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USING THE THEORY OF PLANNED BEHAVIOR TO PREDICT TEXAS PHARMACISTS' INTENTION TO REPORT SERIOUS ADVERSE DRUG EVENTS

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by

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Dedication

This dissertation is dedicated to my sons Tatenda Vashee and Takudzwa Gavaza.

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USING THE THEORY OF PLANNED BEHAVIOR TO PREDICT TEXAS PHARMACISTS' INTENTION TO REPORT SERIOUS ADVERSE DRUG EVENTS

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The purpose of this dissertation was to use the theory of planned behavior (TPB) to predict Texas pharmacists' intention to report serious adverse drug effects (ADEs) to the Food and Drug Administration (FDA). The study explored the utility of the TPB model constructs (attitude [A], subjective norm [SN], perceived behavioral control [PBC]), as well as past reporting behavior (PRB), and perceived moral obligation (PMO) to predict pharmacists' intention to report serious ADEs to the FDA. The study also determined if the pharmacists' A, SN and PBC were related to practice characteristics and demographic factors.

A survey was developed based on two focus group interviews, pretested and mailed to 1,500 Texas practicing pharmacists. An overall response rate of 26.4 percent was obtained (n = 377 pharmacists). Overall, pharmacists intended to report serious ADEs, had a favorable attitude towards reporting, were somewhat influenced by social norms regarding reporting and perceived themselves to have some control over reporting

serious ADEs to the FDA. For direct measures, A and SN were significant predictors of intention to report serious ADEs, but PBC was not. The TPB constructs together accounted for 34.0 percent of the variance in intention to report serious ADEs to the FDA. Using indirect measures, A, SN and PBC were significant predictors of intention and together accounted for 28.8 percent of the variance in intention to report serious ADEs. PRB and PMO improved the explanatory power of the regression models (direct and indirect measures) over and above the TPB constructs. Unlike most other practice characteristics and demographic factors examined, knowledge was significantly related with the TPB constructs.

In summary, A, SN, PBC (indirect measures), PRB, and PMO influence the formation of pharmacists' intention to report serious ADEs. The TPB has utility in predicting ADE reporting behavior. Pharmacy educators should explore pharmacists' attitudes, beliefs, and expectations of important others in designing educational programs. Strategies to help pharmacists report more serious ADEs should focus on altering their perception of social pressure towards reporting and addressing the barriers towards ADE reporting (e.g., lack of knowledge).

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List of Abbreviations

A	Attitude
ACCP	American College of Clinical Pharmacy
ADE	Adverse drug event
ADR	Adverse drug reaction
AE	Adverse event
AERS	Adverse event reporting system
AIDS	Acquired immunodeficiency syndrome
ANOVA	Analysis of variance
APhA	American Pharmacists Association
ASHP	American Society of Health-System Pharmacists
CAPA	Capital Area Pharmacy Association
CDER	Center for Drug Evaluation and Research
CE	Continuing education
CFI	Comparative fit index
CFR	Code of Federal Regulations
CIOMS	Council for International Organization for Medical Sciences
CMS	Centers for Medicare and Medicaid Services
CNMP	Chronic non-malignant pain
CNMs	Certified nurse-midwives
CR	Controlled release
CSM	Committee on Safety of Medicines
DIC	Drug Information Centers
EC	Emergency contraception
EG	For example
EU	European Union
FDA	The Food and Drug Administration
FDAAA	The Food and Drug Administration Amendments Act
GDP	Gross domestic product
GPs	General practitioners
HCP	Healthcare professional
HIV	Human immunodeficiency virus
HRQOL	Health-related quality of life
ICH	International Conference on Harmonization
IDUs	Intravenous drug users
INN	International nonproprietary number
IOM	Institute of medicine
IRB	Institutional review board
IT	Information technology
MTMS	Medication therapy management services
NCCMERP	The National Coordinating Council for Medication Error Reporting and Prevention

NHS	National Health System
NYPORTS	New York Patient Occurrence and Tracking System
OSE	Office of Surveillance and Epidemiology
OTC	Over the counter
PB	Past behavior
PBC	Perceived behavioral control
PBMs	Pharmacy Benefits Management
PDUFA	Prescription Drug User Fee Act
PMO	Perceived moral obligation
PMS	Postmarketing surveillance
PRB	Past reporting behavior
PRR	Proportional reporting ratio
QALY	Quality adjusted life year
RMSEA	Root mean square error of approximation
ROR	Reporting odds ratio
RPB	Recent past behavior
SA	Self assessment
SARS	Severe acute respiratory syndrome
SD	Standard deviation
SEM	Structural equation modeling
SN	Subjective norm
SPC	Summary of product characteristics
SPSS	Statistical package for the social sciences
SR	Spontaneous reporting
SRMR	Standardized root mean square residual
SRS	Spontaneous reporting system
TLI	Tucker-Lewis Index
TSBP	Texas State Board of Pharmacy
UK	United Kingdom
UMC	Uppsala Monitoring Centre
UNESCO	United Nations Educational, Scientific and Cultural Organization
URI	Upper respiratory infections
US	United States
USP	United States Pharmacopeia
VAERS	Vaccine adverse event reporting system
WHO	World Health Organization

CHAPTER ONE: INTRODUCTION

1.1 BACKGROUND

Although patients expect positive health outcomes from the health system, healthcare interventions including medicines can also cause significant patient harm (Institute of Medicine Report, 2001). Medical practice is potentially dangerous and inherently unsafe (Chantler, 1999). Many people are unintentionally harmed by treatments and in the process of being treated (Institute of Medicine of the National Academies, 2007b; Sandars, 2007; Vincent et al., 2006). Healthcare lags behind other high risk industries on safety. The use of medicines is associated with risks, hazards and adverse outcomes (adverse events) that compromise patient safety. These drug-related injuries occur for various reasons including lack of patient compliance, inadequate initial testing, poor postmarketing surveillance and prescribing errors (Moore, Psaty, & Furberg, 1998).

Drug-related injuries or adverse drug events (ADEs) are common and account for about 20 percent (range: 1.5% to 35%) of hazards related to the medication use process in hospitalized patients (Bates et al., 1995b; Brennan et al., 1991; Leape et al., 1991). The Food and Drug Administration (FDA) defines an ADE as any adverse event that is associated with the use of a drug whether or not that event is considered drug-related. Common ADEs include failure of expected pharmacologic action, drug abuse, drug withdrawal and overdoses (accidental or intentional) (Trontell, 2001). A serious adverse event is defined as any event that is fatal, life threatening, is permanently/significantly disabling, requires or prolongs hospitalization, causes a congenital anomaly and requires intervention to prevent permanent impairment or damage. In the United States (U.S.), about 1.5 million people are injured by prescription drugs annually (Institute of Medicine of the National Academies, 2007b). Some of these people are hospitalized and approximately 100,000 die as a result of these injuries (Institute of Medicine Report,

2001). In the U.S., ADEs are the 4th leading cause of death; more people die from ADEs than from pulmonary disease, diabetes, AIDS, pneumonia, accidents and automobile deaths (FDA/Center for Drug Evaluation and Research, 2002).

An important ADE is the adverse drug reaction (ADR) accounting for an estimated 7,000 deaths annually (Institute of Medicine, 2000). The incidence of ADRs is high among hospital patients, an estimated 6.7 percent of whom have serious ADRs (Lazarou, Pomeranz, & Corey, 1998). These figures do not include ADRs occurring in ambulatory settings and those occurring in nursing homes (over 300,000 annually) (Gurwitz et al., 2000).

Drug-related injuries are the most frequent cause of procedure-related malpractice claims (National Association of Insurance Commissioners, 1980). An estimated three (3) to eight (8) percent of hospital admissions in internal medicine are related to ADEs (Einarson, 1993). ADEs compromise patient safety and are a considerable public health problem. ADEs are the most common threat to patient safety in secondary care (Sandars, 2007). In addition, ADEs account for a significant part of healthcare expenditures and costs. In 1995, the cost of drug-related morbidity and mortality in the ambulatory care was estimated to be $76.6 (range: $30.1 – $136.6) billion annually in the U.S. (Johnson & Bootman, 1995). In 2001, the cost of drug-related morbidity and mortality was estimated to exceed $177.4 billion, more than double the 1995 estimate (Ernst & Grizzle, 2001). Many patients' hospital and doctor visits are attributable to ADEs (20%) (Leape et al., 1991). ADEs also increase patients' hospital stay.

Because of the significant health and economic costs associated with ADEs, regulatory authorities invest significantly (e.g., staff and resources) in evaluating the risks of treatments and in monitoring the safety of drugs throughout the lifetime of their use. This occurs mainly through pharmacovigilance and postmarketing surveillance (PMS). PMS, the continuous safety monitoring of all drugs, plays a critical role in drug safety and drug therapy decision-making. PMS monitors drug safety through collecting and

analyzing voluntary spontaneous reports submitted by healthcare professionals (HCPs), pharmaceutical companies and patients. HCPs are encouraged to voluntarily report ADEs (mostly suspected ADEs) to drug regulatory authorities or programs (Belton & The European Pharmacovigilance Research Group, 1997). Voluntary spontaneous reporting is the primary and most common method of pharmacovigilance or PMS (Ahmad, 2003; Lexchin, 2006; Rawlins, 1988a, 1988b; Strom, 2004; Wysowski & Swartz, 2005). Voluntary reporting of ADEs through spontaneous reporting systems (SRSs) is an important component of any comprehensive surveillance program of risks induced by drug use.

Voluntary ADE reporting by HCPs is widely accepted and is considered standard practice in many countries. SRSs are simple to operate, relatively inexpensive, comprehensive (i.e., cover all drugs and entire patient population) and are not intrusive (Cosentino, Leoni, Banfi, Lecchini, & Frigo, 1997). SRSs are the best and most common method for identifying and highlighting new and rare ADEs and the factors predisposing patients to ADEs (Bates et al., 1997; Classen, Pestotnik, Evans, Lloyd, & Burke, 1997; Rawlins, 1988b). Data gathered through such schemes make a priceless contribution to patient safety and facilitate improved understanding of the benefits and risks of drugs. This information is valuable for drug manufacturers (useful in modifying product information, warnings, and the product or its use and withdrawing the product from the market), patients (identify risks and prompt discussion about these risks with their HCPs) and HCPs including pharmacists (make better clinical decisions). SRSs provide valuable feedback to manufacturers, practitioners and their patients on medicines that have problems (Edgar, Lee, & Cousins, 1994). Thus, ADE reporting helps minimize injury due to drugs, improves risk management and quality of care and informs prevention efforts (Barwick, 1996; Solberg, Moaser, & McDonald, 1997). Also, the existence of SRSs reinforces the importance of drug safety issues to HCPs. To date there is no real substitute for it.

HCPs, including pharmacists, can play an important role in improving the safety of treatments through reporting ADEs. The success of pharmacovigilance programs requires the participation and support of pharmacists. Findings from previous studies show that HCPs have favorable beliefs and opinions concerning ADE reporting (Lawton & Parker, 2002; McArdle, Burns, & Ireland, 2003; Uribe, Schweikgart, Pathak, Marsch, & Fraley, 2002). In addition, subjective norm supporting ADE reporting and strong perceived behavioral control (PBC) may be positive and significant predictors of intention to report ADEs.

1.2 ADE REPORTING IN THE U.S. AND STATEMENT OF THE PROBLEM

Formal ADE reporting has a long history in the U.S., dating back to 1969. Pharmacovigilance in the U.S. is spearheaded by the FDA, an agency of the Department of Human and Health Services. In addition to approving drugs, the FDA's Center for Drug Evaluation and Research (CDER) is responsible for monitoring the safety of all marketed drugs. Physicians, pharmacists, dentists, nurses and consumers in the U.S. are encouraged to report serious ADEs they encounter to the FDA. The submitted reports are stored and analyzed in the adverse event reporting system (AERS) database. The AERS database is maintained by the CDER's Office of Surveillance and Epidemiology (OSE), formerly known as the Office of Drug Safety. The AERS is the cornerstone of the FDA's drug PMS activities. The database has over 2 million reports of ADEs and is the world's largest (Moore, Cohen, & Furberg, 2007). In 1993, the FDA's ADE reporting system was renamed MedWatch. MedWatch facilitates the reporting of serious ADEs, product quality problems (e.g., device malfunctions, labeling concerns, suspected counterfeit products, product contamination, poor packaging, and therapeutic failure) and medication and device use errors.

On average, the FDA receives approximately 250,000 reports of adverse events annually (Ahmad, 2003). Most (80%) of the HCPs' reports are submitted to the FDA through pharmaceutical companies and approximately 20 percent of the reports go directly to the FDA through MedWatch. Compared to other HCPs in the U.S., pharmacists submit the greatest number of reports to the FDA. In 2001, pharmacists submitted 41 percent of the reports made by individuals. The rest of the reports were made by physicians (11%), nurses (11%), other health care professionals (11%), unknown (18%), and consumers (8%) (Cobert, 2007; Office of Drug Safety, 2001).

Notwithstanding the many advantages of ADE reporting, underreporting by HCPs, including pharmacists, is a major problem (Cullen et al., 1995; Lawton & Parker, 2002), occurring at a rate of 50 to 96 percent annually in the U.S. (Barach & Smith, 2000). It has also been estimated that less than 1 percent of serious adverse events are reported to the FDA (Scott et al., 1987). Underreporting reduces the effectiveness and benefits of SRSs (Fontanarosa, Rennie, & DeAngelis, 2004; Hazell & Shakir, 2006). There are many factors that affect the reporting of ADEs by HCPs (including pharmacists). These include reluctance to send reports based on mere suspicion, fear of personal repercussions, sense of professional responsibility, difficulty in accessing the means of reporting, lack of information, the type and nature of the ADE, attention drawn to a particular drug and ADE, beliefs and opinions and 'lack of time' among others (Vallano et al., 2005; Wakefield et al., 1999). In addition, underreporting by pharmacists may be explained by their attitude toward ADE reporting.

No known studies have evaluated the U.S. pharmacists' beliefs and attitudes concerning ADE reporting using a theoretical framework. Thus, little is known about pharmacists' attitudes or intentions to report serious ADEs.

1.3 PURPOSE OF THE STUDY

The purpose of the study is to explore the predictive utility of the theory of planned behavior (TPB) in understanding Texas pharmacists' intentions to report serious ADEs. The study also identifies and examines the factors affecting Texas pharmacists' beliefs (attitude, subjective norm and perceived behavioral control) toward reporting serious ADEs using the TPB model.

1.4 THE THEORY OF PLANNED BEHAVIOR

The theory of planned behavior (TPB) is an extension of the theory of reasoned action (TRA) (Ajzen, 1991; Ajzen & Fishbein, 1980). The TPB is the most widely used social cognition theory for predicting human behavior (Hardeman et al., 2002). Over 600 empirical studies have predicted behavior and behavioral change using the TPB in the past two decades (Francis et al., 2004). The theory stipulates that behavior is predicted by behavioral intention. Behavioral intention is in turn predicted by attitude, subjective norm and perceived behavioral control. The TPB has been successfully used to predict the intentions and behaviors of patients and healthcare professionals (Armitage & Conner, 2001; Godin, Belanger-Gravel, Eccles, & Grimshaw, 2008; Sheppard, Hartwick, & Warshaw, 1988). Many studies found attitude, subjective norm and perceived behavioral control to be reliable predictors of intentions to perform health-related behaviors (Armitage & Conner, 2001; Godin et al., 2008; Godin & Kok, 1996). Many theory-guided health interventions have been successfully implemented using the TPB framework (Valois, Turgeon, Godin, Blondeau, & Cote, 2001; Walker, Grimshaw, & Armstrong, 2001; Walker, Watson, Grimshaw, & Bond, 2004).

1.5 IMPORTANCE OF THE STUDY

Pharmacists have the opportunity and responsibility to promote safe and effective use of medications. Their actions with respect to identifying and reporting serious ADEs is one way they can do so effectively. The literature lacks information that addresses pharmacists' attitude, subjective norm and perceived behavioral control concerning ADE reporting. Policy makers, public health officials and regulatory agencies need this critical information in order to improve medication safety. In addition, continuing education (CE) programs need this information in order to better design and target their interventions to meet the needs of pharmacists, to increase their willingness to report serious ADEs, and thus better serve the community.

Once the pharmacists' beliefs are identified, the next step is to use them to develop appropriate interventions. The long-term goal is to facilitate pharmacists' education and monitoring activities and to promote the safe and appropriate use of medications in Texas, U.S.

Taken together, the findings of this study will contribute to the extant literature by identifying modifiable factors and processes for increasing the pharmacists' reporting of serious ADEs. This data can be used to inform strategies to improve the safety of treatments and the medication use processes.

1.6 OVERVIEW OF THE STUDY

This dissertation will consist of six chapters and appendices. This chapter provides an overview of the study: background, ADE reporting in the U.S., statement of the problem and the purpose and importance of the study. Chapter Two will present a summary of the current literature on patient safety, pharmacovigilance, HCPs' perceptions about ADE reporting, and pharmacists' beliefs concerning ADE reporting. Chapter Three will discuss the research model to be used in the study as well as the study

hypotheses. The study will be based on the TPB model. Chapter Four will present the research methodology of the study and Chapter Five will detail the main study findings or results. The last chapter, Chapter Six, will present a discussion of the study findings, recommendations based on findings, limitations of the study and conclusions of the research. It will also provide the implications for future research.

CHAPTER TWO: LITERATURE REVIEW

It may seem a strange principle to enunciate as the very first requirement in a hospital that it should do the sick no harm (Nightingale 1863).

2.1 HEALTHCARE AND MEDICATION USE

Medical care has grown in scope and complexity over the years. There has been a marked increase in the number and types of medical treatments (e.g., medicines and hospital beds) and diagnostic procedures. Healthcare interventions and procedures promote health by preventing, managing and treating diseases. When used appropriately, healthcare interventions and products (including pharmaceuticals) save lives and improve quality of life. Healthcare is an integral part of life and is the largest industry[1] in the United States (U.S.), accounting for 16 percent of the Gross Domestic Product (GDP) (Borger et al., 2006; Zuvekas & Cohen, 2007).

Drug therapy is one of the most widely used interventions in healthcare (Kohn, 2001). About a third of the U.S. population takes at least five different medications in a day. More than 80 percent of U.S. adults take at least one medication, vitamin/mineral, or herbal supplement per week (Institute of Medicine of the National Academies, 2007b). Forty four percent (44%) of the U.S. population take at least one prescription drug in any given month (National Center for Health Statistics, 2004). Prescription drug use per capita is high and is expected to increase owing to the growing population, changing age structure of the population and increasing prevalence of chronic diseases, human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) and other infectious diseases. According to the Henry J. Kaiser Family Foundation, an average

[1] In 2006, total estimated spending on healthcare was $2.2 trillion. The share of the gross domestic product (GDP) accounted for by health is projected to rise to 20 percent in 2015 (Borger et al., 2006).

American took 12.6 prescriptions in 2007 (Lundy, 2008). In Texas, the per capita retail prescription drugs filled at pharmacies in 2008 was 10.8 (The Henry J. Kaiser Family Foundation, 2008). Other states have higher figures: West Virginia = 18.7 percent, Arkansas = 17.5 percent, South Carolina = 17.4 percent and Alabama = 17.2 percent (The Henry J. Kaiser Family Foundation, 2008).

