www.nccmerp.org/pdf/taxo2001-07-31.pdf.

50. (2009) *Guideline On Medication Error Reporting*.

51. Aronson, JK, *Medication errors: definitions and classification.* Br J Clin Pharmacol, 2009. **67**(6): p. 599-604.

52. Ferner, RE and Aronson, JK, *Clarification of Terminology in Medication Errors: Definitions and Classification.* Drug Saf, 2006. **29**: p. 1011-1022.

53. von Laue, N, Schwappach, D, and Koeck, C, *The epidemiology of preventable adverse drug events: A review of the literature.* Wien Klin Wochenschr, 2003. **115**(12): p. 407-415.

54. Howard, R, Avery, A, and Bissell, P, *Causes of preventable drug-related hospital admissions: a qualitative study.* Qual Saf Health Care, 2008. **17**(2): p. 109-116.

55. Aronson, JK, *Medication errors: what they are, how they happen, and how to avoid them.* The Quarterly Journal of Medicine, 2009(102): p. 513-521.

56. McDowell, SE, Ferner, HS, and Ferner, RE, *The pathophysiology of medication errors: how and where they arise.* Br J Clin Pharmacol, 2009. **67**(6): p. 605-613.

57. USP. *The Medication Use Process*. [cited 2011 10 March]; Available from: http://www.usp.org/pdf/EN/patientSafety/medicationUseProcess.pdf.

58. Barber, N, *Should we consider non-compliance a medical error?* Qual Saf Health Care, 2002. **11**(1): p. 81-84.

59. Edwards, IR and Aronson, JK, *Adverse drug reactions: definitions, diagnosis, and management.* The Lancet, 2000. **356**(9237): p. 1255-1259.

60. Rawlins, MD and Thompson, JW, *Mechanism of adverse drug reactions*, in *Textbook of adverse drug reactions*, Davies, D.M., Editor. 1991, Oxford University Press: Oxford. p. 18-41.

61. Figueiras, A, Pedros, C, Valsecia, M*, et al.*, *Therapeutic Ineffectiveness: Heads or Tails?* Drug Saf, 2002. **25**: p. 485-487.

62. Hallas, J, Harvald, B, Gram, LF*, et al.*, *Drug-related hospital admission: the role of definition and intensity of data collection and the possibility of prevention.* J Int Med, 1990. **228**: p. 83-90.

63. Nelson, KM and Talbert, RL, *Drug-related hospital admissions.* Pharmacotherapy, 1996. **16**(4): p. 701-707.

64. Meyboom, RHB, Lindquist, M, and Egberts, ACG, *An ABC of Drug-Related Problems.* Drug Saf, 2000. **22**(6): p. 415-423.

65. Camidge, DR, Wood, RJ, and Bateman, DN, *The epidemiology of self-poisoning in the UK.* Br J Clin Pharmacol, 2003. **56**(613-619).

66. Buykx, P, Dietze, P, Ritter, A*, et al.*, *Characteristics of medication overdose presentations to the ED: how do they differ from illicit drug overdose and self-harm cases?* Emerg Med J, 2010. **27**(7): p. 499-503.

67. Haddad, PM and Anderson, IM, *Recognising and managing antidepressant discontinuation symptoms.* Advances in Psychiatric Treatment, 2007. **13**: p. 447-457.

68. Britton, JW, *Antiepileptic Drug Withdrawal: Literature Review.* Mayo Clin Proc, 2002. **77**: p. 1378-1388.

69. Meredith, PA, *Therapeutic implications of drug 'holidays'.* Eur Heart J, 1996. **17 (Supplement A)**: p. 21-24.

70. Graves, T, Hanlon, JT, Schmader, KE*, et al.*, *Adverse events after discontinuing medications in elderly outpatients.* Arch Intern Med, 1997. **157**(19): p. 2205-2210.

71. Pirmohamed, M, James, S, Meakin, S*, et al.*, *Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients.* BMJ, 2003. **329**(7456): p. 15-19.

72. Ramesh, M, Pandit, J, and Parthasarathi, G, *Adverse drug reactions in a South Indian hospital - their severity and cost involved.* Pharmacoepidemiology and Drug Safety, 2003. **12**(8): p. 687-692.

73. Schoenemann, JH, Muller-Oerlinghausen, B, Munter, K-H*, et al.*, *Adverse Drug Reactions (ADR) Causing Hospital Admissions. .* Pharmacoepidemiology and Drug Safety, 1998. **7**: p. S1-S3.

74. Jha, AK, Kuperman, GJ, Rittenberg, E*, et al.*, *Identifying hospital admissions due to adverse drug events using a computer-based monitor.* Pharmacoepidemiol and Drug Saf, 2001. **10**(2): p. 113-119.

75. Jha, AK, Kuperman, GJ, Teich, JM*, et al.*, *Identifying adverse drug events: Development of a computer-based monitor and comparison with chart review and stimulated voluntary report.* J Am Med Inform Assoc, 1998. **5**(3): p. 305-314.

76. Barker, KN, Flynn, EA, Pepper, GA*, et al.*, *Medication Errors Observed in 36 Health Care Facilities.* Arch Intern Med, 2002. **162**(16): p. 1897-1903.

77. Buckley, MS, Erstad, BL, Kopp, BJ*, et al.*, *Direct observation approach for detecting medication errors and adverse drug events in a pediatric intensive care unit*.* Pediatr Crit Care Med, 2007. **8**(2): p. 145-152 110.1097/1001.PCC.0000257038.0000239434.0000257004.

78. Leape, LL, Cullen, DJ, Clapp, MD*, et al.*, *Pharmacist Participation on Physician Rounds and Adverse Drug Events in the Intensive Care Unit.* JAMA, 1999. **282**(3): p. 267-270.

79. Mehuys, E, Van Bortel, L, De Bolle, L*, et al.*, *Effectiveness of pharmacist intervention for asthma control improvement.* European Respiratory Journal 2008, 2008. **31**: p. 790-799.

80. van der Hooft, CS, Sturkenboom, MC, van Grootheest, K*, et al.*, *Adverse drug reaction-related hospitalisations. A nationwide study in The Netherlands.* Drug Saf, 2006. **29**(2): p. 162-168.

81. Carrasco-Garrido, P, de Andres, L, Barrera, V*, et al.*, *Trends of adverse drug reactions related-hospitalizations in Spain (2001-2006).* BMC Health Serv Res, 2010. **10**(1): p. 287.

82. Morimoto, T, Gandhi, TK, Seger, AC*, et al.*, *Adverse drug events and medication errors: detection and classification methods.* Qual Saf Health Care, 2004. **13**(4): p. 306-314.

83. Hallas, J, Gram, LF, Grodum, E*, et al.*, *Drug related admissions to medical wards: a population based survey.* Br J Clin Pharmacol, 1992. **33**(1): p. 61-68.

84. Rivkin, A, *Admissions to a medical intensive care unit related to adverse drug reactions.* American Journal of Health-System Pharmacists, 2007. **64**: p. 1840-1843.

85. Brvar, M, Fokter, N, Bunc, M*, et al.*, *The frequency of adverse drug reaction related admissions according to method of detection, admission urgency and medical department specialty.* BMC Clin Pharmacol, 2009. **9**(8).

86. Chan, A, Garratt, E, Lawrence, B*, et al.*, *Effect of Education on the Recording of Medicines on Admission to Hospital.* J Gen Intern Med, 2010. **25**(6): p. 537-542.

87. Lau, HS, Florax, C, Porsius, AJ*, et al.*, *The completeness of medication histories in hospital medical records of patients admitted to general internal medicine wards.* Br J Clin Pharmacol, 2000. **49**(6): p. 597-603.

88. FitzGerald, RJ, *Medication errors: the importance of an accurate drug history.* Br J Clin Pharmacol, 2009. **67**(6): p. 671-675.

89. Rozich, JD, Haraden, CR, and Resar, RK, *Adverse drug event trigger tool: a practical methodology for measuring medication related harm.* Qual Saf Health Care, 2003. **12**(3): p. 194-200.

90. Griffin, FA and Resar, RK, *IHI Global Trigger Tool for Measuring Adverse Events*, in *IHI Innovation Series white paper*. 2007, Institute for Healthcare Improvement: Cambridge, Massachusetts.

91. Singh, R, McLean-Plunckett, EA, Kee, R*, et al.*, *Experience with a trigger tool for identifying adverse drug events among older adults in ambulatory primary care.* Qual Saf Health Care, 2009. **18**(3): p. 199-204.

92. Al-Tajir, GK and Kelly, WN, *Epidemiology, Comparative Methods of Detection, and Preventability of Adverse Drug Events.* Ann Pharmacother, 2005. **39**(7): p. 1169-1174.

93. Ferner, RE, *The epidemiology of medication errors: the methodological difficulties.* Br J Clin Pharmacol, 2009. **67**(6): p. 614-620.

94. Hurdle, JF, Weir, CR, Roth, B*, et al. Critical gaps in the world's largest electronic medical record: ad hoc nursing narratives and invisible adverse drug events.* in *AMIA Symp*. 2003.

95. Schneider, P, *Workshop summaries.* Am J Health Syst Pharm, 2002. **59**(23): p. 2333-2336.

96. Gandhi, TK, Seder, DL, and Bates, DW, *Methodology matters. Identifying drug safety issues: from research to practice.* Int J Qual Health Care, 2000. **12**(1): p. 69-76.

97. Gandhi, T, Burstin, H, Cook, E*, et al.*, *Drug complications in outpatients.* J Gen Intern Med, 2000. **15**(3): p. 149-154.

98. *The use of the WHO-UMC system for standardised case causality assessment.* 2005 [cited 2008 July 30]; Available from: http://www.who-umc.org/graphics/4409.pdf.

99. Naranjo, CA, Busto, U, Sellers, EM*, et al.*, *A method for estimating the probability of adverse drug reactions.* Clinical Pharmacology and Therapeutic, 1981. **30**(2): p. 239-245.

100. O'Neil, AC, Petersen, LA, Cook, EF*, et al.*, *Physician Reporting Compared to Medical-Record Review to Identify Adverse Medical Events.* Ann Intern Med, 1993. **119**(5): p. 370-376.

101. *National Coordinating Council for Medication Error Reporting and Prevention*. 1 May 2008]; Available from: http://www.nccmerp.org/.

102. *Institute of Safe Medication Practices Canada*. 24 December 2009]; Available from: https://www.ismp-canada.org/err_report.htm.

103. *National Patient Safety Agency: National Reporting and Learning Service*. 20 December 2009]; Available from: http://www.nrls.npsa.nhs.uk/report-a-patient-safety-incident/.

104. *New Zealand National Poisons Centre*. 20 December 2009]; Available from: http://poisons.co.nz/.

105. *National Capital Poisoning Center*. 20 December 2009]; Available from: http://www.poison.org/.

106. *National Poisons Information Service*. 20 December 2009]; Available from: http://www.npis.org/.

107. *National Poison Centre, Universiti Sains Malaysia*. 20 December 2009]; Available from: http://www.prn.usm.my/.

108. Hazell, L and Shakir, SAW, *Under-reporting of adverse drug reactions : a systematic review.* Drug Saf, 2006. **29**: p. 385-396.

109. Nita, Y, Plumridge, RJ, and Batty, KT, *Adverse drug reaction reporting in Australian hospitals.* Int J Pharm Pract, 2004. **12**(3): p. 155-161.

110. Thiessard, F, Roux, E, Miremont-SalamÃ©, G*, et al.*, *Trends in Spontaneous Adverse Drug Reaction Reports to the French Pharmacovigilance System (1986-2001).* Drug Saf, 2005. **28**(8): p. 731-740.

111. Classen, DC, Pestotnik, SL, Evans, RS*, et al.*, *Computerized surveillance of adverse drug events in hospital patients.* Qual Saf Health Care, 2005. **14**(3): p. 221-226.

112. Taxis, K and Barber, N, *Causes of intravenous medication errors: an ethnographic study.* Qual Saf Health Care, 2003. **12**(5): p. 343-347.

113. Davydov, L, Caliendo, GC, Smith, LG*, et al.*, *Analysis of Clinical Intervention Documentation by Dispensing Pharmacists in a Teaching Hospital.* Hosp Pharm, 2003. **38**(4): p. 346-350.

114. Lada, P and Delgado, G, *Documentation of pharmacists' interventions in an emergency department and associated cost avoidance.* American Journal of Health-System Pharmacists, 2007. **64**: p. 63-68.

115. Westerlund, T, AlmarsdÓTtir, AB, and Melander, A, *Drug-related problems and pharmacy interventions in community practice.* Int J Pharm Pract, 1999. **7**(1): p. 40-50.

116. Waller, P, Shaw, M, Ho, D*, et al.*, *Hospital admissions for 'drug-induced' disorders in England: a study using the Hospital Episodes Statistics (HES) database.* Br J Clin Pharmacol, 2005. **59**(2): p. 213-219.

117. Winterstein, A, Sauer, B, Hepler, C*, et al.*, *Preventable drug-related hospital admissions.* Ann Pharmacother, 2002. **36**(7): p. 1238-1248.

118. Beijer, HJM and de Blaey, CJ, *Hospitalisations caused by adverse drug reactions (ADR): a meta-analysis of observational studies.* Pharm World Sci, 2002. **24**(2): p. 46-54.

119. Leendertse, AJ, Visser, D, Egberts, ACG*, et al.*, *The Relationship Between Study Characteristics and the Prevalence of Medication-Related Hospitalizations: A Literature Review and Novel Analysis.* Drug Saf, 2010. **33**(3): p. 233-244

120. Kongkaew, C, Noyce, PR, and Ashcroft, DM, *Hospital Admissions Associated with Adverse Drug Reactions: A Systematic Review of Prospective Observational Studies.* Ann Pharmacother, 2008. **42**(7): p. 1017-1025.

121. van der Hooft, CS, Dieleman, JP, Siemes, C*, et al.*, *Adverse drug reaction-related hospitalisations: a population-based cohort study.* Pharmacoepidemiology and Drug Safety, 2008. **17**(4): p. 365-371.

122. Al-Jahdali, H, Al-Johani, A, Al-Hakawi, A*, et al.*, *Pattern and Risk Factors for Intentional Drug Overdose in Saudi Arabia.* The Canadian Journal of Psychiatry—Brief Communication, 2004. **49**: p. 331-334.

123. Mjörndal, T, Boman, MD, Hägg, S*, et al.*, *Adverse drug reactions as a cause for admissions to a department of internal medicine.* Pharmacoepidemiology and Drug Safety, 2002. **11**(1): p. 65-72.

124. Alexopoulou, A, Dourakis, SP, Mantzoukis, D*, et al.*, *Adverse drug reactions as a cause of hospital admissions: A 6-month experience in a single center in Greece.* European Journal of Internal Medicine, 2008. **19**: p. 505-510.

125. Lessing, C, Schmitz, A, Albers, B*, et al.*, *Impact of sample size on variation of adverse events and preventable adverse events: systematic review on epidemiology and contributing factors.* Qual Saf Health Care, 2010.

126. Bhopal, R, *Concepts of epidemiology: an integrated introduction to the ideas, theories, principles, and methods of epidemiology*. 2002, New York: Oxford University Press.

127. Davies, EC, Green, CF, Mottram, DR*, et al.*, *Adverse drug reactions in hospital in-patients: a pilot study.* J Clin Pharm Ther, 2006. **31**(4): p. 335-341.

128. Bates D, Leape L, and Petrycki S, *Incidence and preventability of adverse drug events in hospitalized adults.* J Gen Intern Med, 1993. **8**(6): p. 289-294.

129. Kidon, MI and See, Y, *Adverse drug reactions in Singaporean children.* Singapore Med J, 2004. **45**(12): p. 574-577.

130. Martinez-Mir, I, Garcia-Lopez, M, Palop, V*, et al.*, *A prospective study of adverse drug reactions as a cause of admission to a paediatric hospital.* Bri J of Clin Pharmacol, 1996. **42**(3): p. 319-324.

131. Haffner, S, von Laue, N, Wirth, S*, et al.*, *Detecting Adverse Drug Reactions on Paediatric Wards: Intensified Surveillance Versus Computerised Screening of Laboratory Values.* Drug Saf, 2005. **28**(5): p. 453-464.

132. Caamaño, F, Pedone, C, Zuccalà, G*, et al.*, *Socio-demographic factors related to the prevalence of adverse drug reaction at hospital admission in an elderly population.* Arch Gerontol Geriatr, 2005. **40**(1): p. 45-52.

133. Cunningham, G, Dodd, TRP, Grant, DJ*, et al.*, *Drug-related problems in elderly patients admitted to Tayside hospitals, methods for prevention and subsequent reassessment.* Age Ageing, 1997. **26**(5): p. 375-382.

134. Green, CF, Mottram, DR, Rowe, PH*, et al.*, *Adverse drug reactions as a cause of admission to an acute medical assessment unit: a pilot study*. J Clin Pharm Ther, 2000. **25**: p. 355-361.

135. Hopf, Y, Watson, M, and Williams, D, *Adverse-drug-reaction related admissions to a hospital in Scotland.* Pharm World Sci, 2008. **30**: p. 854-862.

136. Onder, G, Pedone, C, Landi, F*, et al.*, *Adverse drug reactions as cause of hospital admissions: results from the Italian Group of Pharmacoepidemiology in the Elderly (GIFA).* J Am Geriatr Soc, 2002. **50**(12): p. 1962-1968.

137. Zopf, Y, Rabe, C, Neubert, A*, et al.*, *Risk Factors Associated with Adverse Drug Reactions Following Hospital Admission: A Prospective Analysis of 907 Patients in Two German University Hospitals.* Drug Saf, 2008. **31**(9): p. 789-798.

138. van den Bemt, PMLA, Egberts, ACG, Lenderink, AW*, et al.*, *Risk factors for the development of adverse drug events in hospitalized patients.* Pharmacy World & Science, 2000. **22**(2): p. 62-66.

139. Leendertse, AJ, Egberts, ACG, Stoker, LJ*, et al.*, *Frequency of and Risk Factors for Preventable Medication-Related Hospital Admissions in the Netherlands.* Arch Intern Med, 2008. **168**(17): p. 1890-1896.

140. Saha, L, Pandhi, P, Malhotra, S*, et al.*, *Adverse Drug Event (ADE) related Medical Emergency Department visits and hospital admissions: a prospective study from a North Indian Referral Hospital.* Journal of Clinical and Diagnostic Research 2008. **2**: p. 600-604.

141. Pouyanne, P, Haramburu, F, Imbs, JL*, et al.*, *Admissions to hospital caused by adverse drug reactions: cross sectional incidence study.* BMJ, 2000. **320**(7241): p. 1036.

142. Ahmed, MeBK, *Drug-associated admissions to a district hospital in Saudi Arabia.* J Clin Pharm Ther, 1997. **22**(1): p. 61-66.

143. Bergman, U and Wiholm, BE, *Drug-related problems causing admission to a medical clinic.* Eur J Clin Pharmacol, 1981. **20**(3): p. 193-200.

144. Rodenburg, EM, Stricker, BHC, and Visser, LE, *Sex-related differences in hospital admissions attributed to adverse drug reactions in the Netherlands.* Br J Clin Pharmacol, 2011. **71**(1): p. 95-104.

145. Drici, M-D and Clément, N, *Is Gender a Risk Factor for Adverse Drug Reactions?: The Example of Drug-Induced Long QT Syndrome.* Drug Saf, 2001. **24**(8): p. 575-585.

146. Zargarzadeh, AH, Emami, MH, and Hosseini, F, *Drug-related hospital admissions in a generic pharmaceutical system.* Clin Exp Pharmacol Physiol, 2007. **34**: p. 494-498.

147. Howard, RL, Avery, AJ, Howard, PD*, et al.*, *Investigation into the reasons for preventable drug related admissions to a medical admissions unit: observational study.* Qual Saf Health Care, 2003. **12**: p. 280-285.

148. Hardmeier, B, Braunschweig, S, Cavallaro, M*, et al.*, *Adverse drug events caused by medication errors in medical inpatients.* Swiss Med Wkly, 2004. **134**: p. 664-670.

149. Chua, SS, Tea, MH, and Rahman, MHA, *An observational study of drug administration errors in a Malaysian hospital (study of drug administration errors).* J Clin Pharm Ther, 2009. **34**(2): p. 215-223.

150. Abdullah, DC, Ibrahim, NS, and Mohamed Ibrahim, MI, *Medication Errors Among Geriatrics At The Outpatient Pharmacy In A Teaching Hospital In Kelantan.* Malaysian J Med Sci, 2004. **11**(2): p. 52-58.

151. Chua, S, Chua, H, and Omar, A, *Drug administration errors in paediatric wards: a direct observation approach.* Eur J Pediatr, 2010. **169**(5): p. 603-611.

152. Franceschi, A, Tuccori, M, Bocci, G*, et al.*, *Drug therapeutic failures in emergency department patients: A university hospital experience.* Pharmacol Res, 2004. **49**: p. 85-91.

153. Malhotra, S, Karan, RS, Pandhi, P*, et al.*, *Drug related medical emergencies in the elderly: role of adverse drug reactions and non-compliance.* Postgrad Med J, 2001. **77**(913): p. 703-707.

154. Davidsen, F, Haghfelt, T, Gram, LF*, et al.*, *Adverse drug reactions and drug non-compliance as primary causes of admission to a cardiology department.* Eur J Clin Pharmacol, 1988. **34**(1): p. 83-86.

155. Hassan, NB, Hasanah, CI, Foong, K*, et al.*, *Identification of psychosocial factors of noncompliance in hypertensive patients.* J Hum Hypertens, 2006. **20**: p. 23-29.

156. Lim, TO, Ngah, BA, Rahman, RA*, et al.*, *The Mentakab Hypertension Study Project. Part V-Drug Compliance in Hypertensive Patients* Singapore Med J, 1992. **33**: p. 63-66.

157. Suleiman, A, Sulaiman, S, and Albarq, A, *Hospital Admission and Poor Adherence To Antihypertensive Therapy: Is There Any Relationship?* International Journal of Pharmacy and Pharmaceutical Sciences, 2009. **2**(1): p. 38-46.

158. Abdul Aziz, AM and Mohamed Ibrahim, MI, *Medication Noncompliance - A Thriving Problem.* Med J Malaysia, 1999. **54**(2): p. 192-199.

159. Liam, CK, Lim, KH, Wong, CMM*, et al.*, *Attitudes and knowledge of newly diagnosed tuberculosis patients regarding the disease, and factors affecting treatment compliance.* Int J Tuberc Lung Dis, 1999. **3**(4): p. 300-309.

160. Chuah, SY, *Factors associated with poor patient compliance with antituberculosis therapy in Northwest Perak, Malaysia.* Tubercle, 1991. **72**: p. 261-264.

161. Liu, WJ and Zaki, M, *Medication Compliance Among Renal Transplant Patients: A Hospital Kuala Lumpur Experience.* Med J Malaysia, 2004. **59**(5).

162. ONS. *Injury and poisoning mortality, England and Wales*. Statistical Bulletin 2009 22 July 2011; 1-13]. Available from: http://www.statistics.gov.uk/pdfdir/poi0311.pdf.

163. Paulozzi, LJ and Xi, Y, *Recent changes in drug poisoning mortality in the United States by urban–rural status and by drug type.* Pharmacoepidemiol Drug Saf, 2008. **17**(10): p. 997-1005.

164. Ab Rahman, AF, *Drug and chemical poisoning admissions at a teaching hospital in Malaysia.* Hum Exp Toxicol, 2002. **21**(7): p. 377-381.

165. Rajasuriar, R, Awang, R, Hashim, SBH*, et al.*, *Profile of poisoning admissions in Malaysia.* Hum Exp Toxicol, 2007. **26**(2): p. 73-81.

166. Oguzturk, H, Turtay, MG, Pamukcu, E*, et al.*, *Demographic features of acute drug poisoning admitted to Inonu University Hospital in Malatya, Turkey.* Sci Res Essays, 2010. **5**(18): p. 2761-2767.

167. Fathelrahman, AI, Ab Rahman, AF, Zain, ZM*, et al.*, *Factors associated with adult poisoning in Northern Malaysia: a case-control study.* Hum Exp Toxicol, 2006. **25**(4): p. 167-173.

168. Morgan, O and Majeed, A, *Restricting paracetamol in the United Kingdom to reduce poisoning: a systematic review.* J Public Health (Oxf), 2005. **27**(1): p. 12-18.

169. Liisanantti, JH, Ohtonen, P, Kiviniemi, O*, et al.*, *Risk factors for prolonged intensive care unit stay and hospital mortality in acute drug-poisoned patients: An evaluation of the physiologic and laboratory parameters on admission.* J Crit Care, 2011. **26**(2): p. 160-165.

170. Buykx, P, Loxley, W, Dietze, P*, et al.*, *Medications used in overdose and how they are acquired – an investigation of cases attending an inner Melbourne emergency department.* Aust N Z J Public Health, 2010. **34**(4): p. 401-404.

171. Tountas, C, Sotiropoulos, A, Skliros, SA*, et al.*, *Voluntary self-poisoning as a cause of admission to a tertiary hospital internal medicine clinic in Piraeus, Greece within a year.* BMC Psychiatry, 2001. **1**: p. 4.

172. Fathelrahman, AI, Ab Rahman, AF, and Mohd Zain, Z, *MS 04-044: Demographic Features of Drug and Chemical Poisoning in Northern Malaysia.* Clin Toxicol, 2005. **43**: p. 89–94.

173. Fathelrahman, AI, Ab Rahman, AF, and Mohd Zain, Z, *Self-poisoning by drugs and chemicals: variations in demographics, associated factors and final outcomes.* Gen Hosp Psychiatry, 2008. **30**(5): p. 467-470.

174. Awang, R, Ab Rahman, AF, Wan Abdullah, WZA*, et al.*, *Trends in Inquiries on Poisoning: A Five-Year Report from the National Poison Centre, Malaysia.* Med J Malaysia, 2003. **58**(3).

175. Mita, Y, Akishita, M, Tanaka, K*, et al.*, *Improvement of inappropriate prescribing and adverse drug withdrawal events after admission to long-term care facilities.* Geriatrics and Gerontology International, 2004. **4**: p. 146-150.

176. Iyer, S, Naganathan, V, McLachlan, AJ*, et al.*, *Medication Withdrawal Trials in People Aged 65 Years and Older: A Systematic Review.* Drugs Aging, 2008. **25**(12): p. 1021-1031.

177. Karachalios, GN, Charalabopoulos, A, Papalimneou, V*, et al.*, *Withdrawal syndrome following cessation of antihypertensive drug therapy.* Int J Clin Pract, 2005. **59**(5): p. 562-570.

178. Gerety, MB, Cornell, JE, Plichta, DT*, et al.*, *Adverse events related to drugs and drug withdrawal in nursing home residents.* J Am Geriatr Soc, 1993. **41**(12): p. 1326-1332.

179. Therrien, F and Markowitz, JS, *Selective serotonin reuptake inhibitors and withdrawal symptoms: a review of the literature.* Hum Psychopharmacol Clin Exp, 1997. **12**(4): p. 309-323.

180. Sellers, EM, *Alcohol, barbiturate and benzodiazepine withdrawal syndromes: clinical management.* Can Med Assoc J, 1988. **139**(2): p. 113-120.

181. Dormann, H, Criegee-Rieck, M, Neubert, A*, et al.*, *Lack of Awareness of Community-Acquired Adverse Drug Reactions Upon Hospital Admission: Dimensions and Consequences of a Dilemma.* Drug Saf, 2003. **26**: p. 353-362.