Pharmaceuticals contribute significantly towards the health and well-being of society. Vaccines have vanquished killer diseases like polio and measles. Medicines provide effective cures (e.g., antibiotics), stave off death, and relieve suffering (e.g., pain and disabilities) (Farley & Cohen, 2005) and have eliminated the need for surgery in some cases. Medicines have also eliminated or reduced the need for institutionalization for some patient populations (McKinnell & Kador, 2005). However, medical science—characterized by constant change in knowledge and uncertainty of information—is far from being perfect. As a people-driven and people-centered business, healthcare is prone to human error (Al-Assaf, Bumpus, Carter, & Dixon, 2003) and all medical professionals are fallible (Esmail, 2006). As a consequence, medical practice is potentially dangerous and unsafe (Chantler, 1999).

2.2 PATIENT AND DRUG SAFETY

Health interventions should not only be effective, efficient, patient-centered, timely and affordable, but they should also be safe (Institute of Medicine Report, 2001). Although patients expect positive health outcomes from the health system, healthcare (including medicines) causes significant patient harm, ranging from short-term illness to permanent disability or death (Institute of Medicine, 2000; Institute of Medicine Report, 2001). Modern medicine's products and procedures cannot always be used harmlessly (Schimmel, 1964). Patients are harmed by treatments and in the process of being treated via three main ways: lethal/dangerous treatments, errors, and unintended consequences

(Institute of Medicine of the National Academies, 2007b; Sandars, 2007; Sharpe & Faden, 1998; Vincent, 2006). Healthcare interventions (including drugs) can produce unwanted adverse effects (Edwards & Aronson, 2000). "New innovations bring new risks, greater power brings greater possibility of harm and new technology offers new possibilities for unforeseen outcomes and lethal hazards" (Vincent, 2006, p. 2). The occurrence of these risks, unforeseen outcomes (adverse events), errors and hazards in the health system compromise patient safety (Institute of Medicine of the National Academies, 2007b). Patient safety is not synonymous with absence of errors or harm. Patient safety is attained when mistakes are reduced to the minimum humanly possible (Al-Assaf et al., 2003) and the instances in which an error harms a patient are minimized (Nolan, 2000).

Notable patient safety improvements have been seen over the years partly spurred by litigation and the need to avoid the high cost of dealing with the consequences of negligently inflicted injuries (Jones, 2006). In the U.S. and United Kingdom (U.K.), patient safety issues received considerable attention from the landmark publications: 1) *To Err is Human: Building a Safer Health System, 2) Building a Safer NHS for Patients: Improving Medication Safety* and *3) A Spoonful of Sugar: Medicines Management in the NHS Hospitals* (Audit Commission, 2001; Department of Health, 2001; Institute of Medicine, 2000). The publication of the U.S. Institute of Medicine's 1999 report *To Err is Human* is considered to be the single most important spur to the development of patient safety initiatives. In addition, the media has featured reports of dangerous doctors and killer medicines, thus further heightening public awareness of the dangers of modern medicine (Walshe & Boaden, 2006). Notwithstanding these efforts and initiatives, healthcare still lags far behind other high-risk industries in its attention to patient safety. There is little emphasis on patient safety and more could be done to reduce or prevent harm (Al-Assaf et al., 2003).

Many problems that compromise the quality of health care systems and patient safety are associated with the use of medicines and are referred to as drug safety (Walshe, Bennett, & Ingram, 1995). Given that every medicine carries some degree of risk even when it is used correctly, drug safety is relative and involves weighing the benefits and risks of drugs. Safe drugs are those whose benefits outweigh their risks for the intended use and for the population the drug is intended to treat (Meadows, 2002). Only drugs that are deemed to be safe (benefits > risks) are approved for marketing. Thus, safe medicines are not necessarily harmless.

Regulatory agencies and pharmaceutical manufacturers are constantly grappling with safety concerns about approved drugs that are increasingly attracting media attention. The harm or risk associated with medicines is a cause for concern and has become a major public health issue worldwide (Institute of Medicine, 2000; Vincent, 2006). The risks associated with drugs manifest mainly in the form of medication errors and adverse drug events (ADEs) including adverse drug reactions (ADRs)[2].

2.3 Relationship Between Medication Errors, ADEs and ADRs

Medication errors, ADEs and ADRs are hazards or irregularities related to the medication use process (Manasse, 1989), and are collectively referred to as incidents or medication misadventures (*American Journal of Health-System Pharmacy*, 1998; Morimoto, Gandhi, Seger, Hsieh, & Bates, 2004). Researchers may prefer to use the terms incidents and medication misadventures to refer to medication errors, for example, because they are less judgmental. Incidents and misadventures are 'catch all' terms and are often used before a classification decision is made (Morimoto et al., 2004). Another collective term used in the literature to refer to all harm emanating from the practice of

[2] There are many other drug-related problems such as drug use without indication, failure to receive drugs (for pharmacological, psychological, sociological or economic reasons), and improper drug selection (patient is taking the wrong drug) (Gharaibeh, Greenberg, & Waldman, 1998).

medicine is iatrogenic disease. Medication errors and ADRs are the major causes of iatrogenic disease.

There are interrelationships and similarities between medication errors, ADEs, and ADRs (see Table 2.1 and Figure 2.1). The diagram is only illustrative and the sizes of the parts of the diagram are imprecise. Medication errors may harm or kill patients via ADEs and ADRs (categories E to I; Table 2.1). Examples of these medication errors include failure to appropriately monitor or manage an ADR and injury resulting from administering chloroquine to a person known to be allergic to chloroquine. Unintended errors may also cause ADRs. Such incidents are both medication errors and ADRs (see category III; Figure 2.1) and are generally preventable. In one study, medical errors were responsible for 58 percent of the adverse events (AEs) (Leape et al., 1991).

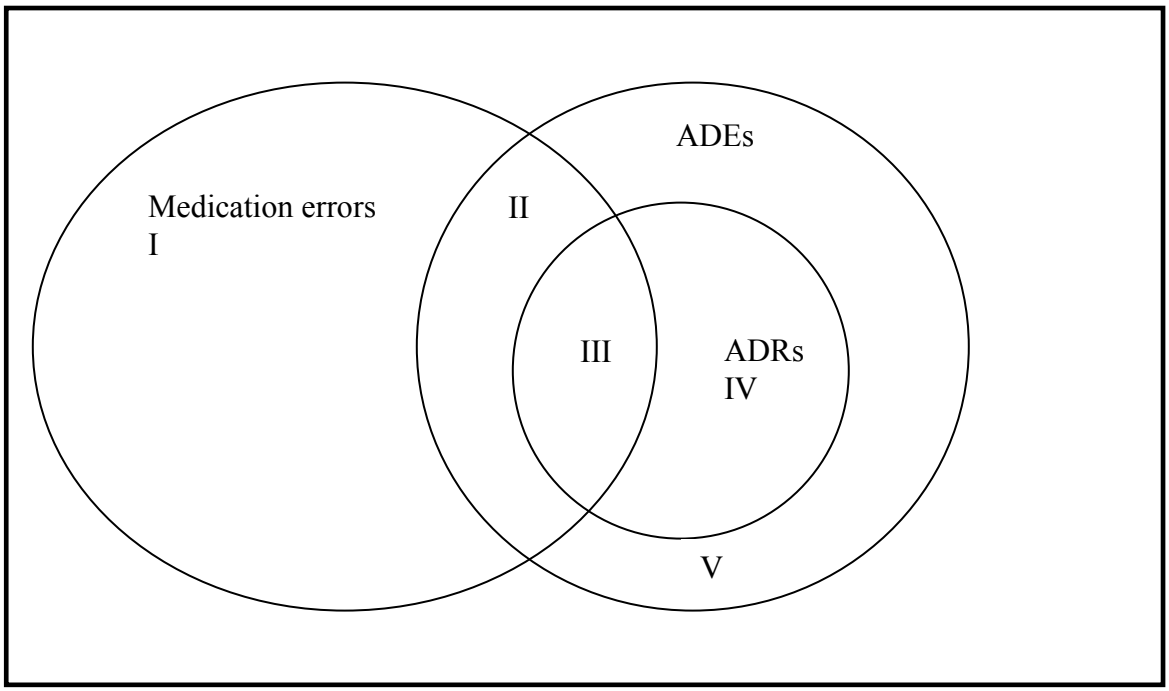
Table 2.1: Classification of Medication Errors and ADEs

Category	Description
No error	
A	Circumstances or events that have the capacity to cause error.
Error, no harm	
B	An error occurred but the error did not reach the patient.
C	An error occurred that reached the patient, but did not cause patient harm.
D	An error occurred that reached the patient and required monitoring to confirm that it resulted in no harm to the patient and/or required intervention to preclude harm.
Error, harm	
E	An error occurred that may have contributed to or resulted in temporary harm to the patient and required intervention.
F	An error occurred that may have contributed to or resulted in temporary harm to the patient and required initial or prolonged hospitalization.
G	An error occurred that may have contributed to or resulted in permanent patient harm.
H	An error occurred that required intervention necessary to sustain life.
Error, death	
I	An error occurred that may have contributed to or resulted in the patient's death.

Source: National Coordinating Council for Medication Error Reporting and Prevention (NCCMERP)

In addition, although the terms medication errors, ADEs and ADRs are often used interchangeably in the literature (Gharaibeh, Greenberg, & Waldman, 1998), there are important differences between them. Some medication errors do not harm patients either because they are trivial or they are caught before they reach the patient (see categories B, C and D in Table 2.1) (*American Journal of Health-System Pharmacy*, 1998; Bates, Boyle, Vander Vliet, Schneider, & Leape, 1995a). Also, not all ADEs are (or are caused by) medication errors (see categories V and IV; Figure 2.1). ADEs may be due to factors other than medication errors such as nonadherence (White, Arakelian, & Rho, 1999). Some ADEs (see category V; Figure 2.1) represent unavoidable injuries that are not a mistake (e.g., expected side effects). Similarly some ADRs are not caused by medication errors (see category IV; see Figure 2.1). Only a small proportion of ADEs are associated with medication errors (see category II; Figure 2.1).

Figure 2.1: Relationships Among Medication Errors, ADEs and ADRs



Source: *American Journal of Health-System Pharmacy* (1998) inspired by Bates et al., (1995).

Collectively, medication errors, ADEs and ADRs (incidents), constitute the potential risk or adverse effects associated with the use of medicines. These are discussed in turn below. Much research in the literature especially outside the U.S. has been on ADRs. However, because this thesis is on ADEs, subsequent sections focus on ADEs.

2.3.1 Medical and Medication Errors

Error is defined as, "the failure of a planned action to be completed as intended or the use of a wrong plan to achieve an aim" (Institute of Medicine, 2000, p. 28). Healthcare-related errors are called medical errors—the most common category of which is medication error. There are many definitions of a medication error. A medication error has been defined as, "A dose of medication that deviates from the physician's order as written in the patient's chart or from standard hospital policy and procedures" (*American Journal of Hospital Pharmacy*, 1982, p. 321). This definition excludes errors of prescribing and does not consider the clinical significance of the harm. This later aspect was incorporated in Dean and colleagues' (2000, p. 233) definition as follows: "A clinically meaningful prescribing error occurs when, as a result of a prescribing decision or prescription writing process, there is an unintentional significant (1) reduction in the probability of treatment being timely and effective or (2) increase in the risk of harm when compared with generally accepted practice."

The National Coordinating Council For Medication Error Reporting and Prevention (NCCMERP) defines a medication error 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 prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use"

(Santell, Hicks, McMeekin, & Cousins, 2003, p. 761). The critical aspects of many definitions of a medication error are captured in the following definition: "A medication error is a failure in the treatment process that leads to, or has the potential to lead to, harm to the patient" (Ferner & Aronson, 2000, p. 1013).

Most errors occur during dispensing and are referred to as dispensing errors, pharmacy errors or pharmacist errors. A dispensing error occurs when there are unauthorized deviations from the doctors' orders. There are many types of dispensing errors including: wrong administration technique, wrong drug preparation, administration of wrong dosage form, improper dose and unauthorized drug and wrong time errors among others (Flynn, Barker, & Carnahan, 2003; Manasse, 1989).

In medical error research, a variety of terms are used to refer to medical and medication errors including: mistakes, noxious episodes, negligence, incompetence, misconduct, slips, violations, substandard care, complications, accidents, mishaps, potentially compensatable events, preventable adverse events, iatrogenic illness and critical incidents. These terms are sometimes used interchangeably in the literature.

2.3.1.1 Categorization of Medication Errors

Medication errors can be classified as either errors of omission or errors of commission. Errors can either be intentional or unintentional and can be said to be potential (they are detected and corrected before the patient uses the drug) or actual (incidents whereby the drug reaches the patient). Medication errors can either be latent (errors waiting to happen such as faulty interface design and system defects that set people to fail) or active errors. Active errors are space and time-specific and occur at the provider level (the frontline). An active error may result from latent errors (Thomas & Petersen, 2003).

The NCCMERP's medication error index categorizes errors according to severity of the outcome (e.g., whether the error reached the patient, if the patient was harmed and if so to what degree?) (The National Coordinating Council for Medication Error Reporting and Prevention, 2005). The index has nine categories which are classified into four classes ranging from no error to error, death (see Table 2.1). This classification is widely used by many organizations including the United States Pharmacopeia (USP).

2.3.1.2 Causes and Consequences of Medication Errors

There are many causes of medication errors including technological faults, human inadequacies and systemic frailties. Most errors and accidents occurring in hospitals are systems-related (e.g., faulty or complicated systems) (Leape, 1997; Olsen, 2002; Santell et al., 2003). The opportunity of error increases with the increasing complexity of the health system. In the community and ambulatory sites, errors may be proximally caused by lack of knowledge of the drug or patient, faulty drug identity checking, and inadequate monitoring among other issues. The pharmacists' work environment (e.g., lighting, interruptions and distractions, and noise) and workload (prescription volume) can also impact dispensing error rates (Bond & Raehl, 2001; Flynn et al., 1999; Flynn et al., 1996).

Medication errors are associated with significant health (increased mortality and morbidity), psychological and economic consequences (Flynn & Barker, 2006; Flynn, Barker, & Carnahan, 2003; West, 2006). Some medication errors may result in patient harm and may also affect healthcare professionals (HCPs) (Morimoto et al., 2004). An estimated 1.5 percent to 4 percent of errors have potentially harmful effects (Allan, Barker, Malloy, & Heller, 1995; Guernsey et al., 1983; Kistner, Keith, Sergeant, & Hokanson, 1994). Among others, medication errors affect the relationship between HCPs and their patients. Medication errors may result in patient anger, suspicion and breach of

trust (Mulcahy & Rosenthal, 1999). The impact of ADEs on patients and their HCPs is discussed in the subsequent sections.

2.3.1.3 Extent of Medication Errors

Many studies have been conducted to quantify the occurrence of medication errors. Kaushal and colleagues (2001) reviewed 10,778 medication orders of 1,120 pediatric inpatients at two academic institutions and found 616 medication errors (5.72% of orders). Bates and colleagues (1995b) found that medication errors occurred at a rate of five per 100 medication orders (5%). The Institute of Medicine (IOM) estimated that a hospital patient is subject to at least one medication error per day (Institute of Medicine of the National Academies, 2007b). A similar estimate—one error per patient per day—was also reported by Barker and colleagues (1984). The failure rate in medicine has been estimated to be a minimum of one percent. In other words, one in 100 activities taken by HCPs goes wrong (Smith, 1999).

Barker and colleagues (2002) studied 36 different healthcare facilities and found that the administration error rate (excluding wrong time errors) ranged from 0 to 26 percent, with a median value of 8.3 percent. Gopher and colleagues (1989) found that 1.7 errors (1%) occurred per day per patient (who each had an average of 178 "activities" per day). Two to 14 percent of hospital in-patients experienced medication errors (Classen, Pestotnik, Evans, & Burke, 1991; Lesar et al., 1990; Raju, Kecskes, Thornton, Perry, & Feldman, 1989). Palmer and colleagues (1983) found that operational errors (e.g., failure to treat promptly or to get a follow-up culture) occurred in 52 percent of patients in a study of children with positive urine cultures.

The rates of errors reported by researchers depend on the definition of error used and the intensity of the error detection methods (Institute of Medicine of the National Academies, 2007b). The use of different methods makes it difficult to compare reported

error rates across studies. Although the true frequency of medication errors is unknown and cannot be determined, it is generally agreed that the rates of medication errors are high in the U.S. healthcare system (Institute of Medicine, 2000; Institute of Medicine Report, 2001; Leape, 1994).

There is an urgent need to minimize errors, most of which are preventable. The IOM proposed that medical errors can be prevented through "building a safer health system" that among other things limits the ability of HCPs to make mistakes. Some strategies to reduce medication errors include: increased patient counseling, medication error reporting, improved working conditions, higher standards of care, education, training and registration of medical practitioners, improved motivation of HCPs, better identification of bad doctors (incompetent and ill), improved access to information, increased use of information technology, error proofing, standardization of tasks and identification of psychological precursors to error (e.g., fatigue) (Vincent & Reason, 1999).

2.3.2 Adverse Events and Adverse Drug Events

About 100,100 patients are estimated to die from medical errors annually in the U.S (American Hospital Association, 1999; Institute of Medicine, 2000). ***[Unless stated otherwise all the data (costs, statistics, and facts) cited in this section and subsequent sections pertain to the U.S.]***. This is more than the number of people who die from highway accidents, AIDS, breast cancer or workplace accidents (Institute of Medicine, 2000). Recently, the IOM estimated that at least 1.5 million people are harmed by treatments annually (Institute of Medicine of the National Academies, 2007b). Medical treatment may cause adverse events (AEs). An AE is an injury caused by medical management rather than by the disease process (Harvard Medical Practice Study, 1990) or any unintended, undesirable and harmful response to medical care (McLamb &

Huntley, 1967). AEs exhibit three key characteristics: negativity (by nature undesirable or detrimental to the health care process or to the patient); patient involvement/impact (in some way involve patients); and causation (some relationship to some part of a healthcare process either through commission or omission) (Walshe, 2000). AEs may manifest as new findings (signs, symptoms, diagnoses, and laboratory values) or alterations in pre-existing conditions.

AEs may be drug-related (Leape et al., 1991; Sandars, 2007). The Harvard Medical Practice Study, a classic AE study, found that drug complications (19%) were the most common type of AEs. AEs that are associated with the use of drugs are known as adverse drug events (ADEs) (Brennan et al., 1991). ADEs are injuries resulting from medicines (Bates et al., 1995b) and instances where patients are unintentionally harmed as a result of drug use. According to the FDA, an ADE is any adverse event that is associated with the use of a drug whether or not that event is considered drug-related. Common ADEs include failure of expected pharmacologic action, drug abuse, drug withdrawal, and overdoses (accidental or intentional) (Trontell, 2001). ADEs are the most common threat to patient safety in secondary care (Sandars, 2007).

ADEs may arise from overdoses of drugs, underuse of drugs (e.g., untreated indication, failure to receive drugs, sub-therapeutic dosage), improper drug selection and when the patient is taking a drug for no medically valid indication (Gharaibeh, Greenberg, & Waldman, 1998). Some examples of ADEs include symptoms (e.g., headache, nausea), syndromes of disease, physical findings [e.g., lump, elevated blood pressure (BP)], abnormal lab values and toxicities (Bates et al., 1995a; Morimoto et al., 2004). ADEs can occur inside and outside of hospitals. ADEs injure or kill over 770,000 people annually in the U.S. (Classen et al., 1997; Cullen et al., 1995; Cullen et al., 1997), with an estimated cost of up to $5.6 million per hospital per annum. This cost does not include costs of resultant admission, estimated to be between $1.56 and $5.6 billion

annually, and malpractice or litigation (Bates et al., 1995b; Bates et al., 1997; Thomas et al., 1999).