182. Riedl, MA and Casillas, AM, *Adverse drug reactions: types and treatment options.* Am Fam Physician, 2003. **68**(9): p. 1781-1790.

183. Ferner, RE and Butt, TF, *Adverse drug reactions.* Medicine (Baltimore), 2008. **36**(7): p. 364-368.

184. Lindley, C, Tully, M, Paramsothy, V*, et al.*, *Inappropriate Medication is a Major Cause of Adverse Drug Reactions in Elderly Patients.* Age Ageing, 1992. **21**: p. 294-300.

185. Spinewine, A, Schmader, K, Barber, N*, et al.*, *Appropriate prescribing in elderly people: how well can it be measured and optimised?* Lancet, 2007. **370**: p. 173-184.

186. Hamilton, H, Gallagher, P, and O'Mahony, D, *Inappropriate prescribing and adverse drug events in older people.* BMC Geriatr, 2009. **9**(5).

187. Azhar, S, Hassali, MA, and Mohamed Ibrahim, MI, *Doctors' Perception and Expectations of the Role of the Pharmacist in Punjab, Pakistan.* Trop J Pharm Res, 2010. **9**(3): p. 205-222.

188. Azhar, S, Hassali, MA, Mohamed Ibrahim, MI*, et al.*, *A survey evaluating nurses' perception and expectations towards the role of pharmacist in Pakistan's healthcare system.* J Adv Nurs, 2011. **[Epub ahead of print]**.

189. Tahaineh, LM, Wazaify, M, Albsoul-Younes, A*, et al.*, *Perceptions, experiences, and expectations of physicians in hospital settings in Jordan regarding the role of the pharmacist.* Res Soc Adm Pharm, 2009. **5**(1): p. 63-70.

190. Zaidan, M, Singh, R, Wazaify, M*, et al.*, *Physicians' perceptions, expectations, and experience with pharmacists at Hamad Medical Corporation in Qatar.* J Multidiscip Healthc, 2011. **85–90**: p. 85-90.

191. Doucette, WR, McDonough, RP, Klepser, D*, et al.*, *Comprehensive Medication Therapy Management: Identifying and Resolving Drug-Related Issues in a Community Pharmacy.* Clin Ther, 2005. **27**(7): p. 1104-1111.

192. Langebrake, C and Hilgarth, H, *Clinical pharmacists' interventions in a German University Hospital.* Pharm World Sci, 2010. **32**(2): p. 194-199.

193. Blix, H, Viktil, K, Moger, T*, et al.*, *Characteristics of drug-related problems discussed by hospital pharmacists in multidisciplinary teams.* Pharmacy World & Science, 2006. **28**(3): p. 152-158.

194. Hammerlein, A, Griese, N, and Schulz, M, *Survey of Drug-Related Problems Identified by Community Pharmacies.* Ann Pharmacother, 2007. **41**(11): p. 1825-1832.

195. Krähenbühl, J-M, Kremer, B, Guignard, B*, et al.*, *Practical evaluation of the drug-related problem management process in Swiss community pharmacies.* Pharm World Sci, 2008. **30**(6): p. 777-786.

196. Kucukarslan, S, Peters, M, Mlynarek, M*, et al.*, *Pharmacists on rounding teams reduce preventable adverse drug events in hospital general medicine units. .* Archive of Internal Medicine, 2003. **163**: p. 2014-2018.

197. Chua, SS, Kuan, MN, and Ramli, MN, *Outpatient Prescription Intervention Activities by Pharmacists in a Teaching Hospital.* Malaysian J Pharm, 2003. **1**(3): p. 86-90.

198. Hassan, Y, Aziz, NA, Awang, J*, et al.*, *An analysis of clinical pharmacist interventions in an intensive care unit.* J Clin Pharm Ther, 1992. **17**(6): p. 347-351.

199. Zaidi, STR, Hassan, Y, Postma, MJ*, et al.*, *Impact of pharmacist recommendations on the cost of drug therapy in ICU patients at a Malaysian hospital.* Pharm World Sci, 2003. **25**(6): p. 299-302.

200. Fortescue, EB, Kaushal, R, Landrigan, CP*, et al.*, *Prioritizing Strategies for Preventing Medication Errors and Adverse Drug Events in Pediatric Inpatients.* Pediatrics, 2003. **111**(4 Pt 1): p. 722-729.

201. Bates, DW, Leape, LL, Cullen, DJ*, et al.*, *Effect of Computerized Physician Order Entry and a Team Intervention on Prevention of Serious Medication Errors.* JAMA: The Journal of the American Medical Association, 1998. **280**(15): p. 1311-1316.

202. *Task Force on Medicines Partnership and The National Collaborative Medicines Management Services Programme. Room for review: a guide to medication review: the agenda for patients,practitioners and managers*. 2003: London: Pharmaceutical Press.

203. Zermansky, AG, Alldred, DP, Petty, DR*, et al.*, *Clinical medication review by a pharmacist of elderly people living in care homes—randomised controlled trial.* Age Ageing, 2006. **35**(6): p. 586-591.

204. Krska, J and Ross, S, *Medication review: whose job it is?* Int J Pharm Pract, 2002. **10**(S1): p. R86-R86.

205. Krska, J, Ross, SM, and Watts, M, *Medication reviews provided by general medical practitioners (GPs) and nurses: an evaluation of their quality.* Int J Pharm Pract, 2005. **13**(1): p. 77-84.

206. Holland, R, Smith, R, and Harvey, I, *Where now for pharmacist led medication review?* J Epidemiol Community Health, 2006. **60**(2): p. 92-93.

207. Bradley, C, *Uncomfortable prescribing decisions: a critical incident study.* BMJ, 1992. **304**: p. 294-296.

208. Aronson, J, *A prescription for better prescribing.* Br J Clin Pharmacol, 2006. **61**(5): p. 487-491.

209. Gall, M, Harmer, J, and Wanstall, H, *Prescribing of oral nutritional supplements in Primary Care: can guidelines supported by education improve prescribing practice?* Clin Nutr, 2001. **20**(6): p. 511-515.

210. *Annual Report*. 2009 [cited 2011 25 July]; Available from: http://www.pharmacy.gov.my/index.cfm?&menuid=16&parentid=163&lang=EN.

211. Lim, PC and Lim, K, *Evaluation of a pharmacist-managed diabetes medication therapy adherence clinic.* Pharm Pract (Internet), 2010. **8**(4): p. 250-254.

212. *Yellow Card*. Available from: http://yellowcard.mhra.gov.uk/.

213. *Report of suspected adverse reaction to medicines/vaccines*. Available from: http://www.tga.gov.au/adr/bluecard.htm.

214. *Irish Medicines Board*. [cited 2011 25 July]; Available from: http://www.imb.ie/.

215. Vessal, G, Mardani, Z, and Mollai, M, *Knowledge, attitudes, and perceptions of pharmacists to adverse drug reaction reporting in Iran.* Pharm World Sci, 2009. **31**(2): p. 183-187.

216. Cosentino, M, Leoni, O, Banfi, F*, et al.*, *Attitudes To Adverse Drug Reaction Reporting By Medical Practitioners In A Northern Italian District.* Pharmacol Res, 1997. **35**(2): p. 85-88.

217. Green, CF, Mottram, DR, Rowe, PH*, et al.*, *Attitudes and knowledge of hospital pharmacists to adverse drug reaction reporting.* Br J Clin Pharmacol, 2001. **51**: p. 81-86.

218. Sweis, D and Wong, ICK, *A survey on factors that could affect adverse drug reaction reporting according to hospital pharmacists in Great Britain.* Drug Saf, 2000. **23**(2): p. 165-172.

219. Belton, KJ, Lewis, SC, Payne, S*, et al.*, *Attitudinal survey of adverse drug reaction reporting by medical practitioners in the United Kingdom.* Br J Clin Pharmacol, 1995. **39**: p. 223-226.

220. Irujo, M, Beitia, G, Bes-Rastrollo, M*, et al.*, *Factors that Influence Under-Reporting of Suspected Adverse Drug Reactions among Community Pharmacists in a Spanish Region.* Drug Saf, 2007. **30**(11): p. 1073-1082.

221. Su, C, Ji, H, and Su, Y, *Hospital pharmacists' knowledge and opinions regarding adverse drug reaction reporting in Northern China.* Pharmacoepidemiology and Drug Safety, 2010. **19**(3): p. 217-222.

222. Toklu, H and Uysal, M, *The knowledge and attitude of the Turkish community pharmacists toward pharmacovigilance in the Kadikoy district of Istanbul.* Pharmacy World & Science, 2008. **30**(5): p. 556-562.

223. Aziz, Z, Siang, TC, and Badarudin, NS, *Reporting of adverse drug reactions: predictors of under-reporting in Malaysia.* Pharmacoepidemiology and Drug Safety 2007. **16**(2): p. 223-228.

224. Belton, KJ, *Attitude survey of adverse drug-reaction reporting by health care professionals across the European Union.* Eur J Clin Pharmacol, 1997. **52**(6): p. 423-427.

225. Ekman, E and Bäckström, M, *Attitudes among hospital physicians to the reporting of adverse drug reactions in Sweden.* Eur J Clin Pharmacol, 2009. **65**(1): p. 43-46.

226. Elkalmi, RM, Hassali, MA, Ibrahim, MIM*, et al.*, *A qualitative study exploring barriers and facilitators for reporting of adverse drug reactions (ADRs) among community pharmacists in Malaysia.* J Pharm Health Serv Res, 2011. **2**(2): p. 71-78.

227. Figueiras, A, Tato, F, Fontainas, J*, et al.*, *Physicians' attitudes towards voluntary reporting of adverse drug events.* J Eval Clin Pract, 2001. **7**(4): p. 347-354.

228. Hasford, J, Goettler, M, Munter, KH*, et al.*, *Physicians' knowledge and attitudes regarding the spontaneous reporting system for adverse drug reactions.* J Clin Epidemiol, 2002. **55**(9): p. 945-950.

229. Herdeiro, MT, Figueiras, A, PolÃ³nia, J*, et al.*, *Influence of Pharmacists' Attitudes on Adverse Drug Reaction Reporting: A Case-Control Study in Portugal.* Drug Saf, 2006. **29**(4): p. 331-340.

230. van Grootheest, AC, van Puijenbroek, EP, and de Jong–van den Berg, LTW, *Contribution of pharmacists to the reporting of adverse drug reactions.* Pharmacoepidemiology and Drug Safety, 2002. **11**(3): p. 205-210.

231. Ting, KN, Stratton-Powell, D, and Anderson, C, *Community pharmacists views on adverse drug reactions reporting in Malaysia: a pilot study.* Pharm World Sci, 2010. **32**: p. 339-342.

232. Granas, AG, Buajordet, M, Stenberg-Nilsen, H*, et al.*, *Pharmacists' attitudes towards the reporting of suspected adverse drug reactions in Norway.* Pharmacoepidemiology and Drug Safety, 2007. **16**(4): p. 429-434.

233. *Institutes for Safe Medication Practices*. [cited 2011 25 July]; Available from: http://www.ismp.org/.

234. Terzibanjana, AR, Laaksonenb, R, Weissb, M*, et al. Medication Error Reporting Systems – Lessons Learnt. Executive Summary Of The Findings*. [cited 2011 25 July]; Available from: http://www.fip.org/files/fip/Patient%20Safety/Medication%20Error%20Reporting%20-%20Lessons%20Learnt2008.pdf.

235. ISMP. *Examples of the Impact of the ISMP Medication Error Reporting Program (MERP)*. [cited 2011 20 July]; Available from: http://www.ismp.org/about/merpimpact.asp.

236. Sarvadikar, A, Prescott, G, and Williams, D, *Attitudes to reporting medication error among differing healthcare professionals.* Eur J Clin Pharmacol, 2010. **66**(8): p. 843-853.

237. Evans, SM, Berry, JG, Smith, BJ*, et al.*, *Attitudes and barriers to incident reporting: a collaborative hospital study.* Qual Saf Health Care, 2006. **15**(1): p. 39-43.

238. Nuckols, TK, Bell, DS, Liu, H*, et al.*, *Rates and types of events reported to established incident reporting systems in two US hospitals.* Qual Saf Health Care, 2007. **16**(3): p. 164-168.

239. Williams, SD and Ashcroft, DM, *Medication errors: how reliable are the severity ratings reported to the national reporting and learning system?* Int J Qual Health Care, 2009. **21**(5): p. 316-320.

240. Sanghera, IS, Franklin, BD, and Dhillon, S, *The attitudes and beliefs of healthcare professionals on the causes and reporting of medication errors in a UK Intensive care unit.* Anaesthesia, 2007. **62**(1): p. 53-61.

241. *Malaysian Adverse Drug Reactions Newsletter*. April 2010, National Pharmaceutical Control Bureau, Ministry of Health Malaysia.

242. (Tuesday March 16, 2010) *The Star Online*. All hospitals must report medication errors, says D-G.

243. Cosentino, M, Leoni, O, Oria, C*, et al.*, *Hospital-based survey of doctors' attitudes to adverse drug reactions and perception of drug-related risk for adverse reaction occurrence.* Pharmacoepidemiology and Drug Safety, 1999. **8**(S1): p. S27-S35.

244. Peyriere, H, Cassan, S, Floutard, E*, et al.*, *Adverse Drug Events Associated with Hospital Admission.* Ann Pharmacother, 2003. **37**(1): p. 5-11.

245. Samoy, L, Zed, P, Wilbur, K*, et al.*, *Drug-related hospitalizations in a tertiary care internal medicine service of a Canadian hospital: a prospective study.* Pharmacotherapy, 2006. **26**(11): p. 1578 - 1586.

246. Kaboli, PJ, Glasgow, JM, Jaipaul, CK*, et al.*, *Identifying medication misadventures: poor agreement among medical record, physician, nurse, and patient reports* Pharmacotherapy, 2010. **30**(5): p. 529-538.

247. Schneeweiss, S, Hasford, J, Go¨ ttler, M*, et al.*, *Admissions caused by adverse drug events to internal medicine and emergency departments in hospitals: a longitudinal population-based study.* Eur J Clin Pharmacol, 2002. **58**: p. 285-291.

248. Naing, L, Winn, T, and Rusli, BN, *Practical Issues in Calculating the Sample Size for Prevalence Studies.* Archives of Orofacial Sciences, 2006. **1**: p. 9-14.

249. *British National Formulary 57ed.*, ed. Comittee, J.F. March 2009, London: British Medical Association and Royal Pharmaceutical Society.

250. *Martindale: The Complete Drug Reference*, Sweetman, S., Editor, Pharmaceutical Press: London.

251. *Stockley's Drug Interactions*, Baxter, K., Editor, Pharmaceutical Press: London.

252. Kundel, HL and Polansky, M, *Measurement of Observer Agreement.* Radiology, 2003. **228**(2): p. 303-308.

253. Hunt, RJ, *Percent Agreement, Pearson's Correlation, and Kappa as Measure of Inter-examiner Reliability.* J Dent Res, 1986. **65**(2): p. 128- 130.

254. Grayon, K and Rust, R, *Interrater Reliability.* Journal of Consumenr Psychology, 2001. **10**(1 & 2): p. 71- 73.

255. Cohen, J, *A Coefficient of Agreement for Nominal Scales.* Educational and Psychological Measurement, 1960. **20**(1): p. 37- 46.

256. Viera, AJ and Garrett, JM, *Understanding Interobserver Agreement: The Kappa Statistic.* Fam Med, 2005. **37**(5): p. 360- 363.

257. Landis, JR and Koch, GG, *The Measurement of Observer Agreement for Categorical Data.* Biometrics, 1977. **33**(1 (Mar., 1977)): p. 159-174.

258. *Report On Suspected Adverse Drug Reactions*. 30 Jan 2008]; Available from: https://www.bpfk.gov.my/quest2/madrac%20-%20reporting%20online.htm.

259. Zambahari, R, *Trends in cardiovascular diseases and risk factors in Malaysia.* International Congress Series, 2004. **1262**: p. 446-449.

260. MOH. *Malaysian Statistics on Medicine 2007*. [cited 2011 20 January]; Available from: http://www.pharmacy.gov.my/aeimages//File/MSOM2007_2.pdf.

261. Sarojini S, Faridah A, Lim CM*, et al.*, *Use of prescription medicines in Malaysia 2005.* Med J Malaysia, 2008. **63**(3): p. 203-206.

262. *Malaysian Clinical Practice Guideline on Management of Type 2 Diabetes Mellitus (4th Edition)*. 2009 [cited 2010 20 June]; Available from: http://www.acadmed.org.my/index.cfm?&menuid=67#Endocrine_Disease.

263. (2009) *My Medicine Price*. My Medicine Price Bulletin.

264. Francisco, C, Claudio, P, Guiseppe, Z*, et al.*, *Socio-demographic factors related to the prevalence of adverse drug reaction at hospital admission in an elderly population.* Arch Gerontol Geriatr, 2005. **40**(1): p. 45-52.

265. Trifirò, G, Calogero, G, Ippolito, FM*, et al.*, *Adverse drug events in emergency department population: a prospective Italian study.* Pharmacoepidemiology and Drug Safety, 2005. **14**(5): p. 333-340.

266. Hong, CY, Chia, KS, Hughes, K*, et al.*, *Ethnic differences among Chinese, Malay and Indian patients with type 2 diabetes mellitus in Singapore.* Singapore Med J, 2004. **45**(4): p. 154-160.

267. Yeo, K, Tai, B, Heng, D*, et al.*, *Ethnicity modifies the association between diabetes mellitus and ischaemic heart disease in Chinese, Malays and Asian Indians living in Singapore.* Diabetologia, 2006. **49**(12): p. 2866-2873.

268. Eliasson, E, *Ethnicity and adverse drug reactions.* Br Med J, 2006. **332**(7551): p. 1163-1164.

269. McDowell, SE, Coleman, JJ, and Ferner, RE, *Systematic review and meta-analysis of ethnic differences in risks of adverse reactions to drugs used in cardiovascular medicine.* BMJ, 2006. **332**(7551): p. 1177-1181.

270. Lee, JK, Grace, KA, and Taylor, AJ, *Effect of a Pharmacy Care Program on Medication Adherence and Persistence, Blood Pressure, and Low-Density Lipoprotein Cholesterol.* J Am Med Assoc, 2006. **296**(21): p. 2563-2571.

271. Murray, MD, Ritchey, ME, Wu, J*, et al.*, *Effect of a Pharmacist on Adverse Drug Events and Medication Errors in Outpatients With Cardiovascular Disease.* Arch Intern Med, 2009. **169**(8): p. 757-763.

272. Hawton, K, Townsend, E, Deeks, J*, et al.*, *Effects of legislation restricting pack sizes of paracetamol and salicylate on self poisoning in the United Kingdom: before and after study.* Brit Med J, 2001. **322**(7296): p. 1203.

273. Gunnell, D, Hawton, K, Murray, V*, et al.*, *Use of paracetamol for suicide and non-fatal poisoning in the UK and France: are restrictions on availability justified?* J Epidemiol Community Health, 1997. **51**: p. 175-179.

274. *Malaysian Clinical Practice Guideline on Management of Non-variceal Upper Gastrointestinal Bleed*. 2003 [cited 2011 20 January]; Available from: http://www.acadmed.org.my/index.cfm?&menuid=67.

275. Lanas, A, Fuentes, J, Benito, R*, et al.*, *Helicobacter pylori increases the risk of upper gastrointestinal bleeding in patients taking low-dose aspirin.* Aliment Pharmacol Ther, 2002. **16**(4): p. 779-786.

276. Lazzaroni, M and Bianchi Porro, G, *Prophylaxis and treatment of non-steroidal anti-inflammatory drug-induced upper gastrointestinal side-effects.* Dig Liver Dis, 2001. **33**(Supplement 2): p. S44-S58.

277. Service, FJ, *Hypoglycemia.* Endocrinol Metab Clin North Am, 1997. **26**(4): p. 937-955.

278. McAulay, V, Deary, IJ, and Frier, BM, *Symptoms of hypoglycaemia in people with diabetes.* Diabet Med, 2001. **18**(9): p. 690-705.

279. Guettier, J-M and Gorden, P, *Hypoglycemia.* Endocrinol Metab Clin North Am, 2006. **35**(4): p. 753-766.

280. NHS. *Hypoglycaemia - Prevention*. [cited 2011 06 Aug]; Available from: http://www.nhs.uk/Conditions/Hypoglycaemia/Pages/Prevention.aspx.

281. Benjamin, EM, *Self-Monitoring of Blood Glucose: The Basics.* Clin Diabetes, 2002. **20**(1): p. 45-47.

282. Evans, JMM, Newton, RW, Ruta, DA*, et al.*, *Frequency of blood glucose monitoring in relation to glycaemic control: observational study with diabetes database.* Brit Med J, 1999. **319**(7202): p. 83-86.

283. Franciosi, M, Pellegrini, F, De Berardis, G*, et al.*, *The Impact of Blood Glucose Self-Monitoring on Metabolic Control and Quality of Life in Type 2 Diabetic Patients.* Diabetes Care, 2001. **24**(11): p. 1870-1877.

284. Bergenstal, RM and Gavin, JR, *The role of self-monitoring of blood glucose in the care of people with diabetes: report of a global consensus conference.* Am J Med, 2005. **118**(Suppl 9A): p. 1S - 6S.

285. *The Befrienders*. Available from: http://www.befrienders.org.my/index.html. Last accessed: 4 August 2011.

286. Bowling, A, *Research methods in health: investigating health and health services: second edition*. 2002, Maidenhead: Open University Press.

287. (2008) *Annual Report Of The Malaysian Adverse Drug Reactions Advisory Committee (MADRAC)*.

288. Chua, SS, Cheong, NK, and Teh, LK, *Utilization of community pharmacists by the general public in Klang Valley.* In: FAPA 2002 Abstracts, 2002: p. pp. 202 (Seoul: The Federation of Asian Pharmaceutical Association).

289. Koneri R, PK, Mishra V, Rajan H, *Drug-Related Hospitalizations at a Tertiary Level Hospital in Bangalore: A Prospective Study.* Journal of Clinical and Diagnostic Research [serial online], 2008. **2**(2): p. 736-740.

290. Viktil, KK and Blix, HS, *The Impact of Clinical Pharmacists on Drug-Related Problems and Clinical Outcomes.* Basic Clin Pharmacol Toxicol, 2008. **102**(3): p. 275-280.

291. Chen, YF, Neil, KE, Avery, AJ*, et al.*, *Prescribing errors and other problems reported by community pharmacists.* Ther Clin Risk Manag, 2005. **1**(4): p. 333-342.

292. Ashcroft, DM, Quinlan, P, and Blenkinsopp, A, *Prospective study of the incidence, nature and causes of dispensing errors in community pharmacies.* Pharmacoepidemiology and Drug Safety, 2005. **14**(5): p. 327-332.

293. Knudsen, P, Herborg, H, Mortensen, AR*, et al.*, *Preventing medication errors in community pharmacy: root-cause analysis of transcription errors.* Qual Saf Health Care, 2007. **16**(4): p. 285-290.

294. Yeap, JS, Hon, SK, and Yeap, JK, *Postal surveys: A review of articles published in the Medical Journal of Malaysia between 1991-2000.* Med J Malaysia, 2002. **57**(1).

295. Bahari, M and Ling, Y, *Factors contributing to customer satisfaction with community pharmacies in Malaysia.* J Public Health, 2010. **18**(1): p. 35-41.

296. Bogden, PE, Abbott, RD, Williamson, W*, et al.*, *Comparing Standard Care with a Physician and Pharmacist Team Approach for Uncontrolled Hypertension.* J Gen Intern Med, 1998. **13**(11): p. 740-745.

297. NHS. *The Initial Management of Overdose (Self-poisoning) in Adults on Inpatient Units/Wards*. [cited 2011 23 August]; Available from: http://www.awp.nhs.uk/FOI%20Documents/Support%20documents/Inpatient%20Units.pdf.

298. Wallace, CI, Dargan, PI, and Jones, AL, *Paracetamol overdose: an evidence based flowchart to guide management.* Emerg Med J, 2002. **19**(3): p. 202-205.

299. Chua, SS and Sabki, NH, *Use of nonprescription medications by the general public in the Klang Valley.* Journal of Applied Pharmaceutical Science, 2011. **01**(09): p. 93-98.

300. Foundation, TH (March 2012) *Evidence scan: Reducing prescribing errors*.

APPENDICES

Appendix 1 : Piloted data collection form

ADE- Related Hospital Admissions:

A PILOT STUDY

Ref. No.

Patient's ID:	Year of birth:	Gender: M / F	Race:	Ward: 8A / 8B
				Date of admission:

Presenting complaints:

Drugs on admission:

Drug	Dosage Regimen

Past Medical History:

Diabetes Mellitus	
Hypertension	
Asthma	
Hyperlipidaemia	
Heart Disease	
Stroke	
Liver Disease	
Renal Failure	
Tuberculosis	
Cancer	
HIV / AIDS	
Alcoholic	
Smoker	
Drug abuser	
Hepatitis B carrier	
Others	

Past Medication History (including OTC/ Herbal products):

Drug	Dosage Regimen

Initial diagnosis:
Confirmed diagnosis:

Laboratory data

Tests	Normal Range					

Other details:

Appendix 2: Modified trigger tool

Trigger tool list

T1 Antihistamines : Calamine Lotion, Loratidine (Clarityne), Cetirizine (Zyrtec), Chlopheniramine Maleate (Piriton), Diphenhydramine (Benadryl), Dexchlopheniramine (Polaramine), Promethazine (Phenergan)

T2 Vitamin K (Konakion) : anti-haemorrhagic

T3 Flumazenil (Anexate) : for benzodiazepine overdose

T4 Antiemetics: metoclopromide (maxolon), prochlorperazine (stemetil)

T5 Anti-diarrheals: Charcoal, Diphenoxylate (Lomotil), oral rehydration salt, Loperamide (Imodium)

T6: Sodium/Calcium Polysterene Sulphonate (Resonium A): for hyperkalaemia

T7: Antacids: Magnesium Trisilicate, Cimetidine (Tagamet), Ranitidine (Zantac), Omeprazole (Losec), Pantoprazole (Controloc), Lansoprazole (Prevacid), Sucralfate

T8: Anti-constipation: Liquid Paraffin, Bisacodyl (Dulcolax), Lactulose

T9: Clostridium difficile positive stool

T9: Abrupt cessation of medication/ change in doses

T10: Abnormalities in laboratory data(s)

T11: Rash/ Steven-Johnson Syndrome

T12: Over sedation/ lethargy/ low BP / HR/ fall

T13: Uncontrolled disease/ recurrent/ worsening of a disease

Appendix 3: WHO's ADR causality scale

Causality Scale	Description
C1: 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.
C2: 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.
C3: Possible	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration 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.
C4: 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 plausible explanations.
C5: 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 are under examination.
C6: Unassessible/ Unclassifiable	A report suggesting an adverse reaction which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified.