Although ADEs are epidemic, their actual prevalence is largely unknown given the methodological challenges of arriving at these figures (Dean, 2003). In the U.S., it has been estimated that there are 6.5 ADEs per 100 admissions (Bates et al., 1995b). Other studies reported different figures varying from 0.7 percent to 25 percent of hospitalized patients (Bates, 1998; Leape et al., 1991; Rozich, Haraden, & Resar, 2003).

An Australian review of drug-related hospital admissions studies published between 1988 and 1996 reported that 2.4 percent to 3.6 percent of all hospital admissions were drug-related. Among the elderly, a higher percentage (15-22%) of emergency admissions were reported to be drug-related (Roughead, Gilbert, Primrose, & Sansom, 1998). Kanjanarat and colleagues (2003) found that the median ADE rate was 1.8 percent of hospitalized patients. In a review of 15 studies, Winterstein and colleagues (2002) found that an average of 4.3 percent of all hospital admissions were drug-related. The authors concluded that drug-related morbidity is a significant problem.

ADEs have a huge economic cost to patients, prescribers, health care organizations and society at large. ADEs result in extended hospital stays, malpractice suits (litigation costs), injury to the patient and many other associated costs. In one study, ADEs increased the patients' average hospital stay by eight to 12 days and hospitalization cost by $16,000 to $24,000 (Winterstein et al., 2002). The total economic impact of AEs, including lost income and disability, has been estimated to be $38 to $50 billion a year in the U.S. (Sandars, 2007). A significant part of these costs are directly attributed to serious ADEs. In addition to the enormous economic costs, serious ADEs also have a significant psychological and social effect on HCPs, patients and their families. The occurrence of these events, especially preventable ones, also result in loss of public trust in the healthcare system.

2.3.3 Adverse Drug Reactions

An important type of an ADE or drug-related hazard is the adverse drug reaction (ADR). ADRs are as old as medicine itself and have been widely researched (Routledge, 1998). The World Health Organization (WHO) defines an ADR as, "a response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function" (World Health Organization, 2002a, p. 40). This definition however is incomplete as it excludes the effects of intentional or accidental overdose. Another definition of an ADR by Edwards and Aronson (2000) only consider responses that cause significant harm: "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" (Edwards & Aronson, 2000, p. 1255). Beard and Lee (2006) define an ADR as, "an unwanted or harmful reaction experienced after the administration of a drug or combination of drugs under normal conditions of use and suspected to be related to the drug" (p. 1). All drugs have the potential to produce unintended harmful or even beneficial reactions in some patients. The literature and medical practice however mainly focuses on the harmful and serious reactions (Martin, 1978).

2.3.3.1 Categories of ADRs

Traditionally, ADRs have been classified into two main categories: type A reactions and type B reactions (Beard & Lee, 2006; Wiffen, Gill, Edwards, & Moore, 2002). Type A reactions are an exaggeration of a drug's known therapeutic effects and are caused by known toxicity or pharmacological actions of the drug. An example is when taking antihypertensive medicines results in hypotension (too low blood pressure),

resulting in the patient feeling dizzy or light-headed. Another example is when insulin or an oral antidiabetic drug results in hypoglycemia (too low blood glucose). Type A ADRs mostly result from administration of high drug doses, unusual patient sensitivity and drug-drug interactions. Type A ADRs are common, predictable and potentially preventable (Wiffen et al., 2002). Type A ADRs typically are more of a nuisance and sometimes can be dangerous or serious. There are three main type A ADRs: a) extension effect (exaggerated effect), b) side effect, and c) drug interaction effect (Martin, 1978).

Type B reactions, also known as idiosyncratic or allergic reactions, are less common. Most type B reactions are serious, not predictable and are mostly not preventable (Wiffen et al., 2002). Kidney damage, jaundice, skin rashes, anemia, and a decrease in the white blood cell count are some examples of such ADRs. These result from drug intolerance, hypersensitivity (allergic reactions), or idiosyncratic reactions. Some patients for unknown reasons develop exaggerated negative effects with conventional doses. The mechanisms of action of these reactions are not known or understood and therefore are difficult to predict. Genetic differences or some underlying abnormality of the individual may account for the occurrence of these ADRs (Martin, 1978). Some of the differences between type A and type B ADRs and their treatments are provided in Table 2.2.

Table 2.2: Comparison of Type A and Type B ADRs

	Type A	**Type B**
Synonyms	Augmented, predictable, toxic, dose-related	Bizarre, unpredictable, allergic, dose-independent
Mechanism	Predictable, understood	Usually poorly understood
Site	1. Same site of primary drug action. 2. Another site for primary and secondary actions.	Unrelated to the site of action
Incidence	High (70%)	Low (30%)
Morbidity	Mild	Severe
Mortality	Low	High
Treatment	Adjust the dose	Stop treatment

Source: Gharaibeh, Greenberg, and Waldman (1998, p. 327)

ADRs are also classified according to severity (i.e., from minor to severe) (Table 2.3). Although many ADRs are mild, some are severe and even life threatening (Pirmohamed & Park, 2003).

Table 2.3: Classification of ADRs by Severity

Category	**Definition**
Severe	Potentially life threatening, causes permanent damage, or requires intensive medical care.
Moderate	Requires a change in drug therapy or specific treatment to prevent a further adverse outcome, symptoms resolved in >24 hours, prolonged length of stay by >24 hours, caused a hospital admission to a non-intensive medical care unit.
Minor	Requires no therapy or antidote, symptoms resolve in <24 hours, does not contribute to prolonging length of stay.

Source: McDonnell and Jacobs (2002, p. 1332).

2.3.3.2 Extent and Consequences of ADRs

Of the estimated 100,000 deaths due to medical errors in the U.S., the IOM estimated that 7,000 deaths occur due to ADRs (Institute of Medicine, 2000). These fatalities are the fourth leading cause of death, ahead of deaths caused by diabetes and

pneumonia (Lazarou, Pomeranz, & Corey, 1998; White, Arakelian, & Rho, 1999). In a meta analysis of prospective studies, Lazarou and colleagues (1998) found that an estimated 6.7 percent of hospital patients had serious ADRs and 0.32 percent had fatal ADRs. Hospitalized patients have higher incidence of ADRs than outpatients. The incidence of ADRs in hospitalized patients varies widely (1.5% to 35%) by study and the rigor with which the events were sought (Bates et al., 1995b). In addition, an estimated 350,000 ADRs occur in nursing homes annually (Gurwitz et al., 2000). A U.K. study found that 4.3 per 1,000 patients on two or more medications were prescribed interacting drugs (Yen-Fu et al., 2005). In Finland, a study found that 2.1 percent of patients taking at least two drugs were using potentially harmful combinations, while in Sweden, a study reported that 12 percent of prescriptions for two or more drugs contained potential drug interactions (Linnarsson, 1993). The results of a prospective case-control study in hospitalized patients showed that ADRs caused 3.5 percent mortality, complicated 2.3 percent of the cases, and increased hospital stays by 174 percent (Classen et al., 1997).

Significant healthcare costs are associated with ADRs. ADRs account for a significant part of the estimated $177.4 billion annual cost of drug-related morbidity and mortality in the ambulatory setting (Ernst & Grizzle, 2001). ADRs also cause patient suffering, negatively affect the physician-patient relationship and reduce the therapeutic effect of drugs (Yen-Fu et al., 2005).

2.3.3.3 Factors Predisposing Patients to ADRs

Many factors explain the occurrence of ADRs. First, the widespread use of medications by the population increases the risk of ADRs (Hutchinson, Flegel, Kramer, Leduc, & Kong, 1986). An estimated 3.6 billion prescriptions were filled in 2008—about 12 prescriptions for every person (The Henry J. Kaiser Family Foundation, 2008). Many people also use over-the-counter (OTC) medications and traditional medicines alongside

prescription medicines. Patients taking four or more medications are at an exponentially higher risk of experiencing ADRs (Jacubeit, Drisch, & Weber, 1990). A study of over 9,000 Italian patients (>60 years old) showed that the ADR rate increased from 1.2 percent with one medicine to about 50 percent with 10 medicines (Carbonin, Pahor, Bernabei, & Sgadari, 1991). In another study, the ADR rate was 5 percent with one or two medicines, rising to 20 percent or more above five medicines (Grymonpre, Mitenko, Sitar, Aoki, & Montgomery, 1988).

Second, age is often suspected to be an independent risk factor for ADRs (Hoigne et al., 1984). The elderly and the very young are at greater risk of experiencing severe ADRs (McInnes & Brodie, 1988). The variable drug absorption and metabolism in both these groups increase their risk of ADRs (Osterberg & Blaschke, 2005). Children have an elevated risk of ADRs because many drugs prescribed for children are not licensed for use in children (unlicensed use) and are commonly prescribed outside the terms of the product license (off-label use) (Conroy et al., 2000). Enzyme systems that are responsible for the metabolism of drugs are immature in neonates, resulting in reduced clearance of many drugs (Ajayi, Sun, & Perry, 2000). With respect to the elderly, most have poor compliance, have altered pharmacokinetics and pharmacodynamics, and their illnesses tend to be treated with drugs with a poor therapeutic ratio (Wiffen et al., 2002). Also, the presence of many diseases in the elderly which are treated by more medicines is a risk factor for ADRs. However, one study found that age was not an independent risk factor after controlling for the number of drugs prescribed to a particular patient (Jacubeit, Drisch, & Weber, 1990).

Third, being female was reported to be associated with a higher incidence of ADRs than being male (Drici & Clement, 2001; Fattinger et al., 2000; Grymonpre et al., 1988; Pouyanne, Haramburu, Imbs, & Bagaud, 2000; Rademaker, 2001; Tran, Knowles, Liu, & Shear, 1998). “Female patients have a 1.5- to 1.7-fold greater risk of developing an ADR compared with male patients” (Rademaker, 2001, p. 349). The higher percentage

of women experiencing ADRs than men can be related to fat distribution, body size differences and gender-related polymorphisms in pharmacokinetics and pharmacodynamics as well as differences in the use of medications by gender (Gharaibeh, Greenberg, & Waldman, 1998; Gray, Mahoney, & Blough, 1999; Rademaker, 2001). The mechanisms explaining the different incidences of ADRs between male and female patients remain unclear. However, similar ADR rates between men and women have also been reported (Hallas et al., 1992; Schneitman-McIntire, Farnen, Gordon, Chan, & Toy, 1996).

Fourth, certain classes of medicine are associated with higher ADR rates than others. For example, warfarin and digoxin carry a higher risk for causing ADRs than other drugs because of their narrow therapeutic indices (Osterberg & Blaschke, 2005). In addition, the use of aspirin, antibiotics, opioids, diuretics, hypoglycemic agents and NSAIDS are associated with higher ADR rates (Wiffen et al., 2002).

Fifth, poor patient adherence may increase the rate of ADRs. Nonadherence rates for patients with chronic conditions have been found to be between 50 percent and 60 percent on average (Ashcroft, Morecroft, Parker, & Noyce, 2006). For some conditions like HIV and breast cancer, nonadherence is associated with dangerous adverse effects. Adherence is influenced by several factors such as affordability of medication, access to care (insurance coverage), knowledge, beliefs regarding treatment, and patient information (labeling and education) (Bardel, Wallander, & Svardsudd, 2007; Escobar et al., 2003; Kane, Brixner, Rubin, & Sewitch, 2008; Wu, Moser, Lennie, & Burkhart, 2008).

Finally, other factors such as disease state, genetic factors, past history of allergies, quality of prescribing, inadequate monitoring and poor administration are also associated with ADR rates (Gharaibeh, Greenberg, & Waldman, 1998). The rates of ADRs are affected by many other factors that affect drug response such as lactation,

pregnancy, tobacco or marijuana smoking, alcohol intake, stress, and dietary factors (Merck Manual, 2003).

2.3.3.4 Diagnosing ADRs

It is critical for HCPs to be able to determine the presence of ADRs, their causes and their mechanisms of action. This helps them to "initiate corrective action for a particular patient, to prevent future incidence for patients in general, and to avoid medicolegal complications" (Gharaibeh, Greenberg, & Waldman, 1998, p. 335). Knowing the harmful reactions helps in achieving optimal pharmacotherapy—balancing the drug's effectiveness against its possible undesirable reactions. However, diagnosing ADRs is extremely difficult for HCPs including physicians, resulting in most of the ADRs reported in the literature being only suspected—not proved (Martin, 1978). Diagnosing ADRs is complicated by the fact that ADRs resemble many diseases or syndromes, and are vague, confusing and rarely specific. In addition, ADRs can affect any tissue or organ and a host of ADRs are mild (Beard & Lee, 2006; Gharaibeh, Greenberg, & Waldman, 1998). Making a causal association between the drug and the observed clinical outcomes is complex. Causal association may be assessed using several criteria available including Irey's criteria (see Table 2.4).

Table 2.4: Criteria for Assessing ADRs

Category	Description
Temporal eligibility	To be responsible for an ADR, the drug must have been administered before the reaction is observed.
Latency period	This refers to the expected interval from the time of drug administration to the appearance of the ADR.
Singularity of the drug	If the patient is taking only one drug and develops a suspected ADR, it increases the likelihood of a causal relationship.
Exclusion	Sometimes, cessation of one or more drug treatments suggests the identity of the offending drug causing the ADR.
Dechallenge	Many ADRs are reversible upon discontinuing the suspected drug.
Rechallenge	Although there is some risk associated with this maneuver, readministration of a suspected drug might be accompanied by the reappearance of the ADR in question.
Pattern	Many drugs elicit ADRs with a characteristic clinicopathological pattern, which suggests an association with a particular drug.
Drug quantitation	Determination of the levels of drug in blood and body fluids may yield insights into the causal relationship of drug administration and ADRs.
Drug qualitation	Qualitative identification of the drug in tissues may be of diagnostic significance in establishing the etiology of an ADR.

Source: Gharaibeh and colleagues (1998, p. 330) and Irey (1982).

Irey suggested five degrees of causation including: a) causative or definitive—there is an objective laboratory finding which documents causal association, b) probable or consistent with—no objective laboratory finding to document the causal association, c) possible—the relationship can neither be denied nor confirmed, d) coincidental—a nondrug cause is more likely responsible for the reaction, and e) negative—it is confirmed that the drug was not in the patient's system at the time of the illness after suspecting an ADR (Irey, 1982).

The difficulty of separating disease-related symptoms from drug-related ones (Jacubeit, Drisch, & Weber, 1990) means that HCPs may mistake ADRs for disease progression or dismiss them as being a side effect. On the other hand, clinicians may wrongly ascribe an adverse reaction to a drug (Osterberg & Blaschke, 2005). Accurate diagnosis of ADRs is complicated by polypharmacy, variability of clinical responses of patients to most diseases, incomplete information, absence of objective diagnostic criteria

and in cases where there is a long time between drug administration and the effect. There is low agreement (less than 50%) between expert physicians in determining the probability of a causal relationship of ADRs (Naranjo, Shear, & Lanctot, 1992). Medical practitioners lack adequate knowledge and information on drugs and ADRs (Ajayi, Sun, & Perry, 2000).

2.3.3.5 Minimizing and Preventing ADRs

As noted above, some ADRs are preventable and avoidable (McDonnell & Jacobs, 2002; Siddins, 2002) and there are different categories of avoidability (McDonnell & Jacobs, 2002) (Table 2.5). The definitely avoidable and possibly avoidable ADR rates can be reduced through better understanding of possible ADR outcomes, better monitoring of prescribing, better drugs, use of computer systems and improved communication and education (Bates et al., 1998; McDonnell & Jacobs, 2002; Raschke et al., 1998; Wiffen et al., 2002).

Table 2.5: Avoidability of Adverse Drug Reactions

Category	**Description**
Definitely avoidable	The ADR was due to a drug treatment procedure inconsistent with current knowledge of good medical practice.
Possibly avoidable	The ADR could have been avoided by an effort exceeding the obligatory demands of current knowledge of good medical practice.
Unavoidable	The ADR could not have been avoided by any reasonable means.

Source: Hallas and colleagues (1990).

ADRs may be inevitable and justified (Yen-Fu et al., 2005); sometimes prescribers may prescribe dangerous drug combinations by design, after a careful consideration of the patient's condition and the available treatment options. An

interaction may be tolerated in the case of drugs or combination of drugs that treat life-threatening illnesses (Meadows, 2002).

2.4 Integration of Drug Therapy Risk Information in Decision Making

The occurrence of ADEs is a risk—the probability that something negative will happen—associated with drug therapy (Institute of Medicine, 2007). Given that patients with different characteristics (e.g., genetics, age, weight, hepatic and renal function) respond differently to standard regimens and doses (Smith, 1978), a good drug for some patients may be a bad drug for others who are at risk of serious adverse events (Edwards, 2001). In making optimal decisions, drug regulatory authorities, pharmaceutical companies, HCPs and patients consider and weigh the risks and benefits of drug therapy—a process called benefit-risk assessment[3]. For example, patients consider the potential negative effects of medicines in deciding to start or to continue taking medicines. Physicians also consider the risks of drugs in making treatment decisions aimed at minimizing the likelihood of the occurrence of serious ADEs (e.g., ADRs) in their patients. In addition, in approving drugs, regulatory authorities compare the risk associated with a drug with its benefits and approve for marketing only drugs that have higher benefits than the risks.[4] Approved drugs fall in the bottom right hand triangle in Figure 2.2.

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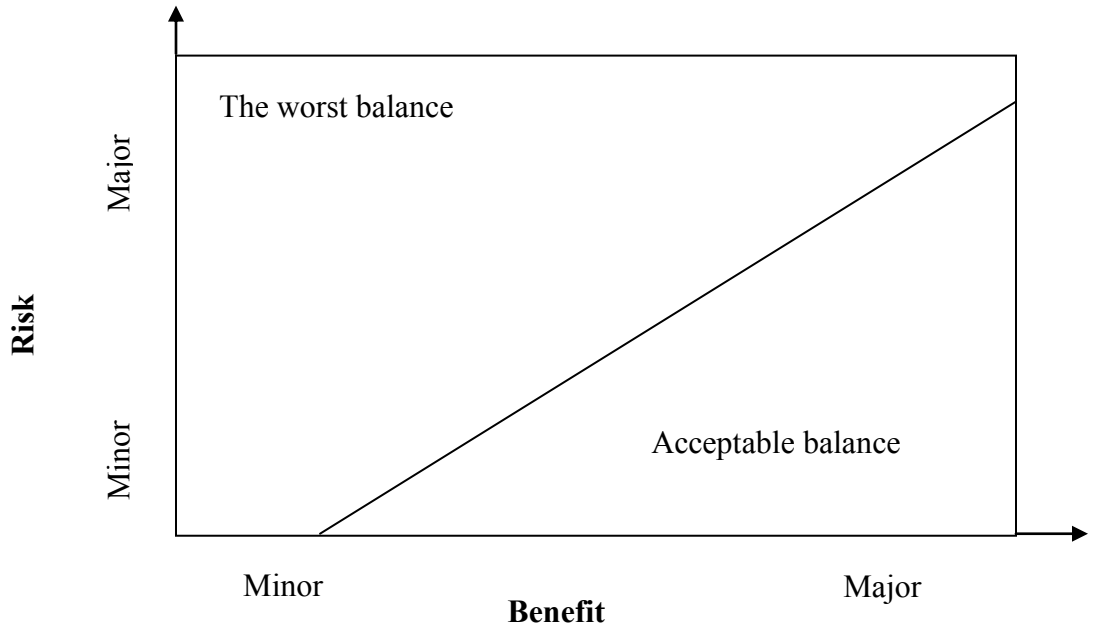
[3]Benefit-risk assessment is the balancing or weighing of a drug's therapeutic effectiveness against its potential risks or adverse effects. Currently there are no tested, standardized, validated, quantitative or semi-quantitative methods to conduct benefit-risk assessment (Institute of Medicine, 2007). Benefit-risk assessment is adhoc, qualitative, informal and relies on human judgments and is compromised by limitations (biases, fallibility, inconsistencies and subjectivity) of human judgment (Institute of Medicine of the National Academies, 2007a). As a result, there is a wide variability in how decisions are made (Tilson, Gibson, & Suh, 2006). The main outcome of a benefit-risk assessment is a benefit-risk ratio that is also called benefit-risk difference, benefit versus risk, safety profile, risk-benefit decision, therapeutic margin and therapeutic index.

[4] Licensing decisions are made based on group data and use a societal perspective (for the population at large) (Hurley, 1985). Currently, there are two methods for weighing a drug's benefits and risks: a) comparative approach —which involves comparing a drug's benefits and risks with those of similar drugs. If a new drug has similar risks and benefits to another drug already being marketed, it is allowed to be

Figure 2.2: Relationship Between Benefits and Risks



There are several challenges that affect the integration of risk information in decision making by patients, regulatory authorities and physicians. First, risks associated with drugs are difficult to quantify. Second, the risks and benefits of drugs are measured in different units and there is currently no quantitative approach to readily compare them (Institute of Medicine, 2007). Third, it is difficult to adequately reflect patient preferences in assessing drug risks at a societal level. Risk perception and acceptability vary widely across individuals and some individuals accept certain risks more readily than others for various reasons (Edwards, 1997; Hurley, 1985). Fourth, although a substantial amount of risk information pertaining to drugs is obtained during clinical trials, getting complete information on benefits and risks takes time, effort and resources. Often decisions cannot wait until complete information is available, resulting in most regulatory decisions being

marketed (Rawlins, 1985a); and b) judgmental approach—the most commonly used method in practice where decisions are made on the basis of views of experts and professionals. The FDA does not currently have standard approaches to conducting benefit-risk assessment (Tollman, 2006).

made on the basis of incomplete data. Uncertainty cannot be eliminated in drug therapy decision-making.

2.4.1 Risk Identification in the Premarketing Stage

Before new drugs are approved, they undergo extensive testing and rigorous evaluation of their safety and efficacy during clinical trials. The common serious ADEs (incidence > 0.1%) are detected during clinical trials (Amery, 1999). However, clinical trials have a simple design (the effects of cormobid conditions or multiple drug use are not assessed), are of a limited duration, use a narrow dosage range and do not include extremities of ages (Edwards, 1997). Clinical trials are held under conditions that do not represent all the situations likely to be encountered in "real life." In addition, clinical studies include a small (about 1,500 patient exposures) (Jefferys, Leakey, Lewis, Payne, & Rawlins, 1998; Meadows, 2002) and homogenous (susceptible patients are excluded) patient population (Edwards, 1997). The small sample sizes increase the chance of missing rare side effects. For example, there is a 95.1 percent chance of missing a rare side effect (e.g., 1 in 20,000 exposures) for a clinical trial involving 500 people (Amery, 1999) (Table 2.6). This chance decreases with increasing patient exposures (Table 2.6).

Table 2.6: Chance of Not Observing a Very Rare Side Effect (0.01%)

Number of Patients Treated	Chance of Missing (%)
500	95.1
1000	90.5
2500	77.9
5000	60.7
7500	47.2
10000	36.8
15000	22.3
20000	13.5
25000	8.2
30000	5.0

Source: Amery (1999, p. 61).

Given the above limitations, all the potential side effects of drugs are not identified before drugs are marketed even with a flawless drug development process (World Health Organization, 2002b). Events and reactions that have a long latency and those that occur discretely after discontinuation of the drug may not appear during the course of the trial given the limited time frame (Brewer & Colditz, 1999; Simon, 2002). In addition, animal toxicology is often not a good predictor of effects in humans, and even detected events will be incompletely described, since they are too few. As a result, serious adverse effects of a majority (51%) of approved drugs are not detected prior to approval (U.S. General Accounting Office, 1990). The safety profile of new medicines is not fully understood at the time of approval and any drug safety conclusions that are made are only provisional (Rawlins, 1995). Once a drug is marketed, more patients will be exposed to it, and the drug may be used for different and unanticipated indications. In addition, the drug may be used for a longer period and in certain subgroups within populations, such as the elderly and children, resulting in the emergence of new and rare events (Institute of Medicine, 2007; Lee & Thomas, 2003). These problems may be identified through pharmacovigilance and postmarketing surveillance.

2.5 Overview of Pharmacovigilance and Postmarketing Surveillance

Pharmacovigilance emerged in response to the drug safety challenges experienced in the 1960s, mainly the thalidomide disaster. The thalidomide disaster revealed the shortcomings and limitations of using clinical trials data in defining the safety profile of drugs (Rawlins, 1995; Simon, 2002). The word pharmacovigilance was coined by the French as, "the study of the undesirable effects of drugs" (Rascol, Pathak, Bagheri, & Montastruc, 2004, p. 611). Pharmacovigilance is "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problem" (World Health Organization, 2002a, p. 42). Pharmacovigilance promotes drug safety and involves detecting, confirming, investigating, monitoring and developing strategies to reduce ADEs (Edwards, 1997).

Although pharmacovigilance occurs both before (pre-marketing) and after a drug is marketed (postmarketing stage) (Begard & Tubert-Bitter, 1993), it is dominant in the postmarketing stage. As a result, many definitions in the literature characterize pharmacovigilance as a postmarketing activity. For example, the U.K.'s Committee on Safety of Medicines (CSM) defines pharmacovigilance as the process of identifying, and then responding to safety issues about marketed drugs (Committee on Safety of Medicines and Medicines Control Agency, 1993). Pharmacovigilance has also been defined as "The study of the safety of marketed drugs under the practical conditions of clinical usage in large communities" (Mann & Andrews, 2002, p. 3).

The objectives of pharmacovigilance are to: a) identify and quantify all previously unidentified drug safety hazards; b) elucidate the factors predisposing patients to the hazards; c) obtain evidence of safety of approved drugs; and d) refute false positive ADE signals (Rawlins, 1995). The following are five activities that are essential to pharmacovigilance:

- Suspected ADR signal generation and formation of hypothesis;

- Analysis of all issues around the signal, particularly confirmation (or refutation) of hypotheses, estimation of the size of the risk and whether susceptible patients exists;
- Consideration of possible changed benefit-to-risk issues in therapy;
- Communication of information to health professionals and patients in a useful way and possible regulatory action; and
- Consequence evaluation (Edwards & Aronson, 2000)

Pharmacovigilance is often equated with postmarketing surveillance (PMS) in the literature (van Grootheest, 2003). PMS is the main task of pharmacovigilance. PMS is the continuous monitoring of the safety of all marketed drugs. It is aimed at identifying and quantifying any emerging drug hazards, mostly serious ADEs. The most common method of PMS and pharmacovigilance is spontaneous reporting (SR) of individual clinical observations by HCPs and patients. Other methods include: case reports, cohort studies, case-control studies, controlled clinical trials, cross-sectional analyses, demographic methods, drug use surveys, automated databases linking drugs and disease and registries (Gharaibeh, Greenberg, & Waldman, 1998; Simon, 2002).

2.6 SPONTANEOUS REPORTING OF ADES

SR is the cornerstone of PMS and pharmacovigilance in many countries (Rawlins, 1988a, 1988b, 1995). SR is "the system whereby case reports of adverse drug events are voluntarily submitted from health professionals and pharmaceutical manufacturers to the national regulatory authority" (World Health Organization, 2002a, p. 43). These case reports are called spontaneous reports. In making reports, HCPs imply a causal association between a drug and the clinical event. The reports are spontaneous, implying that they are voluntary (van der Heijden, van Puijenbroek, van Buuren, & van der Hofstede, 2002).

Many countries operate elaborate spontaneous reporting systems (SRSs) which facilitate the reporting of ADEs. In 2001, 55 countries had operational SRSs (Edwards, 2001). Reports are sent mostly to a government agency, but also to drug manufacturers or a designated third party (Cobert, 2007). SRSs are the principal monitoring technique after a drug is marketed in many countries (Gharaibeh, Greenberg, & Waldman, 1998). The importance of SR in identifying previously unknown ADEs has been documented previously (Rossi et al., 1983). The objective of SRSs is to generate signals—indicators of potential drug safety hazards or problems associated with drug use—and hypotheses (Gharaibeh, Greenberg, & Waldman, 1998; Meyboom et al., 1997a; Strom & Tugwell, 1990).

There are many advantages of SR:

- **SR is cost-effective:** SRSs are relatively inexpensive to operate but are effective. They are the most cost-effective way of monitoring drug safety (Layton, Key, & Shakir, 2003). They detect new and unsuspected ADEs better than other Phase IV postmarketing studies (Rossi et al., 1983).
- **SR is comprehensive:** SRSs cover the entire ADE data for the population in a defined geographic region across all the therapeutic agents (Pirmohamed, Breckenridge, Kitteringham, & Park, 1998; Waller, Coulson, & Wood, 1996). SRSs detect all types of ADEs.
- **SR is rigorous and monitors drugs over a long period of time:** SRSs monitor the safety of drugs throughout their marketed life (Waller, Coulson, & Wood, 1996).
- **SR is directly related to clinical practice**: SR data are based on the experiences of HCPs with the use of a drug in patients. SR involve a clinical judgment and reflect HCPs' clinical concerns about drugs they prescribe (Edwards, 1999).

Drug regulatory agencies in many countries predefine which ADEs ought to be reported. As a result, there are inter-country differences on what is to be reported. For example, in the U.K., all suspected reactions attributable to a new (e.g., first two years of

marketing) drug should be reported whereas only serious and unusual suspected reactions should be reported for established drugs (Inman, 1985). In general, all evidence that casts suspicion on the safety of a drug should be collected. The motto of the *Committee on Safety of Drugs* is 'when in doubt—report' (Committee on Safety of Medicines, 1968).

Although different from country to country, the general content of ADE reports covers four main areas:

- **Patient information**: patient identifier, age at time of event or date of birth, gender and weight;
- **Adverse event or product problem**: description of event or problem, date of event, date of this report, relevant tests/laboratory data (if available), other relevant patient information/history and outcomes attributed to adverse event;
- **Suspected medication(s)**: name [international nonproprietary number (INN) and brand name], dose, frequency and route used, therapy date, diagnosis for use, batch number, expiration date, event abated after use stopped or dose reduced, event reappeared after reintroduction of the treatment, concomitant medical products and therapy dates; and
- **Reporter**: name, address, telephone number, specialty and occupation (World Health Organization, 2002b, p. 16).

2.6.1 Analysis and Evaluation of SR Data

When regulatory centers receive SRs, they acknowledge (e.g., send reporters a 'thank you' note) and validate them. The reported ADEs are then analyzed and evaluated to detect or generate signals—scrutinize spontaneous reports for hazards (Evans, Waller, & Davis, 2001). Signal detection involves analyzing individual case reports as well as aggregated data. The process of generating 'signals' of positive unrecognized hazards from spontaneous ADE reporting data has been likened to looking for a needle in a

haystack (Evans, Waller, & Davis, 2001). Both qualitative methods (where experts or trained assessors assess each incoming report) and quantitative methods (e.g., statistical analyses) are used to detect signals. Quantitative methods are able to detect complex associations and relationships such as drug-drug interactions and drug-induced syndromes (Hauben & van Puijenbroek, 2005; van der Heijden et al., 2002).

The simplest quantitative index that can be calculated is the reporting rate—the ratio of the number of reports for a particular drug over the number of patients exposed to the drug. This can be used as an estimate of ADE incidence. However, the reporting rate is not a good indicator of incidence given the biases in the numerator and the difficulty in getting accurate patient exposure data (the denominator). To avoid the limitations and biases encountered with the use of reporting rates, disproportionality measures such as proportional reporting ratio (PRR) and reporting odds ratio (ROR) are preferred. These measures ascertain whether the number of observed cases differs from the number of expected cases (Egberts, Meyboom, & van Puijenbroek, 2002). Disproportionality analyses are commonly used in pharmacovigilance. Drug and ADE combinations that are disproportionately present among the reported suspected ADEs represent potential signals (Egberts, Meyboom, & van Puijenbroek, 2002).

The identified signals need to be followed up through collecting further information on the following: chronology, dechallenge, rechallenge, clinical symptomatology, other possible explanations, possible predisposition and complementary investigations (Dongoumau, Evreux, & Jouglard, 1978). Spontaneous reports data often need to be complemented by data collected through other methods such as epidemiological studies (Hauben & van Puijenbroek, 2005) thus further delaying the validation of ADEs.

2.6.2 Action Decision

The next step after assessing and evaluating the SR data is to make a decision aimed at improving patient and drug safety. Regulators and pharmaceutical manufacturers are sometimes compelled to act on the basis of spontaneous reports they receive. The actions they can take include: a) changing product information; b) modifying the product or its use; and c) withdrawing the product from the market as discussed in turn below.

First, the most common action taken by pharmaceutical manufacturers and drug regulatory agencies in response to new ADE information gathered through SRSs is updating the product information (i.e., reviewing or adding the newly acquired information to the label) (Moore, Psaty, & Furberg, 1998; Simon, 2002). Possible changes include: a) adding new warnings, ADRs, contraindications, and interactions; b) changing the wording of ADRs; c) restricting the product's indications; and d) removing some information (Council for International Organization of Medical Sciences, 1998). The changes are made to the package insert, summary of product characteristics (SPC) and the drug label (Edwards, 2001) which are important sources of drug treatment information to physicians and patients. In the event of serious ADEs, 'Dear Doctor' letters are written directly to individual HCPs with more urgent warnings (Edwards, 2001).

Second, to minimize risk, manufacturers and drug regulatory agencies may also decide to restrict product availability (Council for International Organization of Medical Sciences, 1998). Possible changes include changing the status of a drug from non-prescription to prescription status, imposing institutional selectivity (restricting a product for distribution only to hospitals or other institutions), and improving professional selectivity (restriction of prescribing to specialists). Limits on reimbursement may also be considered (Council for International Organization of Medical Sciences, 1998).

Third, in rare and extreme circumstances, where a drug's risks are considered to exceed its benefits, regulatory authorities may reassess and change the approval decision (Meadows, 2002; Schafer, 1997). Some of the factors that prompt the decision to withdraw a drug from the market include: occurrence of rare and unpredictable problems, more than expected drug toxicity (when safer options are available), dangerous combinations, improper use and failure of other risk management options (Meadows, 2002). Many drugs have been withdrawn from the market on the basis of spontaneous reports (Edwards, 1997; Jefferys et al., 1998; Moride, Haramburu, Requejo, & Bagaud, 1997; Rawlins, 1995). Arnaiz and colleagues (2001) studied 22 drugs that had been withdrawn from the Spanish market in the 1990s and observed that most of the withdrawals (n = 18) were based on case series or reports. Between 1969 and 2002, more than 75 drugs/drug products (about 1% of marketed drugs) were removed from the market for safety reasons in the U.S. (Wysowski & Swartz, 2005).

Finally, all decisions that are made should be communicated effectively to patients and HCPs. "Dear Doctor" letters, journal publications, educational programs, patient leaflets and advertisements (Council for International Organization of Medical Sciences, 1998) can be used as the communication channels. This information promotes safe use of medicines by the population and is used by patients and HCPs in optimizing the selection of treatment (Davis, Furberg, Wright, Cutler, & Whelton, 2004).

2.7 Reporting ADEs by Patients and HCPs

HCPs (e.g., nurses, doctors and pharmacists) are expected to report the ADEs that they come across (Edwards & Aronson, 2000; Gharaibeh, Greenberg, & Waldman, 1998). In addition to HCPs, consumers in some countries (e.g., U.S. and Canada) can also report ADEs as discussed in turn below.

2.7.1 ADE Reporting by Patients

Patient reporting is when users of drugs (or their caregivers) report suspected ADEs directly to a reporting center (van Grootheest, de Graaf, & de Jong-van den Berg, 2003). Some countries such as Canada, New Zealand, Denmark, Sweden, the Netherlands, the U.K. and Australia allow the users of medicines (consumers or patients) to submit ADE reports. Patients in the U.S. can also directly report ADEs to the FDA through MedWatch, the FDA's Safety Information and Adverse Event Monitoring Program.

Allowing patients to report ADEs has advantages. Studies have found that patients do not tell their physicians all the symptoms they suspect and that physicians, in turn, do not record all symptoms they are informed about (Savett, 2002). As a result, physicians are not aware of all the ADEs (about 50%) that patients suspect (Aspinall, Whittle, Aspinall, Maher, & Good, 2002; Gandhi et al., 2000). Allowing patients to directly report suspected ADEs may identify these problems and also highlight problems related to off-label use and problems associated with the use of over-the-counter (OTC) products. Patient reporting increases the number and heterogeneity of reports. In addition, it makes SRSs relevant to patients to whom they matter most. A recent review (Blenkinsopp, Wilkie, Wang, & Routledge, 2007) of published literature and international experience on patient reporting of suspected ADRs noted several potential benefits of patient reporting including:

- Patients may report ADRs that are different from those reported by HCPs;
- Patients may be more likely to identify a symptom as a suspected ADR than HCPs;
- Patients may report new ADRs that do not feature in existing product information;
- Patients may report suspected ADRs that they would not wish to discuss with their HCPs; and
- Patients report their ADR experiences without filtering or 'interpretation' by a HCP resulting in a better understanding of their experiences.

A three-year study conducted in the Netherlands compared patient ADR reports with reports submitted by HCPs (de Langen, van Hunsel, Passier, de Jong-van den Berg, & van Grootheest, 2008) and concluded that patient reporting is feasible and enhances pharmacovigilance (de Langen et al., 2008). Another study found that the quality of patient reports did not differ significantly from those of physicians (van Grootheest, de Graaf, & de Jong-van den Berg, 2003). However, patient reporting has several potential disadvantages such as: quality of reports, challenges in associating a drug and suspected event and not having sufficient information to carry out causality assessment. Patient reporting might provide noise and thus deter signal detection.

2.7.2 ADE Reporting by HCPs

The effectiveness of SRSs and pharmacovigilance requires the goodwill and cooperation of HCPs including pharmacists through reporting ADEs (Cobert, 2007). Reporting ADEs by HCPs is a professional responsibility and all healthcare providers (e.g., physicians, pharmacists, nurses, and dentists) should report ADEs as part of their professional activities (World Health Organization, 2002b). However, the actual professionals who report are governed by national legislation and vary from country to country.

Pharmacists and physicians account for most of the ADE reports received by pharmacovigilance centers worldwide. Pharmacists' reports reflect their special professional backgrounds and experiences (Edwards, 1999). ADE reporting behavior may differ between pharmacists and physicians (Lawton & Parker, 2002). A study conducted in the Netherlands found that, "Compared to pharmacists, physicians reported statistically significantly more ADEs related to the cardiovascular system, malfunctions of the liver and psychiatric disorders, whereas pharmacists reported a significant greater number of presumed ADEs of 'external' organ systems such as disorders of the skin and

eyes" (van Grootheest, van Puijenbroek, & de Jong-van den Berg, 2002). In the U.S. and the U.K., no difference was found in the quality of reports submitted by pharmacists and physicians (Ahmad, Freiman, Graham, & Nelson, 1996). Although both pharmacists and physicians are critical for effective SRSs and play an integral role in pharmacovigilance (Lee & Thomas, 2003; Olsson, 1999) in most countries, this study focuses on pharmacists. Pharmacists are willing to report and are capable of reporting ADEs (Emerson, Martin, Tomlin, & Mann, 2001; Green, Mottram, Rowe, & Pirmohamed, 2001; Sweis & Wong, 2000). The pharmacists' special training, expert knowledge of pharmacokinetics, pharmacodynamics, and knowledge of chemical relations coupled with their widespread use of computers and their interaction with patients put them in a unique and special position to detect and report ADEs (Inman 1986). In addition, ADE reporting fits in well with pharmacists' responsibility of ensuring safe use of medicines.