Appendix 4: Ethics approval letter to conduct pilot chart review study

PEJABAT TIMBALAN KETUA PENGARAH KESIHATAN
OFFICE OF THE DEPUTY DIRECTOR-GENERAL OF HEALTH
(PENYELIDIKAN & SOKONGAN TEKNIKAL)
(RESEARCH & TECHNICAL SUPPORT)
KEMENTERIAN KESIHATAN MALAYSIA
MINISTRY OF HEALTH MALAYSIA
Aras 12, Blok E7, Parsel E, Presint 1
Level 12, Block E7, Parcel E, Precinct 1
Pusat Pentadbiran Kerajaan Persekutuan
Federal Government Administrative Centre
62590 PUTRAJAYA

Tel : 03 88832543
Faks : 03 88895184

JAWATANKUASA ETIKA & PENYELIDIKAN PERUBATAN
KEMENTERIAN KESIHATAN MALAYSIA
d/a Institut Pengurusan Kesihatan
Jalan Rumah Sakit, Bangsar
59000 Kuala Lumpur

Ruj. Kami : (2) KKM/NIHSEC/08/0804/P08-128

Tarikh : 6 Mei 2008

Cik Mahmathi Karuppannan
Division of Social Research in Medicines & Health
School of Pharmacy
University of Nottingham Malaysia Campus

Puan,

NMRR-08-260-1415
Adverse drug events related medical admissions : a pilot study (Phase 1)

Lokasi projek : Hospital Tg Ampuan Rahimah Klang

Dengan hormatnya perkara di atas adalah dirujuk.

2. Jawatankuasa Etika & Penyelidikan Perubatan (JEPP), Kementerian Kesihatan Malaysia (KKM) mengambil maklum bahawa projek tersebut merupakan syarat akademik program Falsafah Kedoktoran dan telah diluluskan oleh Universiti Nottingham.

3. Sehubungan dengan ini, dimaklumkan juga bahawa pihak JEPP KKM tiada halangan, dari segi etika, ke atas pelaksanaan projek tersebut. JEPP mengambil maklum bahawa projek tersebut tidak mempunyai intervensi ke atas subjek kajian dan hanya melibatkan borang pengumpulan data pesakit. Segala rekod dan data subjek/pesakit adalah SULIT dan hanya digunakan untuk tujuan kajian dan semua isu serta prosedur mengenai *data confidentiality* mesti dipatuhi. Kebenaran daripada Pengarah Hospital di mana kajian akan dijalankan mesti diperolehi terlebih dahulu sebelum kajian dijalankan. Puan perlu akur dan mematuhi keputusan tersebut.

4. Laporan tamat kajian dan sebarang penerbitan dari kajian ini hendaklah dikemukakan kepada Jawatankuasa Etika & Penyelidikan Perubatan selepas tamatnya kajian ini.

Sekian terima kasih.

BERKHIDMAT UNTUK NEGARA

Saya yang menurut perintah,

(DR SHAHNAZ MURAD)
b.p. Pengerusi
Jawatankuasa Etika & Penyelidikan Perubatan
Kementerian Kesihatan Malaysia

Translation: Medical Ethics and Research Committee (MREC) has no objection to the project. MREC understands that the project does not involve any clinical intervention and only requires data collection from subjects' record. All records and data are CONFIDENTIAL and must only be used for research purpose, and all procedure pertaining to data confidentiality must be followed. Permission must be obtained from the Hospital Director before conducting the research. Researcher must accept the final decision made by the Hospital Director.

Appendix 5: Ethics approval letter to conduct the chart review study

PEJABAT TIMBALAN KETUA PENGARAH KESIHATAN
OFFICE OF THE DEPUTY DIRECTOR-GENERAL OF HEALTH
(PENYELIDIKAN & SOKONGAN TEKNIKAL)
(RESEARCH & TECHNICAL SUPPORT)
KEMENTERIAN KESIHATAN MALAYSIA
MINISTRY OF HEALTH MALAYSIA
Aras 12, Blok E7, Parsel E, Presint 1
Level 12, Block E7, Parcel E, Precinct 1
Pusat Pentadbiran Kerajaan Persekutuan
Federal Government Administrative Centre
62590 PUTRAJAYA

Tel : 03 88832543
Faks : 03 88895184

JAWATANKUASA ETIKA & PENYELIDIKAN PERUBATAN
KEMENTERIAN KESIHATAN MALAYSIA
d/a Institut Pengurusan Kesihatan
Jalan Rumah Sakit, Bangsar
59000 Kuala Lumpur

Ruj. Kami : (2) KKM/NIHSEC/08/0804/P08-456

Tarikh :23 Februari 2009

Cik Mahmathi Karuppannan
Fakulti Farmasi
Universiti Teknologi MARA

Puan,

NMRR-08-1532-2877
Phase 2 : Adverse drug events related medical admissions

Lokasi projek : Hospital Tengku Ampuan Rahimah

Dengan hormatnya perkara di atas adalah dirujuk.

2. Jawatankuasa Etika & Penyelidikan Perubatan (JEPP), Kementerian Kesihatan Malaysia (KKM) mengambil maklum bahawa projek tersebut merupakan syarat akademik program Kedoktoran dan telah diluluskan oleh Universiti Teknologi MARA dan The University of Nottingham.

3. Sehubungan dengan ini, dimaklumkan juga bahawa pihak JEPP KKM tiada halangan, dari segi etika, ke atas pelaksanaan projek tersebut. JEPP mengambil maklum bahawa projek tersebut tidak melibatkan intervensi klinikal dan hanya melibatkan pengumpulan data melalui rekod subjek dan borang soal-selidik. Segala rekod dan data subjek adalah SULIT dan hanya digunakan untuk tujuan kajian dan semua isu serta prosedur mengenai *data confidentiality* mesti dipatuhi. Kebenaran daripada Pengarah hospital di mana kajian dijalankan mesti diperolehi terlebih dahulu sebelum kajian dijalankan. Puan perlu akur dan mematuhi keputusan tersebut.

4. Laporan tamat kajian dan sebarang penerbitan dari kajian ini hendaklah dikemukakan kepada Jawatankuasa Etika & Penyelidikan Perubatan selepas tamatnya kajian ini.

Sekian terima kasih.

BERKHIDMAT UNTUK NEGARA

Saya yang menurut perintah,

(DATO' DR CHANG KIAN MENG)
Pengerusi
Jawatankuasa Etika & Penyelidikan Perubatan
Kementerian Kesihatan Malaysia

Translation: Medical Ethics and Research Committee (MREC) has no objection to the project. MREC understands that the project does not involve any clinical intervention and only requires data collection from subjects' record. All records and data are CONFIDENTIAL and must only be used for research purpose, and all procedure pertaining to data confidentiality must be followed. Permission must be obtained from the Hospital Director before conducting the research. Researcher must accept the final decision made by the Hospital Director.

Appendix 6: Data collection form for the chart review study

ADE- Related Hospital Admissions:

PHASE 2 STUDY

Ref. No.

Patient's ID:	Year of birth:	Gender: M / F	Race: M / I / C / Others / Foreigners	Ward: 7A / 8B	Bed:

Presenting complaints:	Date of admission:

BP:	PR:	RR:	T (^{o}C):	RBS (DXT):	SPO2:

Drugs on admission (and any changes in the ward):

Drug	Dosage Regimen	1st day	2nd day	3rd day

	Tick	Type (eg IHD, ESRF, ARF, BA, COAD etc)	Years
Diabetes Mellitus			
Hypertension			
Asthma			
Hyperlipidaemia			
Heart Disease			
Stroke			
Liver Disease			
Renal Failure			
Tuberculosis			
HIV / AIDS			
Seizure/epilepsy			
Gastritis			
Hepatitis B, C			
Others:			
Social History			
Alcoholic			
Smoker			
Drug abuser			

Past Medication History (including OTC/ Herbal products):

Drug	Dosage Regimen	Date/Year started

Initial diagnosis:
Confirmed diagnosis:

Vital signs in the ward:

Date						
BP						
Temperature						
RR						
PR						
SPO2						

Laboratory data

Tests/Date	Normal Range					
DXT (RBS)	<11.1					
Urine glucose						
Urine ketone						
Electrolytes:						
Na	136-145					
K	3.5-5.1					
HCO_3^-	18-24					
Renal function tests						
Urea	2.5-6.4					
Creatinine	62-106					
Liver function tests						
T.Protein	60-85					
Albumin	34-50					
T.Bilirubin	<17.2					
Direct bilirubin	<5.0					
INR						

PT	11.9-14.5					
aPTT	29.5-42.3					
AST	0-37					
ALP	40-130					
FBC						
Hgb	13-17 (m) 12-16 (f)					
Hct	40-58 (m) 37-46 (f)					
RBC	4.5-5.5					
WBC	4.1-10.9x10^3					
Platelet	140-450					
MCH	31-37					
MCV	76-100					
MCHC	32-36%					
Cardiac enzymes						
CK	38-170					
LDH	100-190					
Troponin I	<0.05					

Therapeutic drug monitoring

Drug	Normal level	Results	Remarks (toxic etc)

Other findings

CXR:

CT Scan:

Mantoux test:

OGDS:

Other details/ Patient interview:

Appendix 7: Piloted questionnaire

Confidential

Pharmacists' awareness about adverse drug events: A pilot study

We want to investigate Malaysian pharmacists' awareness about adverse drug events. As a first step we have developed this questionnaire, which we are piloting to find out whether these questions are relevant, clear and understandable. We would appreciated it if you could take time to answer the questions and leave some comments about any area you think were difficult to answer or unclear. The information you provide will help us to improve the questions for our main study and also give us an insight into pharmacists'views.

This questionnaire should take 10 to 15 minutes to complete. All the information provided will remain confidential.

March 2009

Mahmathi Karuppannan[1],
Helen Boardman[1],
Ting Kang Nee[2],
Salmiah Mohd. Ali[3] and
Wong Kok Thong[2]

[1]University of Nottingham, United Kingdom, [2]University of Nottingham, Malaysia Campus, [3]Universiti Teknologi MARA, Shah Alam, Malaysia.

Please tick the appropriate box. At the end of this questionnaire there is a space for you to leave comments regarding the questionnaire. Alternatively, you can leave your comments beside each question.

Section A - Adverse Drug Reactions (ADRs): General

ADR definition: *a response to a drug that is noxious and unintended and occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease, or for modification of physiological function* (WHO, 2002)

1. **In what percentage of patients do you think do the following occur in Malaysia:**

   a) **suspected ADRs (independently of reaction severity)**
   (please tick one only)

Less than 1%	
Between 1% and 5%	
Between 5% and 15%	
More than 15%	

   b) **suspected severe ADRs**
   (lethal, threatening life of physical integrity, which cause ir extend duration of hospitalisation)
   (please tick one only)

Less than 1%	
Between 1% and 5%	
Between 5% and 15%	
More than 15%	

2. **During your daily activity, have you ever observed/ witnessed a suspected ADR?**

Yes	
No	

   If no, please go to question number 7

3. **How frequently do you encounter patients with an ADR?**
   (please tick one only)

At least 1 case per day	
At least 1 case per week	
At least 1 case per month	
Less than 1 case per month	

   Other (please specify) .....

4. **How long is it since you have encountered a suspected ADR?**
(please tick one only)

Less than 7 days	
One week to one month	
More than a month but less than six months	
Six months or longer	

5. **What were the symptoms of the most <u>recent</u> ADR that you have encountered?**
(please tick all that apply)

Rash	
Headache	
Dizziness	
Diarrhoea	
Vomitting	

Other (please specify)…….

6. **What was your course of action when you encountered the suspected ADR described above?**
(please tick all that apply)

Fill in the ADR report form and send to National Adverse Drug Monitoring Centre	
Fill in the ADR report form and send to hospital drug information centre	
Inform the pharmacist in hospital drug information centre	
Inform the physician in-charge	
Inform the associated pharmaceutical company	
Do further evaluation (e.g. patient medication history)	
Make note in patient's chart/ record	
Suggest patient different medication	
Suggest patient medication to relieve the reaction(s)	
Explain to the patient that it may be a reaction to their medicine	
No action	

Other (please specify)……..

7. **Have patients reported ADRs to you?**

Yes	
No	

If no, please go to question number 12 (Section B)

8. **Which group of people who have <u>most often</u> reported ADRs to you?**
(please tick one only)

Elderly patient (>65 years old)	
Adult patients (15-64 years old)	
Parents of a child	
Family members/relatives of a patient	

Other (please specify)……

9. **What is the <u>most frequent</u> patient-reported ADR that you have encountered?**
(please tick one only)

Rash	
Headache	
Dizziness	
Diarrhoea	
Vomitting	

Other (please specify)……

10. **What were the symptoms of the <u>most recent</u> ADR reported to you by a patient?**
(please tick all that apply)

Rash	
Headache	
Dizziness	
Diarrhoea	
Vomitting	

Other (please specify)……

11. **What was you course of action when you received the report from the patient described above?**
(please tick all that apply)

Fill in the ADR report form and send to National Adverse Drug Monitoring Centre	
Fill in the ADR report form and send to hospital drug information centre	
Inform the pharmacist in hospital drug information centre	
Inform the physician in-charge	
Inform the associated pharmaceutical company	
Do further evaluation (e.g. patient medication history)	
Ask patient to contact or inform his/her GP	
Ask patient to go to hospital	

Make note in patient's chart/ record	
Advice patient that those are expected side effects	
Suggest patient different medication	
Suggest patient medication to relieve the reaction(s)	
Explain to the patient that it may be a reaction to their medicine	
No action	

Other (please specify)……

Section B - Adverse Drug Reactions (ADRs): spontaneous reporting

Spontaneous reporting*: System whereby case reports of adverse drug events are voluntarily submitted from health professionals and pharmaceutical manufacturers to the national regulatory authority* (WHO, 2002)

12. Would any of the following encourage you to report a suspected ADR?
(please tick all that apply)

The severity of the reaction	
The explicit request by a pharmaceutical company	
The reaction is widely known	
The specific typology of the reaction (unusual/unexpected)	
The involvement of a new drug	
The obviousness of a causal relationship with the administration of the drug	

Other (please specify)……

13. Would any of the following discourage you from reporting a suspected ADR?
(please tick all that apply)

The low degree of severity of a clinical reaction	
The uncertainty regarding the typology of reactions to be reported	
The uncertainty of a causal relationship with the administration of the drug	
The lack of information from affected patient	
The reaction is widely known	
The lack of knowledge regarding the regulations and procedure for reporting	
The unavailability of a form for reporting	
The complexity of the form to be completed	
The fear of medical-legal consequences	
The pointless of reporting	
The lack of time due to heavy responsibilities	
The lack of support from organisation/ head of department/ colleagues etc	

Other (please specify)……

14. How would you rather report an ADR?
(Please tick all that you would use)

Filling a form and posting it	
Filling in an online form	
Reporting by phone	
Reporting by email	

Other (please specify)…….