Pharmacists in different countries play different roles with respect to reporting ADEs. For example, pharmacists in Finland, Norway, Sweden, Denmark, Iceland and Estonia are not authorized to report ADEs (Olsson, 1999). However, pharmacists can report ADEs in most of the countries that participate in the WHO Programme for International Drug Monitoring (van Grootheest, Olsson, Couper, & de Jong-van den Berg, 2004). It is standard practice for pharmacists to report ADEs in many other countries (Griffin, 1986). In some countries, pharmacists contribute the greatest number of reports. For example, reports submitted by pharmacists accounted for 88 percent of all reports submitted by HCPs in Canada, 40 percent in the Netherlands and 18 percent in the U.S. (van Grootheest et al., 2004). In other countries, the pharmacists' contribution is small.

Serious ADEs occur mostly in the hospital setting and hospital pharmacists who are involved in patient care play an important role in drug safety through reporting those ADEs (Leape et al., 1999a). In many countries, hospital pharmacists submit the bulk of reports submitted by pharmacists (van Grootheest et al., 2004). Much of the literature on

the contribution of pharmacists towards ADR reporting relate to hospital pharmacists (Ahmad et al., 1996; Leape et al., 1999a; Winstanley, Irvin, Smith, Orme, & Breckenridge, 1989). Hospital pharmacists were found to be more likely to report ADRs than community pharmacists (Herdeiro, Figueiras, Polonia, & Gestal-Otero, 2006). ADR reporting was found to be 20-fold higher among hospital than community pharmacists (OR 20.0, 95% CI: 3.3, 125; $p < 0.001$) (Herdeiro et al., 2006). One study reported that ADR reports submitted by hospital pharmacists were of better quality compared to those submitted by community pharmacists (Ahmad et al., 1996). Hospital pharmacists were also reported to be better informed about pharmacovigilance than community pharmacists (Cox, Marriott, Wilson, & Ferner, 2004). This may be explained by the fact that hospital pharmacists have access to additional pertinent information (e.g., lab test results) which is not available to community pharmacists (Emerson et al., 2001). Community pharmacists have a special position in reporting ADEs associated with over-the-counter (OTC) products and alternative therapy (Hammerlein, Griese, & Schulz, 2007; van Grootheest et al., 2004).

2.8 Factors Affecting ADE Reporting by HCPs Including Pharmacists

Inman (1978) published a classical piece on ADR reporting in which he provided the reasons for underreporting of ADRs by HCPs. He termed them the 'seven deadly sins': a) fear of possible involvement in litigation; b) lack of economic incentive; c) ambition to collect and publish; d) complacency; e) difference about reporting mere suspicions; f) indifference; and g) ignorance of ADR reporting requirements (Inman, 1978). Later, he added an eighth 'sin' named insecurity (Inman, 1996). Inspired by this landmark publication, many research studies have shed more light on the factors that affect ADR reporting by HCPs in the literature. Most of the research on the factors influencing reporting or underreporting were conducted on medical practitioners (Aziz,

Siang, & Badarudin, 2007; Bäckström, Mjörndal, Dahlqvist, & Nordkvist-Olsson, 2000; Bateman, Sanders, & Rawlins, 1992; Belton, Lewis, Payne, Rawlins, & Wood, 1995; Belton & The European Pharmacovigilance Research Group, 1997; Eland et al., 1999; Figueiras, Tato, Fontainas, & Gestal-Otero, 1999; Hasford, Goettler, Munter, & Müller-Oerlinghausen, 2002; Herdeiro, Figueiras, Polonia, & Gestal-Otero, 2005; Rogers et al., 1988). Fewer studies investigated the factors affecting underreporting among pharmacists (Generali, Danish, & Rosenbaum, 1995; Green et al., 2001; Herdeiro et al., 2006; Houghton, Woods, Davis, Coulson, & Routledge, 1999; Sweis & Wong, 2000; van Grootheest, Mes, & de Jong-van den Berg, 2002). There are many reasons that have been provided as to why HCPs do or do not report ADEs. Some of the common reasons are discussed below:

First, reluctance to send reports based on mere suspicion. Before submitting a report, HCPs should be able to detect the reaction or event and attribute it to a drug (Council for International Organization of Medical Sciences, 1990). Many pharmacists and doctors are more likely to report an ADE if they are confident of recognizing it (Sweis & Wong, 2000). As a result, uncertainty regarding the cause and effect of an ADE deters reporting (Aziz, Siang, & Badarudin, 2007; Cosentino et al., 1997; Eland et al., 1999; Rogers et al., 1988). In one study, about two-thirds of physicians did not report suspected ADEs due to uncertainty concerning definite causality (Hasford et al., 2002). Most HCPs only report ADEs they believe are directly caused by the drug or if they have a strong suspicion of a causal relationship between a drug and the event (Biriell & Edwards, 1997; Inman, 1985). However, having conclusive evidence that a drug was responsible for an ADR is not required for submitting a report (Committee on Safety of Medicines, 1968; MADRAC, 2002). Nevertheless, many doctors are reluctant to report suspected (as opposed to proven) reactions or events (Belton & The European Pharmacovigilance Research Group, 1997).

Second, pharmacists and doctors may not report ADEs because they feel that self-identification could result in personal repercussions including possible involvement in litigation or investigation (Ashcroft et al., 2006; Bateman, Sanders, & Rawlins, 1992; Inman, 1978). The medico-legal difficulties that may arise from the submission of reports negatively affect ADE reporting (Institute of Medicine Report, 2004; Kaufman, Stoukides, & Campbell, 1994; Vincent et al., 2006). However, this reason has not been consistently supported in the literature (Hasford et al., 2002).

Third, lack of knowledge and misconceptions about the ADEs to be reported, purpose of ADE reporting and the safety of drugs hinder HCPs from reporting (Biriell & Edwards, 1997; Eland et al., 1999). Despite the fact that the Germany Drug Commission regularly publishes ADR reporting criteria in the *German Medical Journal*, which is mailed to all physicians, 86.7 percent of physicians stated that they did not know the criteria of ADRs to be reported (Hasford et al., 2002). Many HCPs do not have optimal knowledge about ADEs (Bateman, Sanders, & Rawlins, 1992). For example, only 26 percent of Dutch medical practitioners knew which ADRs to report (Eland et al., 1999). Some HCPs do not report ADEs because they believe that the association between the ADE and a particular drug is already well known. Others do not make reports because they believe that the regulatory authorities will already be aware of the ADEs (Inman, 1985). Other misconceptions held by HCPs are summarized below:

- Only proven ADRs should be reported;
- Serious ADRs are well-documented before a drug is marketed (Herdeiro et al., 2005; Khoza, Madungwe, Nyambayo, Mthethwa, & Chikuni, 2004);
- Impossible to determine causality; and
- One case reported by an individual doctor will not contribute to medical knowledge.

Fourth, 'lack of time' is associated with underreporting. To compile information for a good case report takes some time, which is scarce. Many HCPs consider themselves too busy to record their observations (Inman, 1985). Thirty eight percent of medical

practitioners in the Netherlands reported that they did not have enough time to report ADRs (Eland et al., 1999). Other studies reported similar findings (Bäckström et al., 2000; Belton & The European Pharmacovigilance Research Group, 1997; Eland et al., 1999; Hasford et al., 2002; Herdeiro et al., 2006). Some HCPs consider reporting ADRs as extra workload and as taking too much time (Bateman, Sanders, & Rawlins, 1992). The lack of time may be explained by the heavy workload that HCPs carry (Bateman, Sanders, & Rawlins, 1992; Figueiras et al., 1999; Inman, 1996). However, other studies did not find lack of time to be a significant predictor of ADR reporting among physicians (Aziz, Siang, & Badarudin, 2007; Li et al., 2004).

Fifth, difficulty in accessing the means of reporting suspected ADEs (e.g., report forms and telephone numbers) and finding the right form deter ADE reporting (Bäckström et al., 2000). The availability of simple reporting forms greatly enhances ADE reporting by HCPs (Biriell & Edwards, 1997).

Sixth, ADE reporting is negatively impacted by a lack of information on how to report ADEs (Belton & The European Pharmacovigilance Research Group, 1997; Li et al., 2004; Perlík et al., 2002). In one study in the Czech Republic, about one-third of the physicians said they did not know the correct way to report ADRs (Perlík et al., 2002). In the U.K., Sweden, and Denmark, 2.7 percent, 8.6 percent and 3.4 percent of physicians, respectively, were unsure how to report suspected ADRs (Belton & The European Pharmacovigilance Research Group, 1997).

Seventh, type and nature (severity, novelty and seriousness) of the ADE or the drug (Hazell & Shakir, 2006) affect ADE reporting. Unexpected and serious ADEs are more likely to be reported than nonserious ones. About three-quarters of medical doctors in Sweden reported "that the severity of the reaction was the main factor determining whether a suspected ADR was reported or not" (Bäckström et al., 2000, p. 731). Similar results were also reported elsewhere (Hasford et al., 2002). Clinicians report events for new treatments (e.g., first 2 years) more than they do for older drugs (Auriche & Loupi,

1993), a phenomenon called the Weber effect or the product life cycle effect (Heeley, Riley, Layton, Wilton, & Shakir, 2001; Martin, Kapoor, Wilton, & Mann, 1998). In the U.K., for example, serious events on new drugs were found to have a five-times greater chance of being reported than similar events on other (established) drugs (Heeley et al., 2001). The number of reports for a particular drug tapers off with the passage of time. Also, ADEs that HCPs consider to be too trivial or to be too well known are less likely to be reported than other types of ADEs (Aziz, Siang, & Badarudin, 2007; Bäckström et al., 2000; Cosentino et al., 1997; Eland et al., 1999; Hasford et al., 2002).

Eighth, attention drawn to a particular drug, also called temporal bias or secular effects, affects ADE reporting (Biriell & Edwards, 1997). The reporting of ADEs for a particular drug or class of drugs can increase after increased media attention, use of medication by a celebrity and a warning from a health agency among others (Cobert, 2007; Sachs & Bortnichak, 1986).

Ninth, many personal characteristics of the reporter have been found to be associated with ADE reporting. The tendency to report ADEs was found to increase with seniority (Irujo et al., 2007; Sweis & Wong, 2000). Other factors associated with ADE reporting found in the literature include age, years of work experience (positive relationship), gender (female less), clinical specialty, and participation in educational activities related to the detection of drug related problems (Bateman, Sanders, & Rawlins, 1992; Eland et al., 1999; Figueiras et al., 1999; Herdeiro et al., 2006; Irujo et al., 2007). In a study of medical practitioners in nine European Union (EU) member states (i.e., Denmark, France, Ireland, Italy, the Netherlands, Portugal, Spain, Sweden, and the U.K.), Belton and others (1997) found that a higher percentage of general practitioners than specialists indicated that they were ‘ever’ reporters. In addition, the reporting environment (e.g., culture of organizations) also affects reporting (Goldman, 1998; Inman, 1985).

Tenth, is the sense of responsibility. “Physicians are motivated by a sense of their responsibility to inform their colleagues of the adverse experiences they have encountered” (Inman, 1985, p. 51). ADE reporting is considered to be a professional responsibility by many HCPs. Many physicians believe that it is their duty to report ADEs (Figueiras et al., 1999).

Eleventh, the nature of the relationship between the agency receiving reports and the reporter affects the willingness of HCPs to report ADEs. If this relationship is positive or at least the reporter perceives it as being positive, the more likely reporting will take place (Biriell & Edwards, 1997). A positive relationship is built and supported through active personal and general feedback and encouragement from the agency to reporters. The content of the feedback to the HCPs also influences reporting rates (Wallerstedt, Brunlöf, Johansson, Tukukino, & Ny, 2007).

Finally, the attitude of HCPs towards reporting affects ADE reporting. Many studies investigated the ‘attitude’ of reporters and potential reporters (Biriell & Edwards, 1997; Eland et al., 1999; Martin et al., 1998; Moride et al., 1997). It has been reported that pharmacists’ and doctors’ attitudes toward their national ADE reporting schemes significantly determine their reporting rates (Bateman, Sanders, & Rawlins, 1992; Herdeiro et al., 2006; Koch-Weser, Sidel, Sweet, Kanarek, & Eaton, 1969; Rogers et al., 1988). HCPs including pharmacists have favorable beliefs concerning ADE reporting (Lawton & Parker, 2002; McArdle, Burns, & Ireland, 2003; Uribe et al., 2002). Community pharmacists in the Netherlands were found to be highly motivated to report ADRs (van Grootheest, Mes, & de Jong-van den Berg, 2002).

2.9 Limitations of Spontaneous Reports Data For Improving Safety

The use of ADE spontaneous reports data in pharmacovigilance has a number of limitations (Goldman, 1998): underreporting, false causality attribution, reporting biases,

inaccurate and unreliable quantification of population risks, inability to identify some dangers and the poor quality of reports.

2.9.1 Underreporting of ADEs

Many ADEs are not reported to the SRS and many HCPs are unaware and unmindful of pharmacovigilance activities (Gogtay, Dalvi, & Kshirsagar, 2003; Kshirsagar, Karande, & Potkar, 1993). Underreporting is an oft-cited weakness of all SRSs. Underreporting of ADEs by HCPs is a widespread problem (Alvarez-Requejo et al., 1998; Cullen et al., 1995; Lawton & Parker, 2002). There are numerous estimates of the magnitude of underreporting of ADEs. In one study, general practitioners (GPs) reported only one out of every 1,144 ADRs they came across to the pharmacovigilance centre (Alvarez-Requejo et al., 1998). A systematic review of 37 ADR studies from 12 countries, found a median underreporting rate of 94 percent (range: 6 - 100%; interquartile range: 82 - 98%) (Hazell & Shakir, 2006). Other studies estimated the rate of underreporting to be equal to or greater than 90 percent (Fletcher, 1991; Rawlins, 1988a). Underreporting is estimated to occur at a rate of 50 percent to 96 percent annually in the U.S. (Barach & Smith, 2000). A study in the Netherlands reported that only one (1) in 70 ADRs was reported (van der Heijden et al., 2002). A study to investigate the rate of underreporting of serious ADRs of selected diagnoses in Sweden found that of 107 patients who had received drugs that could have been a probable or possible cause to the diagnoses, only 15 were reported, giving an overall underreporting rate of 86 percent (Bäckström, Mjörndal, & Dahlqvist, 2004).

Although underreporting varies by the severity and seriousness of the event (Bäckström, Mjörndal, & Dahlqvist, 2004), high rates of underreporting have also been reported for serious ADEs and those with fatal outcomes (Bäckström, Mjörndal, & Dahlqvist, 2004; Hazell & Shakir, 2006; Moride et al., 1997). A systematic review

reported a median underreporting rate for serious ADRs across the studies of 85 percent (Hazell & Shakir, 2006). In the U.K., it was estimated that only 10 to 15 percent of even severe reactions were reported (Rawlins, 1988a). A 100 percent reporting is not achievable even for serious and fatal ADEs (Bäckström, Mjörndal, & Dahlqvist, 2004).

Owing to the high rates of underreporting, SRSs may fail to detect all the risks associated with the use of drugs (Begard & Tubert-Bitter, 1993). Underreporting delays the identification of signals and complicates the analysis of data (van der Heijden et al., 2002). Concerted efforts are required to minimize the rate of underreporting by HCPs (Bäckström, Mjörndal, & Dahlqvist, 2004).

2.9.2 False Causality Attribution

A common and major limitation associated with the use of ADE reporting data is false causality attribution (Edwards, 1997, 1999; Meyboom et al., 1997a; Meyboom, Hekster, Egberts, Gribnau, & Edwards, 1997b; Rawlins, 1995). In making ADE reports, HCPs make an association between a drug and the event/reaction. These subjective associations are at times unreliable. Making a correct association between a drug and the event is complicated by many factors. First, many ADEs mimic disorders that can occur without having any exposure to drugs (Inman, 1985; Stephens, 1985).

Second, some symptoms or injuries that are similar to ADEs are caused by the condition being treated or its complications (Mulcahy & Rosenthal, 1999), making them difficult to differentiate from ADEs. The difficulty of separating disease-related symptoms from drug-related ones (Jacubeit, Drisch, & Weber, 1990) results in two problems. The first is the problem of over ascertainment, which occurs when prescribers wrongly attribute an adverse event to a drug (Osterberg & Blaschke, 2005). For example in one study, thirty-eight percent of the 94 submitted ADE reports were attributed to other causes when additional data about these reports were later obtained (Stephens,

1985). The second problem is under ascertainment, which occurs when prescribers fail to recognize that the ADE is caused by the drug (when it actually is). Prescribers may mistake ADEs for disease progression or dismiss an ADE as being a side effect.

Third, for most suspected ADEs, it is difficult to rule out other explanations for the patient's negative experiences. This is so because even without exposure to a drug, there is always an underlying rate in the population (Goldman, 1998), and even healthy individuals taking no medication have many symptoms that are similar to those attributable to ADEs (Lee & Thomas, 2003).

Thus, the above challenges complicate the signal generation process resulting in two types of errors being experienced: calling a true signal noise (a false negative) and calling noise a signal (a false positive) (Evans, 2007). These errors cannot be completely eliminated given the current state of knowledge and unless true experimentation is done.

2.9.3 Reporting Biases

As noted earlier, ADR reporting is selective and reported cases may differ from those not reported in terms of severity, the length of time the product has been on the market, the groups of users, novelty of the effect of the drug and publicity surrounding the drug or ADE (Gharaibeh, Greenberg, & Waldman, 1998; Inman, 1985; Sachs & Bortnichak, 1986). As a consequence, the reported ADEs may not be representative of the universe of ADEs. Selective reporting makes it inappropriate to compare ADE reporting rates across studies and across drugs. Such a comparison will find spurious differences in toxicity (Moride et al., 1997).

2.9.4 Inaccurate and Unreliable Quantification of Population Risks

It is difficult to accurately quantify the risks associated with a drug in a population using SRS data. An accurate quantification of population risk (incidence) requires an

accurate value for risk (the numerator) and an accurate value for drug utilization (the denominator). The true drug utilization is unknown and sales data is often used as an estimate. However, sales do not accurately reflect actual usage levels. Reporting biases and underreporting also make the numerator inaccurate (Hazell & Shakir, 2006). Therefore, it is inappropriate to calculate ADE rates using spontaneous ADE reporting data and to make safety comparisons among drugs (Griffin & Weber, 1985).

2.9.5 Inability to Identify Some Dangers

Data from spontaneous reports are incapable of identifying some potential dangers associated with the use of approved drugs. Compared to automated (computer database) and manual (chart review) active surveillance, SRSs identify significantly fewer events. SRS data have a low signal, and detect only about 10 percent of ADEs (Classen et al., 1991). Monitoring systems based on spontaneous reports do not readily identify the following dangers:

- A drug that causes an event that might be expected as part of the natural history of the disease being treated (e.g., cardiac arrest caused by flecainide and encainide) (Moore, Psaty, & Furberg, 1998);
- ADEs that manifest themselves as a disease with high prevalence or high background rate in the population (e.g., cancer or heart disease) (Institute of Medicine of the National Academies, 2007a; Moore, Psaty, & Furberg, 1998);
- Negative effects that occur years or even decades after exposure to the drug (e.g., cancer) (Moore, Psaty, & Furberg, 1998); and
- ADEs that occur after discontinuation of the offending medication (Brewer & Colditz, 1999).

2.9.6 Poor Quality of Reports

SRS data make a positive contribution to patient safety if HCPs provide good quality reports. Some reports of valid concerns do not have enough detail to allow for a remote expert assessment and thus are of limited value (Edwards, 1999). The poor quality of the data may be due to the poorly controlled, inexact and voluntary nature of the data (Gharaibeh, Greenberg, & Waldman, 1998) and recall bias. In addition, the amount of information that can be provided through spontaneous reports is limited (Stephens, 1985). Critical information for evaluating an ADE such as chronology, dechallenge, rechallenge, clinical symptomatology, other possible explanations, possible predisposition and complementary investigations (Stephens, 1985) is often missing in reports. These quality limitations compromise the use of the data.

In summary, while the information provided by spontaneous reports makes valuable contribution, it needs to be augmented by information from other sources. However, despite the above limitations, the ability to draw valid conclusions from SRS data is high (Inman, 1985). SRSs are the most informative systems currently in use (Wade & Beeley, 1976).

2.10 Strategies for Increasing ADE Reporting Rates

The effectiveness of SRSs could be greatly enhanced if more HCPs reported serious ADEs (Wade & Beeley, 1976). Many strategies have been implemented to increase the rate of ADE reporting by HCPs. These include legally mandating ADE reporting, making reporting more convenient, improving education and training, having an independent organization to receive the ADE reports and providing encouragement and motivation to HCPs. These are discussed in turn below.

a) Legally Mandating Reporting

Some countries, such as Sweden, mandate the reporting of ADEs by HCPs. In Sweden, all prescribing officers are obliged to report all cases of serious ADEs to the regulatory authority. The Swedish law requires that all unknown side effects and "drug-suspected deaths, reactions leading to life threatening reactions, side effects leading to hospital admissions, new and unexpected reactions and ADRs that seem to increase in frequency and seriousness should be reported" (Bäckström et al., 2000, p. 729). In France, reporting of ADRs has been compulsory since 1984. Physicians are required by law to report serious and unexpected ADRs to their regional pharmacovigilance centers (Sommet et al., 2008).

b) Making ADE Reporting More Convenient

Streamlining the reporting process and procedures increases ADE reporting rates (Brewer & Colditz, 1999). Specific measures that can be taken include increasing availability of forms, giving more options for HCPs to use to submit reports (phone, fax, mail or internet websites), providing a toll-free phone, using postage-paid forms, and developing and using information technology (IT).

c) Improving Education and Information

Improving the HCPs' understanding of the purpose of pharmacovigilance through education and training increases ADE reporting rates (Brewer & Colditz, 1999). Education and training aimed at providing potential reporters with information on what constitutes a good report, and the benefits of reporting in overall patient care boost reporting rates (Cosentino et al., 1997; Davis, Thomson, Oxman, & Haynes, 1992; Lomas et al., 1991; Scott et al., 1990). In 1986, the Rhode Island Department of Health implemented a physician education project targeted at increasing the physicians' reporting rates. The Rhode Island Department of Health provided professional education

to physicians on the reporting system through direct mailings, presentations to physician groups and advertisements and articles in local periodicals (Scott et al., 1990). One year prior to the project, in 1985, only 11 reports were received from over 2,000 physicians in the state. As a result of the project, the number of reports increased from an average of 11.6 per year (1981-1985) to 209 direct reports in 1988, a 17-fold increase. The project demonstrated that reporting of suspected ADRs by HCPs can be stimulated through promotional and educational interventions (Scott et al., 1990).

d) Establishing an Independent Organization to Receive ADE Reports

In most countries, reports are submitted to the regulatory authority (e.g., the FDA in the U.S.). Some HCPs may be unwilling or be hesitant to report ADEs to a regulatory authority or government agency. Establishing an independent organization that coordinates this process increases the confidence and support of the HCPs in the system and eliminates some of the challenges associated with reporting ADEs (van Grootheest, 2003). An example of such an arrangement is the founding of the Netherlands Pharmacovigilance Centre, Lareb which is run by doctors and pharmacists. All large medical and pharmacists' bodies are fully represented on Lareb's Administrative Board.

e) Providing Encouragement and Motivation

HCPs need to be motivated to report suspected serious ADEs. Encouraging HCPs to always be vigilant for the occurrence of serious ADEs, and making all HCPs aware that ADE reports are welcomed increase ADE reporting rates. A special request can be sent to practitioners to encourage them to report serious ADEs. A U.K. study found that reporting among pharmacists increased when reporting was promoted in the hospital (Sweis & Wong, 2000).

Providing incentives to HCPs for reporting is another way to motivate them to report serious ADEs. Monetary (fees) or non-monetary (e.g., credit points for continuing

education (CE) and provision of feedback) rewards can motivate HCPs to report ADEs (Bäckström & Mjörndal, 2006; Bracchi et al., 2005; Feely, Moriarty, & O'Connor, 1990). In one study, researchers offered three pounds to junior doctors for each completed report submitted and reporting rates increased by almost 50-fold (Feely, Moriarty, & O'Connor, 1990). Many of the reactions reported in response to the fee would normally go unreported. The study helped introduce newly qualified doctors to the reporting system (Feely, Moriarty, & O'Connor, 1990). However, reporting rates declined after the fee was stopped.

Reporters and potential reporters are also motivated by receiving assurances that they will not experience any personal negative consequences or retribution (e.g., managerial scrutiny, threats to promotion and employment) for reporting ADEs. ADE reporting rates are boosted by addressing the HCPs' fear of public scrutiny and lawsuits emanating from personal disclosure. To get support from HCPs, the system must protect clinicians and other HCPs from unwarranted public scrutiny.

Pharmacists in the Netherlands were asked to provide the factors that motivated them to report suspected ADRs through an open-ended question (van Grootheest, Mes, & de Jong-van den Berg, 2002). The pharmacists provided the following 10 main suggestions listed in Table 2.7.

Table 2.7: Suggestions to Encourage Reporting ADRs (n = 147)

Suggestion as Mentioned by Respondents	Number who proposed the suggestion
Feedback	29
Publications	26
Information about the national centre	17
Simplification of reporting procedure	14
Promoting reporting as part of professional duty	13
Encouraging patients to report ADRs to the pharmacist	7
Financial compensation	7
More attention to ADR reporting in university curriculum	6
Database of national centre available on the internet	6
Compulsory reporting	2

Source: Van Groothest, 2002.

2.11 PHARMACOVIGILANCE AT THE INTERNATIONAL LEVEL

The WHO plays an important role in pharmacovigilance at the international level. Under the auspices of the WHO, 10 countries started a historic cooperative effort in 1968 which culminated in the setting up of the WHO International Drug Monitoring Programme. The WHO technical report, *"International Drug Monitoring: The Role of National Centres"* (1972) spurred the development of pharmacovigilance (World Health Organization, 1972). The establishment of the WHO Collaborating Centre for Drug Monitoring (The Uppsala Monitoring Centre, UMC) to maintain the international ADR database further spurred the development of pharmacovigilance.

Over the years, there has been a phenomenal increase in the number of countries affiliated with the UMC. More than 72 countries regularly send extracts from their spontaneous databases of local reports to the UMC which is based in Sweden. The UMC database has over 4 million cases. The U.S. is the single largest contributor of reports to the UMC database accounting for about half of the reports. The UMC collates and analyzes these reports and disseminates the information on drug safety to member countries (Edwards & Aronson, 2000; Edwards, 2001). This larger database has increased

power of vigilance that allows more new ADE signals to be identified that may not be apparent to a national centre (Edwards, 2001). The worldwide database contains information from diverse countries and cultures, most of which are not represented in clinical studies (Amery, 1999).

The UMC acts as a communication centre or a drug information clearing house for regulatory authorities and the pharmaceutical industry (Edwards & Biriell, 2007). All of UMC's clients can communicate with the UMC through the UMC's internet homepage (http://www.who-umc.org). The UMC's responsibilities and functions are:

- Providing support to national centers through developing information technology (IT), organizing training courses on pharmacovigilance and giving technical advice;
- Leading in developing guidelines for finding signals (Edwards, Lindquist, Wiholm, & Napke, 1990);
- Harmonizing the definition of pharmacovigilance terms (Edwards, 1997);
- Providing advice and recommendations on the safe use of medicines to HCPs; and
- Participating in refining the concept of benefit-risk analysis (Edwards & Biriell, 2007).

Another organization that played a prominent role in the development of pharmacovigilance at the international level is the Council for International Organization of Medical Sciences (CIOMS). The CIOMS was jointly established by the United Nations Educational and Scientific Organization (UNESCO) and WHO in 1949 as a non-profit international organization (Council for International Organization of Medical Sciences, 2008). The membership of CIOMS comprises mainly representatives of drug manufacturers and regulatory authorities. CIOMS' work champions the standardization of ADR reporting at the international level. CIOMS' efforts have helped improve understanding and communication on drug safety issues (Council for International Organization of Medical Sciences, 1998). CIOMS has also invested heavily in providing

guidance on developing standard approaches to weighing the benefits and risks of drugs (Council for International Organization of Medical Sciences, 1998).

2.12 PHARMACOVIGILANCE IN THE U.S.

The FDA plays an important role in pharmacovigilance or in monitoring the safety of all drugs marketed in the U.S. These PMS activities are premised on the FDA's adverse event reporting system. The Spontaneous Reporting System (SRS) originated in 1969. All reports are collected and stored in the Adverse Event Reporting System (AERS) database. The reporting system has undergone major transformations over the years. In 1993, the system was renamed MedWatch. MedWatch facilitates the reporting of AEs by physicians, pharmacists, dentists, nurses, consumers and pharmaceutical companies in the U.S. and disseminates clinically useful safety information to patients and HCPs. The system went online in 1997. As of 2001, the AERS database had over 2 million reports of adverse events for drug and therapeutic biologics (Trontell, 2001). AERS provides state-of-the-art analytic capabilities and is compliant with International Conference on Harmonization (ICH) agreements. There is a separate system for vaccine safety data called the Vaccine Adverse Event Reporting System (VAERS) and another one for medication error reporting called MEDMARX[5].

The U.S. Code of Federal Regulations (CFR) requires all drug companies to report to the FDA all ADEs for all drugs they market. Pharmaceutical companies collect these reports from HCPs. Pharmaceutical companies are required to report all serious and unexpected ADEs to the FDA within 15 calendar days of receiving them from HCPs or

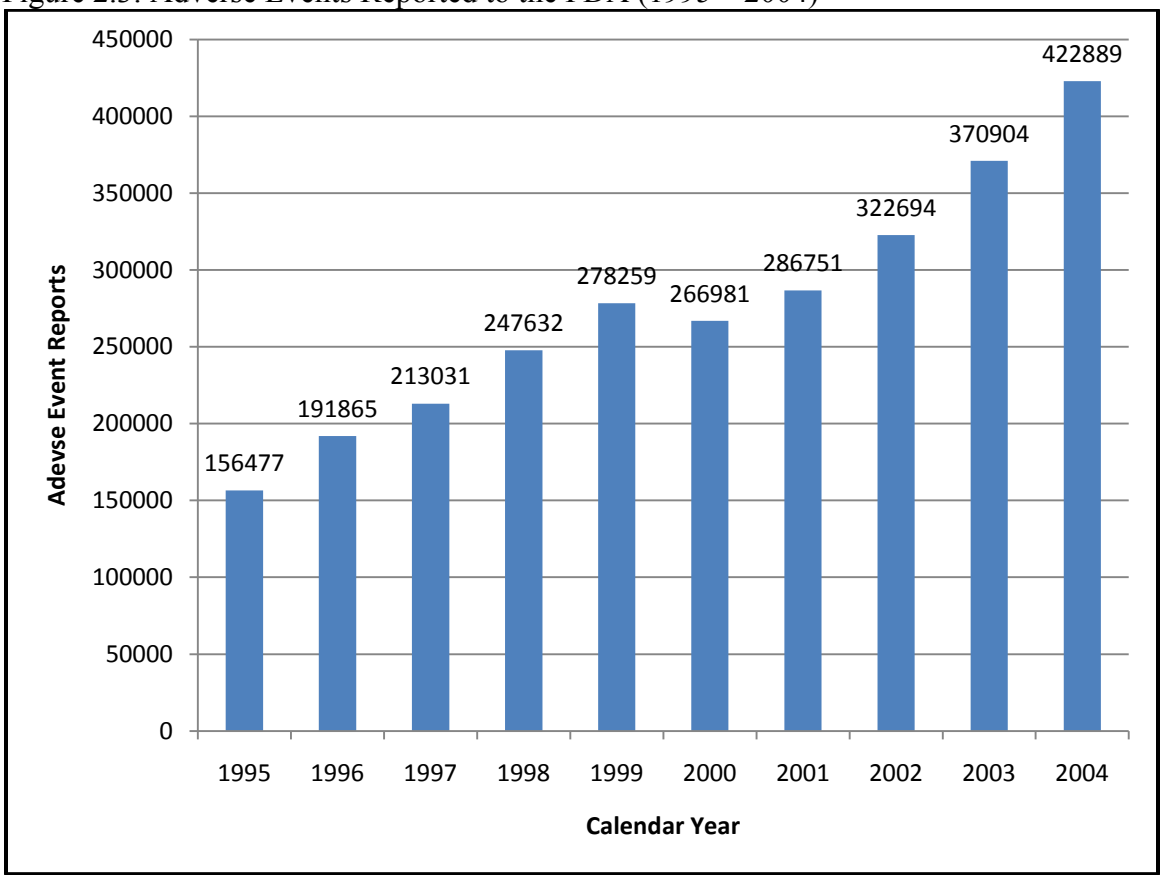
[5] MEDMARX is a national medication error reporting program that was developed and implemented in 1998 by the United States Pharmacopea (USP). MEDMARX is "an anonymous, confidential, de-identified, internet-accessible medication error reporting program" (Santell et al., 2003). MEDMARX facilitates the reporting, tracking, and sharing of medication error data in the U.S. Since its inception, MEDMARX has uncovered previously unknown information and trends and identified problem areas in many hospitals (Santell et al., 2003).

patients. A serious adverse event is defined as any event that is fatal, life threatening, is permanently/significantly disabling, requires or prolongs hospitalization, causes a congenital anomaly and requires intervention to prevent permanent impairment or damage. Other events (i.e., serious and expected, nonserious and unexpected, and nonserious and expected) are to be periodically reported (Trontell, 2001).

The FDA has issued several guidance documents defining and clarifying what is to be reported by HCPs and drug companies. Some of the documents include: *CDER's Guideline for Postmarketing Reporting of Adverse Drug Experiences* (March 1992), and *CDER's Guideline for Adverse Experience Reporting for Licensed Biological Products* (October 1993). Hard copies and electronic versions of these documents are available from the FDA. According to the FDA, a safety report from drug companies should have four elements: a) an identifiable patient, b) an identifiable reporter, c) a suspect drug or biological product, and d) an adverse event or fatal outcome (FDA/Center for Drug Evaluation and Research, 1997). The FDA recommends that only complete reports should be submitted to the FDA.

The FDA receives approximately 250,000 reports of adverse events annually. Most (80%) of the HCPs' reports are submitted to the FDA through pharmaceutical companies and approximately 20 percent of the reports go directly to the FDA through MedWatch. Compared to other HCPs in the U.S., pharmacists submit the greatest number of reports to the FDA. In 2001, pharmacists submitted 41 percent of the reports made by individuals. The rest of the reports were made by physicians (11%), nurses (11%), other health care professionals (11%), unknown (18%), and consumers (8%) (Cobert, 2007; Office of Drug Safety, 2001). In 2004, the FDA received 422,889 reports of suspected drug-related adverse events broken down as follows: MedWatch reports directly from individuals (21,493), manufacturer 15-day (expedited) reports (162,107), serious manufacturer periodic reports (89,960), and nonserious manufacturer periodic reports (149,329). The number of ADE reports has been increasing over the years (Figure 2.3).

Figure 2.3: Adverse Events Reported to the FDA (1995 – 2004)



Source: CDER Report to the Nation: 2004

In reporting AEs through the MedWatch Program, HCPs use a standard form. These forms are widely available (e.g., available in the Physicians' Desk Reference and can be downloaded from the internet). The form is two pages long and asks HCPs to provide information on the event, the patient, the product and about themselves (see Appendix A). Reports can be submitted to the FDA by mail (postage free), fax (1-800-FDA-0178), internet (www.fda.gov/medwatch), or phone (1-800-FDA-1088).

Like all other SRSs, the AERS has strengths and limitations. The strengths of the system include: comprehensive coverage of all drug products, simplicity, low cost relative to active surveillance, and good ability to detect rare events (Trontell, 2001). The system also faces problems similar to those experienced by many other SRSs elsewhere vis-à-vis: poor and incomplete reports, underreporting, biased reporting, and challenges

in detecting signals and in calculating incidence rates (Trontell, 2001). The main challenges and limitations of the conduct of PMS in the U.S. are discussed below. First, there is no independent body (i.e., completely separate from the drug regulators and manufacturers) that monitors and investigates ADEs in the U.S. (Wood, Stein, & Woosley, 1998). The FDA is both the regulator and collector of patient safety information. The need for, and importance of, independent safety monitoring is recognized in the U.S. (Institute of Medicine Report, 2001).

Second, PMS activities in the U.S. are under-funded (Young, 2006). The FDA does not have adequate resources to optimally identify and quantify all drug-induced problems. Until recently, the FDA charged pharmaceutical companies a fee for reviewing drug applications, but did not collect any fees for PMS. In addition, the FDA was prohibited by the Food and Drug Administration Modernization Act of 1997 from spending the fees they collected on PMS or other drug safety programs (Wood, Stein, & Woosley, 1998). This is expected to improve with the passage of the Food and Drug Administration Amendments Act (FDAAA) of 2007 which now allows the FDA to use the funds for PMS.

Third, low priority is given to PMS in the U.S. The IOM reported that the FDA focused mainly on evaluating new drugs and devoted less resources and staff to drug safety monitoring for approved drugs (Institute of Medicine Report, 2004; Moore, Psaty, & Furberg, 1998). As a result, the FDA is not able to review the submitted reports of adverse events in a timely manner (Schultz, 2007) and does not aggressively promote the reporting of ADEs.

Fourth, the FDA has minimal powers to regulate approved drugs. Until recently, the FDA could not order companies to conduct postmarketing studies and to make labeling changes. This is expected to improve with the passing of the FDAAA of 2007 which gave the FDA significant regulatory powers.

Fifth, drug safety in the U.S. is also compromised by lack of information technology (IT) capacity and the shortage of trained experts in drug safety and drug epidemiology at the FDA (Schultz, 2007). The FDA has a limited technological capacity (Cassell, 2008). The Office of Surveillance and Epidemiology (OSE) faces a shortage of trained and skilled personnel. Some scientific positions at the FDA have turnover rates more than double those of other government agencies (Schmit, 2007). These capacity challenges impede the monitoring of products that use new science (Cassell, 2008). The size of the FDA workforce does not match its wideranging responsibilities which also involve regulating the safety of food, cosmetics, feeds, dietary supplements, blood products, veterinary products and medical devices.

The above notwithstanding, information gathered through the AERS is critical and indispensable. According to the IOM: "while AERS is not perfect, it is still all that we have right now in terms of providing a system for patients and physicians to alert the FDA. … there is no real substitute for the information collected through AERS" (Institute of Medicine, 2007, p. 54).