15. Are you aware of the existence of an appropriate form for ADR reporting?

Yes	
No	

If no, please go to question number 18

16. Do you know where you can obtain the form for ADR reporting?

Yes	
No	

If no, please go to question number 18

17. Where do you obtain the form for ADR reporting?
(please tick all that apply)

From MADRAC (*Malaysian ADR Advisory Committee*)	
From MADRAC online webpage	
From drug information centre in hospital	
From a drug information book	

Other (please specify)…….

18. What do you think are the aims of monitoring the spontaneous reporting of suspected ADRs by MADRAC (Malaysian ADR Advisory Committee)?

	Yes	No	Don't know
To measure the incidence of ADRs			
To identify the indication for which the drugs are prescribed			
To identify factors predisposing for ADRs			
To identify uncommon ADRs (Allergic, idiosyncratic, etc.)			
To identify previously unidentified ADRs			
To identify safe drugs			
To maintain a database of ADRs			

19. Which of the following ADRs do you think should be reported to National Adverse Drug Monitoring Centre?

	Yes	No	Don't know
Suspected reactions *(For which the intake of one or more drugs is only one of several possible explanations)*			
Certain [sure, ascertained] reactions *(For which the causal relationship with the intake of one or more drugs is obvious)*			
Mild reactions			
Reactions to drugs that have been in use for a long time			
Reactions to new drugs			
Known reactions *(Listed on the package leaflet or in any case already described in the literature)*			
Unexpected/unusual reactions			
Interactions between drugs			
Teratogenicity phenomena *(Causing harm/malformations to an embryo or fetus)*			
Reactions to vaccinations			
Lack of efficacy of a drug due to development of newly resistant strain			

Section C - <u>Therapeutic failure/ uncontrolled disease (TF)</u>

Therapeutic failure*: a failure to accomplish the goals of treatment as a result of inadequate drug therapy and not related to the natural progression of disease. (Edwards et al 2000)*
e.g. non-compliant to a drug therapy

20. In what percentage of patients do you think therapeutic failure occurs?
(please tick one only)

Less than 5%	
Between 5% and 15%	
Between 15% and 20%	
More than 20%	

21. During your daily activity, have you ever observed/ witnessed patients who you think had therapeutic failure?

Yes	
No	

If no please go to question number 30 (Section D)

22. Which of the following types of therapeutic failure have you ever encountered?
(please tick all that apply)

Inappropriate drug/ dosage	
Patients non-adherence to drug therapy	
Sub-optimal drug therapy	
Drug-drug interaction interfering with drug effectiveness	

23. Which of the following types of therapeutic failure you <u>most commonly</u> encounter?
(please tick one only)

Inappropriate drug/ dosage	
Patients non-adherence to drug therapy	
Sub-optimal drug therapy	
Drug-drug interaction interfering with drug effectiveness	

24. How frequently do you observe patients with therapeutic failure?
(please tick one only)

1 At least 1 case per day	
2 At least 1 case per week	
3 At least 1 case per month	
4 Less than 1 case per month	

Other (please specify)……

25. How long is it since you have encountered a patient with therapeutic failure?
(please tick one only)

Less than 7 days	
One week to one month	
More than a month but less than six months	
Six months or longer	

26. What was the type of therapeutic failure you have encountered <u>most recently</u>?
(please tick one only)

Inappropriate drug/ dosage	
Patients non-adherence to drug therapy	
Sub-optimal drug therapy	
Drug-drug interaction interfering with drug effectiveness	

27. What was your course of action when you last encountered a patient with therapeutic failure described above?
(please tick all that apply)

Further evaluation	
Discuss with physician	
Discuss with other pharmacists	
Make note in patients' chart/ record	
Discuss with patient/ patient's family member	

Other (please specify)……

28. For what types of diseases or therapy do you seen therapeutic failure?
(please tick all that apply)

Diabetes	
Hypertension	
Asthma	
Cardiovascular diseases	
Cancer	
HIV/ AIDS	
Tuberculosis	
Pain management	

Other (please specify).....

29. Which group of patients have you most commonly encountered with therapeutic failure?
(please choose only one for each category)

Age group		Gender		Race	
Elderly (>65 years)		Male		Malay	
Adult (15-64 years)		Female		Chinese	
Children				Indian	
				Other	

Section D – <u>Other adverse drug event</u>

- **Medication error:** *any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer (NCC MERP,2001)*
- **Drug overdose:** *the accidental or intentional use of a drug in an amount that is higher than is normally used (McDonnell 2008)*
- **Adverse drug withdrawal syndrome:** *occurs when a patient abruptly discontinue taking the drug after a long term therapy and experiences withdrawal syndrome*

30. During your daily activities, have you ever observed/ witnessed patients with……..?

	Yes	No
a) Medication error		
b) Adverse drug withdrawal syndrome		
c) Drug overdose		

31. How frequently do you observe a patient with ……..?
(please choose only one for each category)

	At least one per…				Never
	day	week	month	year	
a) Medication error					
b) Adverse drug withdrawal syndrome					
c) Drug overdose					

32. What was the cause of the last drug overdose that you have encountered?
(please tick one only)

I have not encountered any	
Accidental	
Intentional	
I don't know/ not sure	

Please go to question number 34 (Section E

33. Which drug group was associated with the <u>drug overdose</u> you described above?
(please tick one only)

Analgesics	
Anti-depression	
Anti-epilepsy	
Hypoglycemic agents	
Hypertensive agents	

Others (please specify)…….....

Section G – General

34. Are you …

Male	
Female	

35. State of residence ……

36. Highest level of education

Bachelors degree	
Masters degree	
Doctorate degree	

Please state any specialisation……

37. Profession:

Hospital pharmacist	
Community pharmacist	
Industrial pharmacist	
Academician	
Pharmacy student	

Other (please specify)……

If you have a specialisation within your area of profession, please tell us what it is (e.g. clinical pharmacist, renal pharmacist, clinical pharmacology lecturer etc.)……

38. Number of years working as pharmacist:

More than 15 years	
11 – 15 years	
6 – 10 years	
5 years or less	

Section F – Comments about the questionnaire

39. Did you find the questionnaire clear and easy to understand?

Yes	☐
No	☐

If no, please tell us which questions were not and why. (Alternatively, you can leave comments beside each question)

……

……

……

……

……

40. How long did it take you to complete the questionnaire?

☐ **minutes**

41. How would you prefer to answer similar questionnaire in near future?

By post	☐
By email	☐
By phone	☐
By face-to-face	☐

Other (please specify)……..

42. If you have any other comments about the questionnaire, please write them in the space below.

……

……

……

……

……

~ Thank you ~

Appendix 8: Information sheet

The University of Nottingham

UNIVERSITI TEKNOLOGI MARA

Title of Project: Pharmacists' awareness about adverse drug events: A pilot study

INFORMATION SHEET

We are planning to conduct a survey on awareness of Malaysian pharmacists about adverse drug events. Before we embark on our survey we would like to test out our questionnaire.

Taking part in this study is entirely your choice. We estimate the questionnaire will take 10-15 minutes to complete.

All information you provide will be kept confidential.

The results from this study will be used to improve our main study questionnaire. We will present the results of the study at conferences and in journal articles so that other people can learn from our study.

This study is being organised by Mahmathi Karuppannan as a part of a requirement for the completion of an educational qualification (PhD). This research study is conducted under the supervision of Dr Helen Boardman and Dr. Ting Kang Nee from University of Nottingham with Dr. Salmiah Mohd Ali from Universiti Teknologi MARA and advised by Mr.Wong Kok Thong from University of Nottingham, Semenyih.

This study has ethical approval from the Division of Social Research in Medicines and Health, University of Nottingham

If you would like any further information regarding the study, please contact:

Ms. Mahmathi Karuppannan
PhD research student,
School of Pharmacy,
University of Nottingham,
United Kingdom and Malaysian campus.
Email address: paxmk2@nottingham.ac.uk

You may also contact the academic supervisors of this project:

Academic Supervisors	Email	Contact number
Dr. Helen Boardman	Helen.Boardman@nottingham.ac.uk	+44 115 95 14291
Dr. Ting Kang Nee	Kang-Nee.Ting@nottingham.edu.my	03-89248209
Assoc. Prof. Dr. Salmiah	drsalmiah@salam.uitm.edu.my	03-55442761

Thank you for your participation in this research.

Appendix 9: Questionnaire for the pharmacists

Confidential

Pharmacists' experiences about adverse drug events

This questionnaire asks about your experiences with adverse drug events you have encountered as part of your practice during the last six months.

Please help us by taking the time to answer the questionnaire. Your answers are very important.

This questionnaire will take 10-15 minutes to complete. All information you provide will be kept confidential.

January 2010

Mahmathi Karuppannan[1,3],
Helen Boardman[1],
Ting Kang Nee[2],
Salmiah Mohd. Ali[3] and
Wong Kok Thong[2]

[1]University of Nottingham, United Kingdom, [2]University of Nottingham, Malaysia Campus, [3]Universiti Teknologi MARA, Shah Alam, Malaysia.

Please tick the appropriate box.

Section A - General

i) Are you ……..

1 A hospital/ health clinic pharmacist	
2 A retail pharmacist	
3 Working in another area	

} **Please proceed to Section G**

ii) During your daily activities, do you have direct contact with patients?

1 Yes	
2 No	

Section B - Adverse Drug Reactions (ADRs)

ADR definition: *a response to a drug that is noxious and unintended and occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease, or for modification of physiological function* (WHO, 2002)

1. **Have you observed a suspected ADR during the last 6 months?**

1 Yes	
2 No	

If no, please go to question number 6 (Section C)

2. **How frequently have you observed a patient with a suspected ADR during the last 6 months?**
(PPlease tick one only)

1 At least 1 case per day	
2 At least 1 case per week	
3 At least 1 case per month	
4 Less than 1 case per month	

3. **Please tell us about the <u>most recent</u> suspected ADR that you have observed, what were the symptoms?**
(Please tick all that apply)

a. Cough	
b. Dry cough	
c. Dizziness	
d. Oedema periorbital	
e. Itchiness	
f. Rash	
g. Headache	
h. Giddiness	
i. Oedema	
j. Diarrhoea	
k. Nausea	
l. Vomiting	
m. Renal failure	
n. Jaundice	
o. Acute hepatitis	
p. Steven Johnson Syndrome	
q. Erythema	
r. Heartburn	
s. Gastritis	
t. Constipation	
u. Palpitation	
v. Flatulence	
w. Myalgia	
x. Thrombocytopenia	

y. Other (please specify)……

4. **Please tell us about the drug(s) involved in the <u>most recent</u> suspected ADR symptoms that you have observed.**
(Please tick all that apply)

a. Perindopril	
b. Aspirin	
c. Diclofenac	
d. Amlodipine	
e. Metformin	
f. Traditional medicine	
g. Allopurinol	
h. Co-trimoxazole	
i. Heparin	
j. Lovastatin	
k. Cloxacillin	
l. Ticlopidine	
m. Rifampicin	
n. Phenytoin	
o. Amoxycillin	
p. Carbamazepine	
q. Nifedipine	
r. Erythromycin	
s. Captopril	
t. Paracetamol	
u. Atenolol	
v. Cefuroxime	
w. Mefenamic acid	
x. Chlorothiazide	
y. Penicillin G sodium	
z. Vancomycin	
aa. Alendronate	
bb. Isosorbide dinitrate	

cc. Other (please specify)……

5. **Thinking about the <u>most recent</u> suspected ADR you observed, what was your course of action?**
(Please tick all that apply)

a. Fill in the ADR report form and send to MADRAC	
b. Fill in the ADR report form and send to hospital drug information centre	
c. Inform the pharmacist in hospital drug information centre	
d. Inform the physician in-charge	
e. Inform the associated pharmaceutical company	
f. Do further evaluation (e.g. patient medication history)	
g. Make note in patient's chart/ record	
h. Suggest to the patient that they inform their doctor	
i. Suggest to the patient to try a different medicine	
j. Suggest to the patient to stop the medicine	
k. Suggest to the patient a medicine to relieve the reaction(s)	
l. Explain to the patient that it may be a reaction to their medicine	
m. No action	

n. Other (please specify).....