2.13 Summary of Literature Review, Gaps and Areas of Future Research

Healthcare, including drug therapy, provides many benefits to society. However, the common occurrence of serious ADEs, many of which are preventable, threaten patient safety. Though inherently negative, serious ADEs are a valuable source of safety information and can contribute towards clinical and scientific progress (Vincent, 2006). The occurrence of serious and other ADEs provides unique learning opportunities for health systems and HCPs (McIntyre & Popper, 1983). Pharmacovigilance and PMS are the vehicles through which such learning can occur and they play a critical role in drug safety and drug therapy decision-making. PMS monitors drug safety through collecting and analyzing spontaneous reports from HCPs, pharmaceutical companies and patients. SRSs are an important component of any comprehensive surveillance program of risks induced by drug use. Information collected through SRSs informs drug regulatory agencies' and pharmaceutical companies' actions. Possible actions and measures include modifying product information and warnings, modifying the product or its use and withdrawing the product from the market.

Pharmacists play an important and indispensable role in PMS and other efforts aimed at improving patient safety and outcomes through reporting ADEs. Pharmacists, like other HCPs, are encouraged to report ADEs. There are many factors that affect the reporting of ADEs by pharmacists: reluctance to send reports based on mere suspicion, fear of personal repercussions, sense of professional responsibility, difficulty in accessing the means of reporting, lack of information, the type and nature of ADEs, attention drawn to a particular drug and ADE, beliefs and opinions, and 'lack of time,' among others. In addition, pharmacists' attitude towards reporting is a major factor influencing ADE reporting.

The objective of SRSs is to generate signals and hypotheses. SRSs are cost-effective, comprehensive and directly related to clinical practice. However, the

effectiveness of SRSs is compromised by underreporting by HCPs including pharmacists. Underreporting of serious ADEs is a serious problem with an estimated less than one percent of serious ADEs being reported.

Many strategies have been implemented to increase ADE reporting rates among HCPs including mandating reporting, encouraging and motivating HCPs to report, streamlining the reporting process, offering targeted training and education, and establishing independent organizations to coordinate and receive ADE reports. These strategies have had mixed results.

There are several gaps in the literature on ADE reporting. None of the studies reviewed investigated attitudes of pharmacists toward ADE reporting using a theoretical framework. The empirical literature lacks a systematic theoretical framework and fails to define independent and dependent variables in a theoretically justified way (Hoff, Jameson, Hannan, & Flink, 2004). Little is known about the attitude of pharmacists towards ADE reporting. Moreover, many studies in the literature that purported to be studying the attitudes of HCPs more accurately studied their beliefs and opinions, one aspect of attitude, about ADE reporting (Generali, Danish, & Rosenbaum, 1995; Sweis & Wong, 2000). More research applying theoretical models in studying and understanding ADE reporting by healthcare professionals, especially pharmacists, is warranted.

CHAPTER THREE: THEORY

3.1 RATIONALE OF THE STUDY

The literature review shows that increasing the number of ADE reports submitted by HCPs (including pharmacists) is an indispensable part of the drug safety system and is associated with improved safe use of drugs through: a) facilitating the identification and elimination/withdrawal of unsafe products from the market; b) informing better and safer ways of using available drugs (e.g., imposition of restrictions); c) facilitating the education and training of health professionals on the safe use of medicines; and d) identifying other positive effects of drugs. The submitted ADE reports are used by the FDA and pharmaceutical companies in calculating the benefit-risk ratio or in defining the safety profile of a drug. This process helps in formulating strategies to minimize the health (e.g., patient harm and mortality) and economic impact associated with ADEs, by reducing the chances of having drug-related problems in the future.

Pharmacists have the responsibility to promote the safe use of medications. Their actions with respect to identifying and reporting ADEs are one way they can do so effectively. In addition, through reporting ADEs, pharmacists have the opportunity to promote public health and patient safety. However, research regarding pharmacists' participation in reporting ADEs is limited. Even less is known about their decision-making with respect to ADE reporting. No known study has specifically assessed pharmacists' beliefs, attitudes, subjective norms and intentions to report ADEs using a grounded theoretical model. Thus, there is a need to conduct a theory-driven study to identify and understand the factors affecting the likelihood of ADE reporting by pharmacists. This study will contribute to the literature by providing insight into the factors that influence pharmacists' decision-making process regarding ADE reporting. Policy makers, public health officials and regulatory agencies require this critical information in order to improve medication use safety in the U.S. In addition, continuing education (CE) programs need this information in order to better design and target their

interventions to meet the needs of pharmacists, to increase their willingness to report and actual reporting of serious ADEs, and thus better serve the community.

The pharmacists' decision to report serious ADEs may be affected by their attitudes towards ADEs. It may also be affected by their perceptions of the beliefs of significant others (e.g., physicians, other pharmacists, pharmacy managers, and patients). It is also speculated that some external factors (e.g., resources and opportunities) may influence pharmacists' intentions to report serious ADEs.

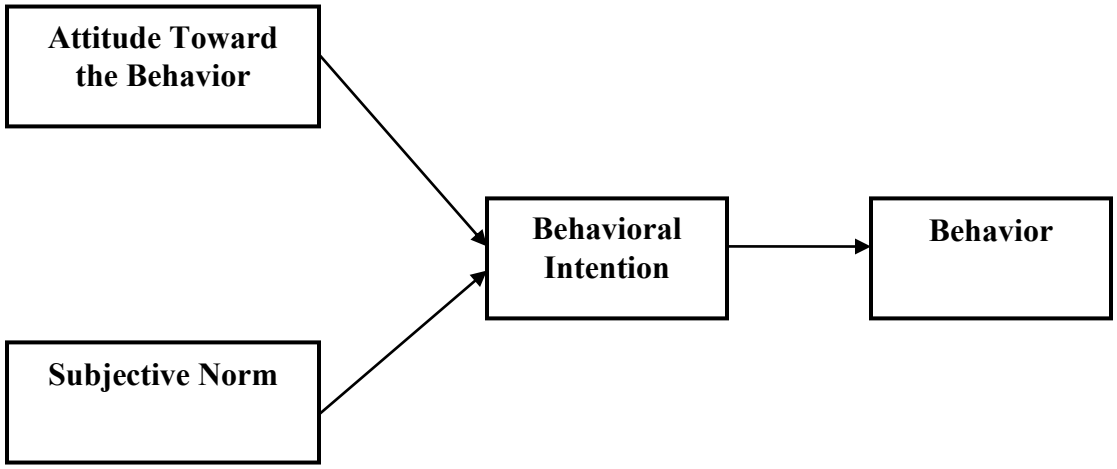
This study seeks to identify and analyze the factors that influence pharmacists' intended reporting behaviors. Once the pharmacists' beliefs and attitudes are identified and analyzed, the next step is to develop appropriate interventions tailored to these beliefs and attitudes. The interventions meant to increase ADE reporting by pharmacists will likely succeed if they are appropriate. The long-term goal is to facilitate pharmacists' education and monitoring activities and to promote the safe and appropriate use of medications in the U.S.

There are many social psychology theories that have been used to predict and understand behavior. Among these theories, Fishbein and Ajzen's (1991) theory of planned behavior has been extensively used. The theory of planned behavior (TPB) is an extension of the theory of reasoned action (TRA). The TPB is well developed and has been used successfully to predict many health-related behaviors (Godin & Kok, 1996; Millstein, 1996) and to predict the intentions of HCPs including physicians, nurses and pharmacists (Coleman, 2003; Feng & Wu, 2005; Millstein, 1996; Nwokeji, 2007). Given this, the TPB might be effective in predicting intentions and behaviors of pharmacists in reporting ADEs as well.

3.2 THEORY OF REASONED ACTION

The TRA has its roots in social psychology, which seeks to explain the association between attitude and behavior. The TRA was developed by Fishbein and Ajzen to explain why people behave the way they do (Ajzen & Fishbein, 1980). According to the TRA, an individual's behavior is determined by intention. Behavioral intentions are in turn a function of attitudes toward engaging in the behavior and subjective norm. The TRA has three main components: a) attitude toward the behavior; b) subjective norm; and c) behavioral intention (Figure 3.1).

Figure 3.1: The Theory of Reasoned Action



Source: Ajzen, I. and M. Fishbein (1980). Understanding attitudes and predicting social behavior. Englewood Cliffs, New Jersey, Prentice Hall.

Attitude toward the behavior or performing the behavior is the positive or negative evaluation by an individual. Other things being equal, if a person has a positive attitude toward the behavior, he/she is more likely to implement that behavior. Attitude is

determined by expectations for the outcome of the behavior and evaluations of the expected outcomes of the behavior as shown below.

$A = \sum e_i b_i$
A = attitude towards the object of behavior
e_i = evaluation of attributes or consequences
b_i = belief about the object's attributes or about the behavior's consequences

Subjective norm, also called social norms, is the social pressure to perform or not to perform a behavior. It reflects the social influences on the individual. Like attitude, subjective norm has two components: a) the individual's perception of the most salient group norms, and b) individual's motivation to comply with these norms. These components are important in the decision making process (Vanlandingham, Somboon, Grandjean, & Sittitrai, 1995). The likelihood of individuals intending to engage in a behavior is higher if the intention is considered important by persons or groups the individual wishes to please. Subjective norm is a function of the individual's normative beliefs about the behavior and the individual's motivation to comply with the referents' wishes as shown below.

$SN = \sum n_i m_i$
SN = subjective norm
n_i = normative belief about the behavior
m_i = motivation to comply with the referent

Behavioral intention defines a person's willingness or ambition to perform a given behavior. The person's degree of willingness can be seen from the degree of effort s(he) intends to invest towards performing the behavior. According to Ajzen, behavioral intention is affected by attitude and subjective norm (Ajzen, 1991).

The TRA has been applied to predict intentions in many behaviors across many settings. Much research supports the predictive validity of this model (Ajzen & Fishbein, 1980). The model has been successfully used in behaviors such as breast feeding,

drinking, smoking, exercise, substance use, HIV and sexually transmitted disease prevention, seat belt use and utilization of health care services (Albarracin, Johnson, Fishbein, & Muellerleile, 2001; Bandawe & Foster, 1996; Beadnell et al., 2008; Bogart, Cecil, & Pinkerton, 2000; Gastil, 2000; Morrison, Spencer, & Gillmore, 1998; Munoz-Silva, Sanchez-Garcia, Nunes, & Martins, 2007). Meta-analyses conducted on the use of the TRA confirmed the theory's predictive ability (Albarracin et al., 2001; Sheppard, Hartwick, & Warshaw, 1988).

In a meta-analysis to investigate the effectiveness of TRA in predicting intentions and behavior, Sheppard, Hartwick and Warsaw (1988) reviewed 87 separate studies involving 174 behaviors including abortion, taking birth control pills, resigning from a job, and voting in presidential elections among others. The results of the meta-analysis showed that, on average, attitude and subjective norm explained 43 percent of the variance in intention and intention accounted for 28 percent of the variance in behavior. These results indicate that the TRA constructs significantly influence intention and behavior and the TRA model performed extremely well (Sheppard, Hartwick, & Warshaw, 1988). In another study, Albarracin and colleagues (2001) conducted a meta-analysis of TRA in predicting condom use behavior. The results of 42 studies reviewed showed that TRA highly predicted condom use intentions and behavior (Albarracin et al., 2001).

The TRA has been applied across many different settings, behaviors and circumstances. It has been successfully applied to study health behaviors, with most of the TRA applications primarily focusing on predicting patients' intentions and behaviors (Bandawe & Foster, 1996; Godin & Kok, 1996; Morrison, Spencer, & Gillmore, 1998). In addition to patients, the TRA model has been found to be relevant for studying healthcare providers' behaviors as well (Godin et al., 2008; Millstein, 1996). This section focuses on the studies that used the TRA model to predict the intentions of healthcare providers.

A total of six (6) studies that used the TRA as the conceptual model to study HCPs' behavior were found in the literature (Coleman, 2003; DiIorio, 1997; Fried, DeVore, & Dailey, 2001; Millstein, 1996; Sable, Schwartz, Kelly, Lisbon, & Hall, 2006; Werner & Mendelsson, 2001) (Table 3.1). One study by Kleier (2004) was excluded from the discussion because it did not use the model correctly (the study did not conduct elicitation interviews to develop the survey items) and did not report the needed statistics (beta weights and R^2) (Kleier, 2004). The number of studies that did not use the model correctly is less than what has been reported by Sheppard, Hartwick and Warshaw (1988). Sheppard, Hartwick and Warshaw (1988) found that only 20 percent and 11 percent of the studies predicting intentions and behavior, respectively, used the models correctly. In addition, one study could not be obtained and thus, was excluded from our discussion (Plianbangchang, 1999).

Table 3.1: Studies Using the TRA to Predict HCPs' Intentions

Study Author (s) & Year	**Behavior**	**Sample (N)**	**Correlation Coefficient (r)/Regression Weights For A-I**	**Correlation Coefficient (r) /Regression Weights For SN-I**	**Intention**
Millstein, 1996	Delivery of preventive services	765 primary care physicians	β = 0.22***	β = 0.28***	R^2 = 0.15**
DiLorio, 1997	Care for persons with HIV/AIDS	368 neuroscience nurses	β = 0.184***	β = 0.048	R^2 = 0.042***
Fried et al., 2001	Self assessment	119 dental hygienists	r = 0.667****	r = 0.278	R^2 = 0.497****
Werner and Mendelsson, 2001	Use of physical restraints with older people	303 nursing staff members	β = 0.66***	β = 0.12**	R^2 = 0.48****
Coleman, 2003	Communication with customers about antibiotics	375 pharmacists	β = 0.197***	NA	R^2 = 0.14
Sable et al., 2006	Prescribe emergency contraception	96 faculty physicians	B = 1.39***	B = 0.05*	NA

A-I = Attitude-Intention; SN-I= Subjective norm-Intention
NA = not available
*p < 0.05, **p < 0.01, ***p < 0.001, ****significant, p value not reported

Millstein (1996) conducted a study that applied the TRA and later the TPB in predicting physicians' behavior with respect to educating their adolescent patients concerning transmission of HIV and other sexually transmitted diseases (also referred to as delivery of preventive services). The study sample consisted of 765 physicians practicing in California who were predominantly male (64%). Using multiple regression analysis, the authors found that both attitude ($\beta = 0.22$, $p < 0.001$) and social norms ($\beta = 0.28$, $p < 0.001$) independently and significantly predicted physicians' behavioral intentions (Millstein, 1996). Social norms or subjective norm was the strongest predictor of behavioral intentions. Overall, the two TRA predictors explained 15 percent of the variance in intention ($p < 0.01$).

Fried, DeVore and Dailey (2001) applied the TRA to study the perceptions of Maryland dental hygienists regarding self-assessment (SA). A total of 119 respondents participated in the study. A majority of respondents received their initial dental hygiene licensure 19 or more years prior to the study (59.6%). Sixty six percent of the respondents had an associate degree in dental hygiene as their highest education ($n = 79$) and 83.2 percent were employed in general dental practice. Results indicated that respondents had high intention to self-assess (SA) ($X = 2.7$; scale: -3 to +3) as well as a favorable attitude ($X = 2.6$) and strong subjective norm ($X = 1.0$). Attitude was strongly correlated with intention ($r = 0.667$, $p < 0.01$), but subjective norm mildly correlated with intention to SA ($r = 0.278$; $p > 0.05$). Taken together, attitude and subjective norm strongly predicted intention to perform self-assessment ($R = 0.705$; $R^2 = 0.497$). Socio-demographic variables except hours of employment did not independently influence intention to perform self-assessment. The dental hygienists who worked less than 20 hours per week were significantly less likely to intend to self-assess than those who worked for 20 or more hours per week ($p = 0.0089$). The study concluded that dental hygienists are influenced more by their own attitudes (i.e., their belief in the benefits of

SA) than by what patients, employers, or other dental hygienists value in terms of their intentions to self-assess (Fried, DeVore, & Dailey, 2001).

Werner and Mendelsson (2001) tested the assumptions of the TRA model in predicting nursing staff members' intentions to use physical restraints with older people in Israel (Werner & Mendelsson, 2001). A total of 303 respondents participated in the study. Participants were predominantly female (95.2%), of Israeli nationality (51.0%) and with an average age of 42.4 (SD = 8.6) years. Results supported the TRA model—findings indicated that attitude and subjective norm explained 48 percent of the variance in nurses' intentions (Werner & Mendelsson, 2001). Both TRA predictors were statistically significant: attitude ($\beta = 0.66$, $p < 0.001$) and subjective norm ($\beta = 0.12$, $p = 0.01$). The authors found that perceived moral obligation (PMO) ($\beta = 0.22$, $p < 0.001$) predicted intentions to use physical restraints with older people over and above the contributions of attitude and subjective norm (Werner & Mendelsson, 2001). In separate univariate analyses, PMO accounted for more variance in intention ($R^2 = 0.25$) than SN.

In 2006, Sable and colleagues published results of their study that applied the TRA in predicting emergency contraception (EC) prescribing behavior among faculty physicians (Sable et al., 2006). A total of 96 faculty physicians from one Southwestern and three Midwestern universities participated in the study. The average age of respondents was 46.9 years (range: 29 - 79 years). A majority of the respondents were family practitioners (52%), board certified (97%) and male (62%). The results of regression analysis showed that attitude toward prescribing ($B = 1.39$, $p < 0.001$) and subjective norm (indirect measure; $B = 0.05$, $p < 0.05$) were significant predictors of intention. The direct measure of SN, did not independently predict EC prescribing intentions. Physicians in the study had very strong opinions about the positive or negative aspects of prescribing EC and they were less influenced by their professional referent groups' perspectives (Sable et al., 2006). The study concluded that physicians' own

attitudes had a greater impact than the influence of significant others on whether or not they actually prescribed EC (Sable et al., 2006).

While the TRA has been applied among HCPs, only one reference to the theory was found in the pharmacy literature. In a national study, Coleman examined the influence of community pharmacists' communication with customers about antibiotics and antibiotic resistance (referred to as discussion) (Coleman, 2003). A majority of the 375 pharmacists in the study were male (57%), and had earned a Bachelor of Pharmacy degree (85%). Pharmacists filled an average of 126 (SD = 75.6) prescriptions per day. Attitude was found to be the strongest predictor of discussion ($\beta = 0.197$, $p < 0.001$). Three demographic and organization variables were significant predictors of discussion: prescriptions written per day ($\beta = -0.169$, $p = 0.001$), hours worked per day ($\beta = 0.116$, $p = 0.023$) and working in a non-chain pharmacy ($\beta = 0.139$, $p = 0.011$). Knowledge and years in practice were not significant predictors of discussion intention ($p > 0.05$).

3.2.1 Summary and Overview of the Studies

The studies above confirm the TRA model's validity in predicting HCPs' behavioral intentions. The TRA predictors (subjective norm and attitude) accounted for a significant proportion of the variance in HCPs' intentions, ranging from 4 percent to 50 percent. The TRA model explained more variance in studies of volitional behaviors (self-assessment by dental hygienists and use of physical restraints by nursing staff members) than in those that were not or less so.

Attitude was expected to significantly influence intentions for behaviors that primarily affect the individual performing the behavior. In all studies that were reviewed, attitude was a significant predictor of intention and subjective norm was not significant in two of the studies. In all studies except one (Millstein, 1996), attitude was a stronger predictor of intentions than subjective norm. This observation re-inforces the fact that

attitude is an important dimension in predicting intentions. HCPs were mostly influenced by their attitude than by what significant others (e.g., patients, employers or other HCPs) value.