Section C - <u>Adverse Drug Reactions (ADRs): spontaneous reporting</u>

Spontaneous reporting definition*: System whereby case reports of adverse drug events are voluntarily submitted from health professionals and pharmaceutical manufacturers to the national regulatory authority (WHO, 2002)*

*In Malaysia the national regulatory authority who collates and assesses spontaneous reports from health professionals (and now patients) is the **Malaysian ADR Advisory Committee (MADRAC)**, which then submits the reports to the WHO's (World Health Organization) Uppsala Monitoring Centre in Sweden.*

6. **Have you ever reported a suspected ADR to MADRAC?**

1 Yes	
2 No	

7. **Are you aware of the existence of an appropriate form for reporting suspected ADRs to MADRAC?**

1 Yes	
2 No	

If no, please go to question number 10

8. **Do you know how to obtain the form to report a suspected ADR to MADRAC?**

1 Yes	
2 No	

If no, please go to question number 10

9. **Where can you obtain the form for ADR reporting?**
(Please tick all that apply)

a. Distributed/posted by MADRAC	
b. From MADRAC online webpage	
c. From drug information centre in hospital	
d. From national or local health department	
e. From a drug information book	

10. **How would you prefer to submit a report about a suspected ADR to MADRAC?**
(Please tick all that you would use)

a. Filling a form and posting it	
b. Filling a form and faxing it	
c. Filling in an online form	
d. Reporting by phone	
e. Reporting by email	

11. Would any of the following <u>encourage</u> you to report a suspected ADR to MADRAC?

	1 Yes	2 No
a. The high degree of severity of a clinical reaction		
b. The explicit request of a pharmaceutical company		
c. The reaction is not widely known		
d. The specific typology of the reaction (unusual/unexpected)		
e. The involvement of a newly licensed drug		
f. The obvious causal relationship with the administration of the drug		

12. Would any of the following <u>discourage</u> you from reporting a suspected ADR to MADRAC?

	1 Yes	2 No
a. The low degree of severity of a clinical reaction		
b. Uncertainty regarding the type of reactions to be reported		
c. The uncertainty of a causal relationship with the administration of the drug		
d. A lack of information from the affected patient		
e. The reaction is widely known		
f. A lack of knowledge regarding the regulations and procedure for reporting		
g. The difficulty in obtaining a form for reporting		
h. The complexity of the form to be completed		
i. The fear of medical-legal consequences		
j. Reporting does not seem worthwhile		
k. A lack of time to report reactions due to heavy responsibilities		
l. A lack of support from your organisation/ head of department/ colleagues etc		

13. Which of the following ADRs do you think should be reported to MADRAC?

	1 Yes	2 No	3 Don't know
a. Suspected reactions *(For which the intake of one or more drugs is only one of several possible explanations)*			
b. Certain [sure, ascertained] reactions *(For which the causal relationship with the intake of one or more drugs is obvious)*			
c. Severe reactions			
d. Mild reactions			
e. Reactions to drugs that have been in use for a long time			
f. Reactions to new drugs			
g. Known reactions *(Listed on the package leaflet or already described in the literature)*			
h. Unexpected/unusual reactions			
i. Interactions between drugs			
j. Teratogenicity phenomena *(Causing harm/malformations to an embryo or foetus)*			
k. Reactions to vaccinations			
l. Lack of efficacy of a drug due to development of newly resistant strain			

14. What do you think are the aims of monitoring the spontaneous reporting of suspected ADRs by MADRAC?

	1 Yes	2 No	3 Don't know
a. To measure the incidence of ADRs			
b. To identify the indication for which the drugs are prescribed			
c. To identify factors predisposing patients to ADRs			
d. To identify uncommon ADRs (allergic, idiosyncratic, etc.)			
e. To identify previously unknown ADRs			
f. To identify safe drugs			
g. To maintain a database of ADRs			

Section D - Therapeutic failure/ uncontrolled disease

Therapeutic failure definition*: a failure to accomplish the goals of treatment as a result of inadequate drug therapy and not related to the natural progression of disease (Edwards et al 2000). e.g. non-adherence to a drug therapy, prescriber fails to monitor and adjust/intensify treatment.*

15. Have you observed patients who you think have had therapeutic failure during the last 6 months?

1 Yes	
2 No	

If no please go to question number 19 (Section E)

16. How frequently have you observed patients with therapeutic failure during the last 6 months?
(Please tick one only)

1 At least 1 case per day	
2 At least 1 case per week	
3 At least 1 case per month	
4 Less than 1 case per month	

17. What types of diseases or therapy were associated with the therapeutic failure that you have most recently observed?
(Please tick all that apply)

a. Diabetes	
b. Hypertension	
c. Asthma	
d. Cardiovascular diseases	
e. Renal failures	
f. Epilepsy or seizure	
g. Cancer	
h. HIV/ AIDS	
i. Tuberculosis	
j. Antibiotic therapy	
k. Pain management	

l. Other (please specify).....

18. Thinking about the <u>most recent</u> patient with therapeutic failure which you observed, what was your course of action?
(Please tick all that apply)

a. Do further evaluation (e.g patient medication history)	
b. Inform physician-in-charge	
c. Suggest to patient that they inform their doctor	
d. Make note in patients' chart/ record	
e. Explain to patient/ patient's family member about the importance of compliance to medications	
f. Counsel the patient the right way to use/ consume their medications	
g. Suggest to the patient to try a different medicine	
h. No action	

i. Other (please specify).....

Section E – <u>Medication error</u>

Medication error definition: *any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer(NCC MERP, 2000)*

19. Have you observed a patient with medication error during the <u>last 6 months</u>?

1 Yes	
2 No	

If no please got to question number 23 (Section F)

20. How frequently have you observed a patient with medication error during the <u>last 6 months</u>?
(Please tick one only)

1 At least 1 case per day	
2 At least 1 case per week	
3 At least 1 case per month	
4 Less than 1 case per month	

21. Which types of medication error have you <u>most recently</u> observed during the last 6 months?
(Please tick all that apply)

a. Prescribing error (*Incorrect drug product selection (based on indications, contraindications, known allergies, existing drug therapy, and other factors), dose, dosage form, quantity, route of administration, concentration, rate of administration, or instructions for use of a drug product ordered or authorized by physician*)	
b. Omission error *(The failure to administer an ordered dose to a patient before the next scheduled dose or failure to prescribe a drug product that is indicated for the patient)*	
c. Wrong time error *(Administration of medication outside a predefined time interval for its scheduled administration)*	
d. Unauthorised drug error *(Dispensing or administration to the patient of medication not authorised by a legitimate prescriber)*	
e. Dose error *(Dispensing or administration to the patient of a dose that is greater than or less than the amount ordered by the prescriber or administration of multiple doses to the patient)*	
f. Dosage form error *(Dispensing or administration to the patient of a drug product in a different dosage form than that ordered by the prescriber)*	
g. Drug preparation error *(Drug product incorrectly formulated or manipulated before dispensing or administration)*	
h. Route of administration error *(Wrong route of administration of the correct drug)*	
i. Administration technique error *(Inappropriate procedure or improper technique in the administration of a drug other than wrong route)*	
j. Deteriorated drug error *(Dispensing or administration of a drug that has expired or for which the physical or chemical dosage-form integrity has been compromised)*	
k. Monitoring error *(Failure to review a prescribed regimen for appropriateness and detection of problems, or failure to use appropriate clinical or laboratory data for adequate assessment of patient response to prescribed therapy)*	

l. Other (please specify) .....

22. Thinking about the <u>most recent</u> patient with medication error which you observed, what was your course of action?
(Please tick all that apply)

a. Make note in patients' chart/ record	
b. Inform physician-in-charge	
c. Inform nurse in-charge	
d. Suggest to the patient that they inform their doctor	
e. Explain to the patient about the error	
f. Correct the error	
g. Suggest ways to minimise the error	
h. Make an incident report/ record	
i. No action	

j. Other (please specify) .....

Section F – <u>Drug overdose</u>

Drug overdose definition**:** *the accidental or intentional use of a drug in an amount that is higher than is normally used (McDonnell 2008)*

23. Have you observed patients with drug overdose(s) during the <u>last 6 months</u>?

1 Yes	
2 No	

If no go to question number 27 (Section G)

24. How frequently have you observed patients with drug overdose(s) during the <u>last 6 months</u>?
(Please tick one only)

1 At least 1 case per day	
2 At least 1 case per week	
3 At least 1 case per month	
4 Less than 1 case per month	

25. Which drug(s) was associated with the <u>most recent</u> drug overdose(s) you have observed?
(Please tick all that apply)

a. Psychiatric drugs	
b. Topical agents	
c. Analgesics	
d. Cough & cold medications	
e. Herbal remedies	
f. Anti-epileptics	
g. Hormones	
h. Anti-infectives	
i. Gastrointestinal drugs	
j. Respiratory drugs	
k. Cardiovascular drugs	
l. Vitamins/ minerals/ food supplements	
m. Hematologic drugs	
n. Cytotoxic drugs	
o. Veterinary drugs	
p. Mixed pharmaceutical drugs	

q. Others (please specify)…….....

26. Thinking about the <u>most recent</u> patient with drug overdose(s) you observed, what was your course of action?
(Please tick all that apply)

a. Inform physician-in-charge	
b. Make note in patients' chart/ record	
c. Refer patient to a hospital	
d. Suggest an antidote	
e. Call national poison centre to clarify about the effects of drug overdoses	
f. Make an incident report/ record	
g. No action	

h. Other (please specify) .....

Section G – General

27. Are you …

1 Male	
2 Female	

28. Highest level of education

1 Bachelors degree	
2 Masters degree	
3 Doctorate degree	

29. Number of years working as pharmacist:

More than 15 years	
11 – 15 years	
6 – 10 years	
5 years or less	

~Thank you for your participation~

Note: Please return your completed questionnaire in the reply paid envelope provided (no stamp needed). A reminder will be sent to non-respondents.

Appendix 10: Questionnaire for doctors and nurses

Confidential

Health care professionals' experiences about adverse drug events

This questionnaire asks about your experiences with adverse drug events that you may have encountered as part of your practice during the last six months.

Please help us by taking the time to answer the questionnaire. Your answers are very important.

This questionnaire will take 10-15 minutes to complete. All information you provide will be kept confidential.

July 2010

Mahmathi Karuppannan[1,3],
Helen Boardman[1],
Ting Kang Nee[2],
Salmiah Mohd. Ali[3] and
Wong Kok Thong[2]

[1]University of Nottingham, United Kingdom, [2]University of Nottingham, Malaysia Campus, [3]Universiti Teknologi MARA, Shah Alam, Malaysia.

Please tick the appropriate box.

Section A - General

i) Are you ……..

1 A consultant/ specialist	
2 A medical officer (MO)	
3 A house officer (HO)	
4 A matron	
5 A sister	
6 A staff nurse	
7 A pharmacist	
8 A physiotherapist	
9 A dietitian	
10 Other health care professional	

Please state.....

Section B - Adverse Drug Reactions (ADRs)

ADR definition: *a response to a drug that is noxious and unintended and occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease, or for modification of physiological function* (WHO, 2002)

1. **Have you observed a suspected ADR during the last 6 months?**

1 Yes	
2 No	

If no, please go to question number 6 (Section C)

2. **How frequently have you observed a patient with a suspected ADR during the last 6 months?**
   (Please tick one only)

1 At least 1 case per day	
2 At least 1 case per week	
3 At least 1 case per month	
4 Less than 1 case per month	

3. **Please tell us about the <u>most recent</u> suspected ADR that you have observed, what were the symptoms?**
(Please tick all that apply)

a. Cough	
b. Dry cough	
c. Dizziness	
d. Oedema periorbital	
e. Itchiness	
f. Rash	
g. Headache	
h. Giddiness	
i. Oedema	
j. Diarrhoea	
k. Nausea	
l. Vomiting	
m. Renal failure	
n. Jaundice	
o. Acute hepatitis	
p. Steven Johnson Syndrome	
q. Erythema	
r. Heartburn	
s. Gastritis	
t. Constipation	
u. Palpitation	
v. Flatulence	
w. Myalgia	
x. Thrombocytopenia	

y. Other (please specify)……

4. Please tell us about the drug(s) involved in the <u>most recent</u> suspected ADR symptoms that you have observed.
(Please tick all that apply)

a. Perindopril	
b. Aspirin	
c. Diclofenac	
d. Amlodipine	
e. Metformin	
f. Traditional medicine	
g. Allopurinol	
h. Co-trimoxazole	
i. Heparin	
j. Lovastatin	
k. Cloxacillin	
l. Ticlopidine	
m. Rifampicin	
n. Phenytoin	
o. Amoxycillin	
p. Carbamazepine	
q. Nifedipine	
r. Erythromycin	
s. Captopril	
t. Paracetamol	
u. Atenolol	
v. Cefuroxime	
w. Mefenamic acid	
x. Chlorothiazide	
y. Penicillin G sodium	
z. Vancomycin	
aa. Alendronate	
bb. Isosorbide dinitrate	

cc. Other (please specify)……

5. **Thinking about the <u>most recent</u> suspected ADR you observed, what was your course of action?**
(Please tick all that apply)

a. Fill in the ADR report form and send to MADRAC	
b. Fill in the ADR report form and send to hospital drug information centre	
c. Inform the pharmacist in hospital drug information centre	
d. Inform the physician in-charge	
e. Inform the associated pharmaceutical company	
f. Do further evaluation (e.g. patient medication history)	
g. Make note in patient's chart/ record	
h. Prescribe a different medicine	
i. Withhold the suspected medicine	
j. Prescribe a medicine to relieve the reaction(s)	
k. Explain to the patient that it may be a reaction to their medicine	
l. No action	

m. Other (please specify) .....

Section C - <u>Adverse Drug Reactions (ADRs): spontaneous reporting</u>

Spontaneous reporting definition*: System whereby case reports of adverse drug events are voluntarily submitted from health professionals and pharmaceutical manufacturers to the national regulatory authority (WHO, 2002)*

*In Malaysia the national regulatory authority who collates and assesses spontaneous reports from health professionals (and now patients) is the **Malaysian ADR Advisory Committee (MADRAC)**, which then submits the reports to the WHO's (World Health Organization) Uppsala Monitoring Centre in Sweden.*

6. **Have you ever reported a suspected ADR to MADRAC?**

1 Yes	
2 No	

7. **Are you aware of the existence of an appropriate form for reporting suspected ADRs to MADRAC?**

1 Yes	
2 No	

If no, please go to question number 10

8. **Do you know how to obtain the form to report a suspected ADR to MADRAC?**

1 Yes	
2 No	

If no, please go to question number 10

9. **Where can you obtain the form for ADR reporting?**
(Please tick all that apply)

a. Distributed/posted by MADRAC	
b. From MADRAC online webpage	
c. From drug information centre in hospital	
d. From national or local health department	
e. From a drug information book	

Other (please specify).....

10. **How would you prefer to submit a report about a suspected ADR to MADRAC?**
(Please tick all that you would use)

a. Filling in a form and posting it	
b. Filling in a form and faxing it	
c. Filling in an online form	
d. Reporting by phone	
e. Reporting by email	

11. Would any of the following <u>encourage</u> you to report a suspected ADR to MADRAC?

	1 Yes	2 No
a. The high degree of severity of a clinical reaction		
b. The explicit request of a pharmaceutical company		
c. The reaction is not widely known		
d. The specific typology of the reaction (unusual/unexpected)		
e. The involvement of a newly licensed drug		
f. An obvious causal relationship with the administration of the drug		

12. Would any of the following <u>discourage</u> you from reporting a suspected ADR to MADRAC?

	1 Yes	2 No
a. The low degree of severity of a clinical reaction		
b. Uncertainty regarding the type of reactions to be reported		
c. The uncertainty of a causal relationship with the administration of the drug		
d. A lack of information from the affected patient		
e. The reaction is widely known		
f. A lack of knowledge regarding the regulations and procedure for reporting		
g. The difficulty in obtaining a form for reporting		
h. The complexity of the form to be completed		
i. The fear of medical-legal consequences		
j. Reporting does not seem worthwhile		
k. A lack of time to report reactions due to heavy responsibilities		
l. A lack of support from your organisation/ head of department/ colleagues etc		

13. Which of the following ADRs do you think should be reported to MADRAC?

	1 Yes	2 No	3 Don't know
a. Suspected reactions *(For which the intake of one or more drugs is only one of several possible explanations)*			
b. Certain [sure, ascertained] reactions *(For which the causal relationship with the intake of one or more drugs is obvious)*			
c. Severe reactions			
d. Mild reactions			
e. Reactions to drugs that have been in use for a long time			
f. Reactions to new drugs			
g. Known reactions *(Listed on the package leaflet or already described in the literature)*			
h. Unexpected/unusual reactions			
i. Interactions between drugs			
j. Teratogenicity phenomena *(Causing harm/malformations to an embryo or foetus)*			
k. Reactions to vaccinations			
l. Lack of efficacy of a drug due to development of newly resistant strain			

14. What do you think are the aims of monitoring the spontaneous reporting of suspected ADRs by MADRAC?

	1 Yes	2 No	3 Don't know
a. To measure the incidence of ADRs			
b. To identify the indication for which the drugs are prescribed			
c. To identify factors predisposing patients to ADRs			
d. To identify uncommon ADRs (allergic, idiosyncratic, etc.)			
e. To identify previously unknown ADRs			
f. To identify safe drugs			
g. To maintain a database of ADRs			

Section D - Therapeutic failure/ uncontrolled disease

Therapeutic failure definition*: a failure to accomplish the goals of treatment as a result of inadequate drug therapy and not related to the natural progression of disease. (Edwards et al 2000) e.g. non-adherence to a drug therapy, prescriber fails to monitor and adjust/intensify treatment.*

15. Have you observed patients who you think have had therapeutic failure during the last 6 months?

1 Yes	
2 No	

If no please go to question number 19 (Section E)

16. How frequently have you observed patients with therapeutic failure during the last 6 months?
(Please tick one only)

1 At least 1 case per day	
2 At least 1 case per week	
3 At least 1 case per month	
4 Less than 1 case per month	

17. What types of diseases or therapy were associated with the therapeutic failure that you have most recently observed?
(Please tick all that apply)

a. Diabetes	
b. Hypertension	
c. Asthma	
d. Cardiovascular diseases	
e. Renal failures	
f. Epilepsy or seizure	
g. Cancer	
h. HIV/ AIDS	
i. Tuberculosis	
j. Antibiotic therapy	
k. Pain management	

l. Other (please specify).....

18. Thinking about the <u>most recent</u> patient with therapeutic failure you observed, what was your course of action?
(Please tick all that apply)

a. Do further evaluation (e.g. patient medication history)	
b. Inform the physician-in-charge	
c. Make note in patient's chart/ record	
d. Explain to patient/ patient's family member about the importance of compliance to medications	
e. Counsel the patient the right way to use/ consume their medications	
f. Prescribe a different medicine	
g. No action	

h. Other (please specify) .....

Section E – <u>Medication error</u>

Medication error definition: *any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer (NCC MERP,2001)*

19. Have you observed patients with medication error during the <u>last 6 months</u>?

1 Yes	
2 No	

If no please go to question number 23 (Section F)

20. How frequently have you observed patients with medication error during the <u>last 6 months</u>?
(Please tick one only)

1 At least 1 case per day	
2 At least 1 case per week	
3 At least 1 case per month	
4 Less than 1 case per month	

21. Which type(s) of medication error have you <u>most recently</u> observed?
(Please tick all that apply)

a. Prescribing error (*Incorrect drug product selection (based on indications, contraindications, known allergies, existing drug therapy, and other factors), dose, dosage form, quantity,route of administration, concentration, rate of administration, or instructions for use of a drug product ordered or authorized by physician*)	
b. Omission error *(The failure to administer an ordered dose to a patient before the next scheduled dose or failure to prescribe a drug product that is indicated for the patient)*	
c. Wrong time error *(Administration of medication outside a predefined time interval for scheduled administration)*	
d. Unauthorised drug error *(Dispensing or administration to the patient of medication not uthorized by alegitimate prescriber)*	
e. Dose error *(Dispensing or administration to the patient of a dose that is greater than or less than the amount ordered by the prescriber or administration of multiple doses to the patient)*	
f. Dosage form error *(Dispensing or administration to the patient of a drug product in a different dosage form than that ordered by the prescriber)*	
g. Drug preparation error *(Drug product incorrectly formulated or manipulated before dispensing or administration)*	
h. Route of administration error *(Wrong route of administration of the correct drug)*	
i. Administration technique error *(Inappropriate procedure or improper technique in the administration of a drug other than wrong route)*	
j. Deteriorated drug error *(Dispensing or administration of a drug that has expired or for which the physical or chemical dosage form integrity has been compromised)*	
k. Monitoring error *(Failure to review a prescribed regimen for appropriateness and detection of problems, or failure to use appropriate clinical or laboratory data for adequate assessment of patient response to prescribed therapy)*	

i. Other (please specify) .....

22. Thinking about the <u>most recent</u> patient with medication error you observed, what was your course of action?
(Please tick all that apply)

a. Make note in patient's chart/ record	
b. Inform the physician in-charge	
c. Inform the nurse in-charge	
d. Explain to the patient about the error	
e. Correct the error	
f. Suggest ways to minimise the error	
g. Make an incident report/ record	
h. No action	

i. Other (please specify) .....

Section F – <u>Drug overdose</u>

Drug overdose definition: *the accidental or intentional use of a drug in an amount that is higher than is normally used (McDonnell 2008)*

23. Have you observed patients with drug overdose(s) during the <u>last 6 months</u>?

1 Yes	
2 No	

If no go to question number 27 (Section G)

24. How frequently have you observed patients with drug overdose(s) during the <u>last 6 months</u>?

1 At least 1 case per day	
2 At least 1 case per week	
3 At least 1 case per month	
4 Less than 1 case per month	

25. Which drug(s) was associated with the <u>most recent</u> drug overdose(s) you have observed?

(Please tick all that apply)

a. Psychiatric drugs	
b. Topical agents	
c. Analgesics	
d. Cough & cold medications	
e. Herbal remedies	
f. Anti-epileptics	
g. Hormones	
h. Anti-infectives	
i. Gastrointestinal drugs	
j. Respiratory drugs	
k. Cardiovascular drugs	
l. Vitamins/ minerals/ food supplements	
m. Hematologic drugs	
n. Cytotoxic drugs	
o. Veterinary drugs	
p. Mixed pharmaceutical drugs	

q. Other (please specify)…….....

26. Thinking about the <u>most recent</u> patient with drug overdose you observed, what was your course of action?

(Please tick all that apply)

a. Inform physician-in charge	
b. Make note in patient's chart/ record	
c. Prescribe an antidote	
d. Call national poison centre to clarify about the effects of drug overdoses	
e. Make an incident report/ record	
f. No action	

g. Other (please specify) .....

Section G – General

27. Are you a…

1 Male	
2 Female	

28. Number of years working in the medical wards

More than 15 years	
11 – 15 years	
6 – 10 years	
5 years or less	

~Thank you for your participation~

Appendix 11: Approval letter from National Institutes of Health to conduct survey of doctors and nurses

NATIONAL INSTITUTES OF HEALTH APPROVAL FOR CONDUCTING RESEARCH IN THE MINISTRY OF HEALTH MALAYSIA

PENGESAHAN INSTITUSI PENYELIDIKAN NEGARA UNTUK MENJALANKAN PENYELIDIKAN DI KEMENTERIAN KESIHATAN

This is an auto computer - generated document.It is issued by one of the research institute under the National Institutes of Health (NIH). These are the Institute for Medical Research (IMR), Clinical Research Centre (CRC), Institute of Public Health (IPH), Institute for Health Management (IHM), Institute for Health Systems Research (IHSR), and Institute for Health Behavioural Research (IHBR)

Dokumen ini adalah cetakan berkomputer. Borang ini dikeluarkan oleh salah satu institusi dibawah National Institutes of Health (NIH) iaitu Institut Penyelidikan Perubatan (IMR), Pusat Penyelidikan Klinikal (CRC), Institut Kesihatan Umum (IKU), Institut Pengurusan Kesihatan (IPK), Institut Pergurusan Sistem Kesihatan (IPSK), Institut Penyelidikan Tingkahlaku Kesihatan (IPTK)

Unique NMRR Registration ID : [Nombor Pendaftaran]	NMRR-10-320-5596
Research Title : [Tajuk]	Health care professionals' experiences about adverse drug events
Protocol Number if available : [Nombor Protokol jika ada]	

#	**Investigator Name** **[Name Penyelidik]**	**Institution Name** **[Nama Institusi]**
1	Mahmathi Karuppannan	Universiti Teknologi MARA (UiTM) - Shah Alam Campus

I have reviewed the above titled research, and approve of its design and conduct.

Saya telah menyemak kajian yang bertajuk seperti di atas dan meluluskan rekabentuk dan perlaksanaannya.

Name of Director : *[Nama Pengarah]*	Pn. Siti Sa'adiah Hassan Nudin
NIH Institute (IMR, CRC, IPH, IHM, IHSR and IHBR) *[Nama Institusi di bawah NIH]*	Institute for Health Behavioural Research (IHBR)
Signature & Official stamp : *[Tandatangan dan Cop Rasmi]*	This is computer generated document, therefore no signature is required.
Date : *[Tarikh]*	16-06-2010

(Note: This is a computer generated document. It may not carry any signature)

Appendix 12: Cover letter for main survey

The University of Nottingham

UNIVERSITI TEKNOLOGI MARA

Date: January 2010

Dear pharmacist,

Pharmacists' experiences about adverse drug events

We are conducting a survey investigating Malaysian pharmacists' experiences of adverse drug events (ADEs) as part of everyday practice. We want to know how frequently you encounter ADEs and what actions you have taken in response to such events. We also want to know about your understanding of the spontaneous reporting system in Malaysia.

The questionnaire is being mailed to all pharmacists who are registered with Malaysian Pharmaceutical Society (MPS) who are recorded as working in hospital or retail pharmacy.

The results from this study will help us understand the experiences and awareness of pharmacists about adverse drug events and provide insight how current systems might be improved. We will present the results of the study at conferences and in journal articles so that other people can learn from our study.

Taking part in this study is entirely your choice. We estimate the questionnaire will take 10-15 minutes to complete. All information you provide will be kept confidential. Please return this questionnaire in the next two weeks.

This study has ethical approval from the Division of Social Research in Medicines and Health, University of Nottingham

If you would like any further information regarding the study, please contact Ms. Mahmathi Karuppannan on 03-89248203 or 03-32584643 or paxmk2@nottingham.ac.uk

Thank you for your participation in this important research.

Yours faithfully,

Mahmathi Karuppannan
PhD research student
School of Pharmacy
University of Nottingham, UK.

Helen Boardman
Lecturer in Pharmacy Practice
School of Pharmacy
University of Nottingham, UK.

Ting Kang Nee
Associate Professor
School of Pharmacy
University of Nottingham,Malaysia Campus

Salmiah Mohd. Ali
Associate Professor
School of Pharmacy
UiTM, Puncak Alam

Wong Kok Thong
Associate Professor
School of Pharmacy
University of Nottingham, Malaysia Campus.

Appendix 13: Reminder cover letter

The University of Nottingham

UNIVERSITI TEKNOLOGI MARA

Date: April 2010

Dear pharmacist,

Reminder: Pharmacists' experiences about adverse drug events

We recently sent you a questionnaire but have not yet received your reply. Please ignore this reminder if you have replied in the last few days.

We are conducting a survey investigating Malaysian pharmacists' experiences of adverse drug events (ADEs) as part of everyday practice. The results from this study will help us understand the experiences and awareness of pharmacists about adverse drug events and provide insight how current systems might be improved.

The questionnaire is being mailed to all pharmacists who are registered with Malaysian Pharmaceutical Society (MPS) who are recorded as working in hospital or retail pharmacy. We have not received a response from you but are still very interested to hear from you.

Taking part in this study is entirely your choice. We estimate the questionnaire will take 10-15 minutes to complete. All information you provide will be kept confidential. We would be grateful if you could return the questionnaire in the next two weeks.

If you would like any further information regarding the study, please contact Ms. Mahmathi Karuppannan on 03-89248203 or 03-32584643 or paxmk2@nottingham.ac.uk

Thank you for your participation in this important research.

Yours faithfully,

Mahmathi Karuppannan
PhD research student
School of Pharmacy
University of Nottingham, UK.

Helen Boardman
Lecturer in Pharmacy Practice
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University of Nottingham, UK.

Ting Kang Nee
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