Millstein (1996) found that the delivery of preventive services by primary care physicians was driven more by SN ($\beta = 0.28$, $p < 0.001$) than by attitude ($\beta = 0.22$, $p < 0.001$). This was expected given that the behavior under investigation (delivery of preventive services) affects others. In such behaviors, behavioral intention is expected to be significantly shaped by social influences. Yet SN was not significant in two of the studies that investigated behaviors that affect others (DiIorio, 1997; Fried, DeVore, & Dailey, 2001). This unexpected finding may be explained by several factors. First, the DiLorio study only explained 4 percent of the variance in intention signifying a possible problem in the way the constructs or variables were operationalized (DiIorio, 1997). In addition, although the Fried and colleagues' study had a high R-squared value, it did not report regression weights (standardized or unstandardized) (Fried, DeVore, & Dailey, 2001).

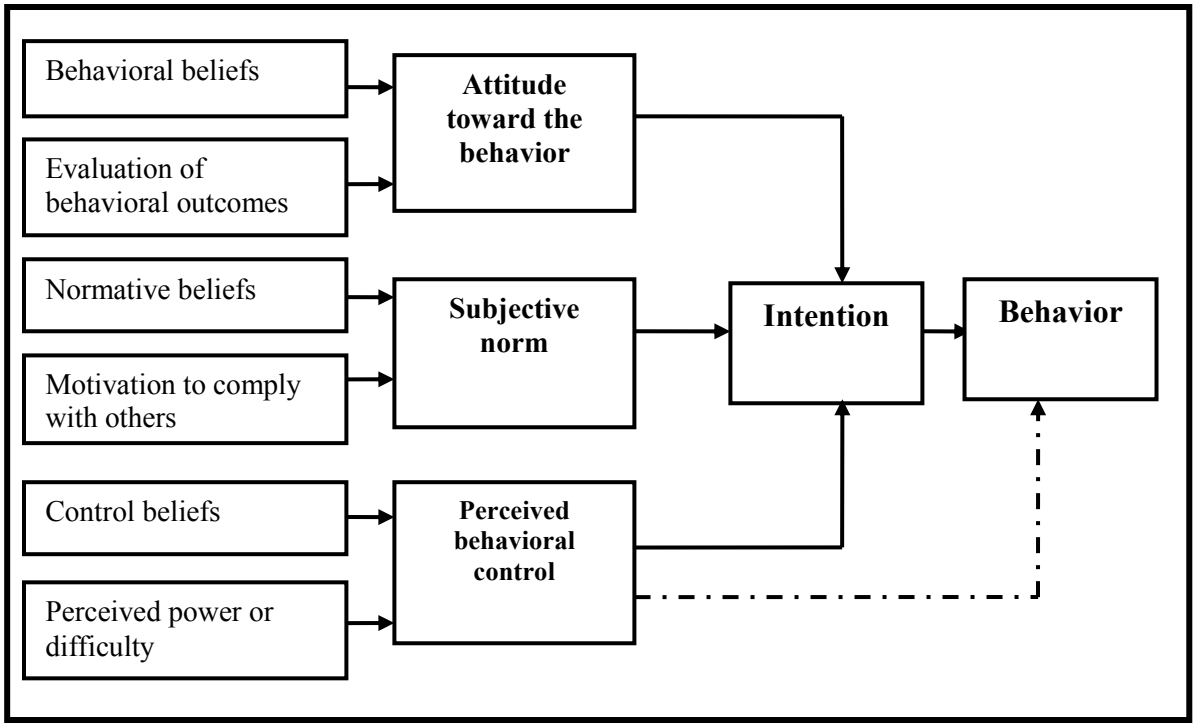
The TRA performs best in predicting behaviors that are under the individual's complete volitional control. Some behaviors require the individual to have some skill or opportunities to implement them. For such behaviors that are not under volitional control, other theories such as the theory of planned behavior (TPB) are preferred and have improved predictability.

3.3 THEORY OF PLANNED BEHAVIOR (TPB)

The TPB adds the construct of perceived behavioral control (PBC) to the TRA predictors. The TPB is similar to the TRA except for this additional component (PBC). Behaviors that are difficult to implement (in which the individual may not expect to successfully complete the behavior) or that require resources, skills or opportunities to

implement the decision are better predicted by TPB than by the TRA. TPB performs better than the TRA in explaining behaviors that are not under complete volitional control (Millstein, 1996). PBC is a stronger predictor of intention and behavior when perceived control is low and PBC has minimal influence on behavior when perceived control is high (Madden, Ellen, & Ajzen, 1992). The TRA and TPB perform nearly similarly in predicting behaviors that are fully volitional. However, the addition of PBC improves the TRA model's predictability even for behaviors that are under volitional control (Netemeyer, Burton, & Johnston, 1991; Richard, Dedobbeleer, Champagne, & Potvin, 1994). The contribution of perceived control towards predicting intentions varies across different behaviors (Levin, 1999).

Figure 3.2: The Theory of Planned Behavior



Source: Ajzen, I. (1991). "The theory of planned behavior" Organizational Behavior and Human Decision Processes **50**(2): 179-211.

According to the TPB, there are three independent determinants of intentions: attitude toward the behavior, subjective norm (SN), and perceived behavioral control (PBC). PBC refers to the perception of one's ability to perform a given behavior. PBC has a direct effect on behavior and an indirect one via behavioral intention. The likelihood of performing a behavior not only depends on the internal motivational factors but also on the external factors including availability of resources, skills and opportunities. PBC incorporates the extent to which a person is actually able to carry out the behavior and the effect of facilitating and inhibiting factors. PBC is the perceived ease or difficulty in performing a behavior (Ajzen, 1991). Perceived control is related to the concept of self-efficacy as espoused by Bandura (Ajzen, 1991; Bandura, Cioffi, Taylor, & Brouillard, 1988).

An individual who has a positive attitude towards the behavior, favorable subjective norm toward the behavior and perceives him/herself to have greater control in performing the behavior will have stronger intention to perform the behavior. On the other hand, a person with a negative attitude, unfavorable subjective norm towards the behavior and who perceives him/herself to have less control of the behavior is less likely to intend to perform the behavior. Other things remaining equal, a person with lower PBC (perceived resources and opportunities) will have less intent to perform the behavior (Madden, Ellen, & Ajzen, 1992).

The PBC component (indirect measures) consists of control beliefs and perceived power. PBC is measured by multiplying each salient control belief by the perceived power of the particular control factor and summing up the resulting products across the salient beliefs as shown below.

$PBC = \sum c_i p_i$
PBC = perceived behavioral control
c_i = the control belief (perceived presence of specific factors that increase or reduce the difficulty of performing the behavior in question).
p_i = the perceived power of a particular control factor to facilitate or inhibit performance of the behavior.

The TPB has been applied to study an array of behaviors such as voting, weight loss (dieting, taking a low fat diet), cheating, attending class, smoking cessation, safe sexual practices (e.g., condom use), choice of leisure, dishonest actions, physical activity (e.g., exercise), household recycling, testicular self-examination, fruit and vegetable consumption, use and misuse of alcohol, health screening (cancer), food choice, blood donation, gift giving and driving violations (Armitage & Conner, 2001; Parker, Manstead, Stradling, Reason, & Baxter, 1992). Meta-analyses have confirmed the efficacy of the TPB. A meta-analysis of the studies utilizing the TPB revealed that the TPB accounted for 39 percent and 27 percent of the variance in behavioral intention and behavior, respectively (Armitage & Conner, 2001). A comparison of the TPB and the TRA showed that the TPB explained significantly more variance in behavioral intention than the TRA (Madden, Ellen, & Ajzen, 1992). PBC independently accounted for six (6) percent of the variance in behavior (Armitage & Conner, 2001).

The usefulness of the TPB in predicting health-related behaviors in the literature was confirmed through systematic reviews (Godin et al., 2008; Godin & Kok, 1996). The review by Godin and Kok (1996) included 56 studies that covered 58 health behaviors that were classified into seven (7) behavioral categories: oral hygiene, eating, automobile, clinical screening, addictive, exercising and HIV/AIDS. "The overall average correlations between intention and attitude, subjective norm and perceived behavioral control were 0.46, 0.34 and 0.46 respectively" (Godin & Kok, 1996, p. 92). PBC significantly added to the prediction of intention in 65 of 76 analyses reported in the studies. The TPB's constructs, on average, explained 41 percent of the variance in intention (range: 32.0% - 46.8%). PBC and attitude were found to be the strongest predictors of intention and explained an average of 34 percent of the variance in intention (Godin & Kok, 1996). Godin and Kok (2008) concluded that PBC was an important construct in explaining health-related behaviors and that the usefulness of the TPB model varied across different health-related behaviors.

Many theory-guided health interventions have been successfully implemented using the TPB framework (Valois et al., 2001; Walker, Grimshaw, & Armstrong, 2001; Walker et al., 2004). Over 600 empirical studies have predicted behavior and behavioral change using the TPB in the past two decades (Francis et al., 2004). The TPB model is useful for guiding behavioral change strategies. Meta-analyses found that communication strategies premised on the TPB were effective in promoting health behaviors (e.g., exercise and condom use) and in reducing health risk behaviors (e.g., speeding, unsafe sex, binge drinking among others) (Armitage & Conner, 2001; Godin & Kok, 1996). Another study that applied the TPB to continuing education for mental health professionals found that "significantly more participants in the theory-guided class than in the standard class (74% versus 42%) had applied the tool by the three-month follow up" (Casper, 2007, p. 1324).

In line with the nature of this project, the rest of this review is restricted to studies of the TPB that involve HCPs (Tables 3.2, 3.3 and 3.5). Some of the studies reviewed had intentions while others had behavior as their final outcome variable. This review will concentrate on the constructs of the model that relate to intention formation. Studies that did not correctly specify the model (Emeis et al., 2007; Kleier, 2004) and were not based on primary research (Ceccato, Ferris, Manuel, & Grimshaw, 2007) were excluded. Although every effort was made to include all relevant studies, it is possible that some articles were inadvertently missed.

Table 3.2: Studies Using the TPB to Predict HCPs' Intentions (Excluding Pharmacists)

Study Author (s), Year	**Behavior**	**Sample (N)**	**B/Beta Weights For A-I**	**B/Beta Weights For SN-I**	**B/Beta Weights For PBC-I**	**Intention**
Millstein, 1996	Deliver preventive services	765 primary care physicians	β = 0.11***	β = 0.21***	β = 0.37***	R^2 = 0.27
DiLorio, 1997	Care for persons with HIV/AIDS	368 neuroscience nurses	β = 0.078 (NS)	β = -0.020 (NS)	β = 0.365**	R^2 = 0.16
Levin, 1999	Use of gloves	527 nurses and lab workers	B = 0.14*	NS	B = 0.29*	R^2 = 0.74
O'Boyle et al., 2001	Adhere to hand hygiene recommendations	120 registered nurses	β = 0.107*	β = 0.192*	β = 0.076*	R^2 = 0.56
Walker et al., 2001	Prescribe antibiotics for sore throat	127 general practitioners	β = 0.33**	β = 0.36*	β = 0.14	R^2 = 0.48
Meyer, 2002	Seek clinical experiences	92 nursing students	β = 0.48***	β = 0.24***	NS	NA
Ko et al, 2004	Care for SARS patients	750 staff and head nurses	β = 0.25***	NS	β = 0.13***	R^2 = 0.35
Nwokeji, 2007	Prescribing of controlled release opioids	267 family physicians	β = 0.45***	β = 0.21***	β = 0.22***	R^2 = 0.49
Shoham and Gonen, 2008	Work with computers	411 registered nurses	β = 0.30*** β = 0.20***	NA	NA	R^2 = 0.49
Bercher, 2008	Home hazard inspections	202 paramedics	β = 0.66***	β = 0.23***	NS	R^2 = 0.575
Hart and Morris, 2008	Screening for depression after stroke	75 healthcare professionals	r = -0.03 (NS)	r = 0.36**	r = -0.09 (NS)	NA

A-I = Attitude-Intention; SN-I = Subjective norm-Intention; NA = not available, NS = not significant, r = correlation coefficient
*p < 0.05, **p < 0.01, ***p < 0.001, ****significant, p value not reported, Lab = laboratory

In 1996, Millstein published the results of a study that used the TPB to predict the physicians' intention and behavior toward educating their adolescent patients about the transmission of HIV and other STDs (referred to as delivery of preventive services) (Millstein, 1996). Millstein (1996) first tested the TRA model and then added the PBC component to test the TPB. The results showed that A ($\beta = 0.11$, $p < 0.001$), SN ($\beta = 0.21$, $p < 0.001$), and PBC ($\beta = 0.37$, $p < 0.001$) independently and significantly predicted intentions. Taken together, the TPB constructs accounted for 27 percent of the variance in behavioral intention and the overall model was significant ($R = 0.52$, $p < 0.001$). When PBC was entered separately in the regression model after running the TRA variables, the change in R^2 was significant (0.12, $p < 0.001$). The study results show that physicians' perceptions about the extent of control they had over the delivery of preventive services to their adolescent patients was an important predictor of their behavioral intention (Millstein, 1996). The PBC construct significantly improved the explanation of behavioral intention in the study. The authors concluded that the TPB, like the TRA, has relevance for studying HCPs' behaviors (Millstein, 1996). Intention and PBC accounted for 17 percent and 22 percent of the variance in behavior, respectively.

Levin (1999) conducted a study to identify predictors of health care workers' intentions and self-reported use of gloves when there was potential for blood exposure. The authors tested the TRA, TPB and an extension of TPB, which included a perceived risk construct as a predictor of glove use and glove use intention. The authors hypothesized that the TPB extension model would explain more variance in nurses' and medical laboratory workers' use of gloves and would fit the data better than both the TRA and the TPB (Levin, 1999). Most respondents were female (91%), white (78%), married (68%) and worked in a hospital setting (74%). The mean age of respondents was 38.7 years (SD = 9.8 years). The TPB model had a better fit than the other two models in explaining intention. The TPB constructs explained 74 percent of the variance in intention and the TPB extension model constructs explained 73 percent of the variance in

intention. Attitude ($\beta = 0.14$, $p < 0.05$), and PBC ($\beta = 0.29$, $p < 0.05$) independently and significantly predicted the nurses' intentions. Perceived control was the strongest predictor of health care workers' intention to wear gloves and SN was not a significant predictor of intention (Levin, 1999). Behavioral intention accounted for 69 percent of the variance in behavior ($\beta = 0.80$, $p < 0.05$).

O'Boyle and colleagues (2001) conducted a study to test an explanatory model for adherence to hand hygiene guidelines based on the TPB. The authors collected longitudinal observational data from 120 registered nurses working in critical care and post critical care units of four teaching hospitals in the Midwest. Data collection also included observing nurses' hand hygiene performance while they provided patient care. Each nurse was observed twice and observations were conducted between two (2) weeks to four (4) months apart. The study did not provide the respondents' demographic or practice characteristics. The authors ran the TPB model using structural equation modeling. The study results supported the TPB model which explained 56 percent of the variance in nurses' intention to adhere to hand hygiene recommendations. Attitude ($\beta = 0.107$, $p < 0.05$), SN ($\beta = 0.192$, $p < 0.05$) and PBC ($\beta = 0.076$, $p < 0.05$) independently and significantly predicted nurses' intention to adhere to hand hygiene recommendations. Nurses' intentions significantly predicted self-report hand hygiene ($\beta = 0.385$, $p < 0.05$), but not observed hand hygiene ($\beta = 0.068$, $p > 0.05$). The study also found a low and positive association between self-reported and observed hand hygiene scores ($r = 0.20$).

A cross-sectional study was conducted to test the utility of the TPB in predicting the U.K.'s general practitioners' (GPs) intentions to prescribe antibiotics for adult patients presenting with an uncomplicated sore throat (Walker, Grimshaw, & Armstrong, 2001). One hundred and twenty six GPs completed a postal questionnaire in 1998. The respondents were predominantly male (76%) and had been in practice for 10 or more years (88%). Taken together, the three TPB constructs accounted for 48 percent (adjusted $R^2 = 0.46$) of the variance in intention. Using multiple regression analysis, A ($\beta = 0.33$, p

< 0.01), and the control belief scale—indirect perceived control measure (β = 0.36, p < 0.01) were significant predictors of intention, but PBC was not (β = 0.14, p > 0.05). The addition of past behavior accounted for an additional 15 percent of the variance in intention. However, the addition of past behavior to the model made the A construct to be statistically insignificant (β = 0.14, p > 0.05), and made PBC to become statistically significant (β = 0.24, p < 0.05). The study concluded that attitude toward antibiotics and control beliefs were important predictors of intention to prescribe but their importance differed based on past behavior (Walker, Grimshaw, & Armstrong, 2001).

Meyer (2002) used the TPB to predict nursing students' intention to ask for assignments to perform nursing behaviors. The study included 92 nursing students enrolled in an associate degree of science in nursing program at a university in Midwestern United States. The study hypothesized the following: a) nursing students' intentions to ask for assignments to perform nursing behaviors after using a self-report database will be predicted from the combination of attitudes towards the behavior and subjective norms; b) nursing students' intentions to ask for assignments to perform nursing behaviors after using a self-report database will be predicted from attitudes toward the behavior, subjective norms, perceived behavioral control, and underlying beliefs; and c) perceived behavioral control will have a significant effect on nursing students' intentions to ask for assignments to perform nursing behaviors after using a self-report database independent of attitudes and subjective norms. The results of the study supported hypothesis one but not hypotheses two and three. Attitude (β = 0.48, p < 0.05) and SN (β = 0.24, p < 0.05) were significant predictors of intention and PBC (β = 0.08, p = 0.377) was not a significant predictor of intention. PBC's influence on intention was completely mediated by SN and A. However, the control beliefs had a significant and negative effect on intention (β = -0.13, 0 < 0.05).

Ko and colleagues (2004) tested the application of the TPB in predicting nurses' intention and volunteering to care for severe acute respiratory syndrome (SARS) patients

in Southern Taiwan. The authors collected data using a questionnaire from 750 staff and head nurses working in a 1,200 bed hospital. Most of the respondents were female (99.3%), single (63.2%) and less than 35 years of age (mean age = 30.3 years, SD = 6.4 years). Most nurses had a positive attitude towards caring for SARS patients. PBC was measured using three scales: SARS-related knowledge, self-efficacy, and the availability of institutional resources. Four variables significantly predicted intentions, namely A ($\beta = 0.25$, $p < 0.001$), self-efficacy ($\beta = 0.39$, $p < 0.001$), availability of resources ($\beta = 0.13$, $p < 0.001$), and hospital experience ($\beta = -0.15$, $p < 0.001$). These variables explained 35 percent of the variance in intention to care for SARS patients. SARS-related knowledge did not significantly predict intentions ($p > 0.05$). SN did not significantly predict intentions in hierarchical regressions. Demographic variables (e.g., age, years of professional experience, and years of working in the study hospital) independently predicted intention over and above the TPB constructs. Nurses who were novice, younger, and with less professional experience had a more positive intention to care for SARS patients (Ko et al., 2004). Intention predicted 15 percent of the variance in behavior (volunteer to care) ($\beta = 0.31$, $p < 0.05$).

Nwokeji examined Texas family physicians' willingness to prescribe controlled-release opiate analgesics (CR opioids) to patients with moderate to severe chronic non-malignant pain (CNMP) using the TPB (Nwokeji, 2007). A total of 267 family physicians participated in the study. The survey respondents were predominantly male (62.7%), worked primarily in an urban setting (35.8%) and were mostly white/European American (74.3%). Overall, the TPB model explained 49 percent of the variance in Texas family physicians' willingness to prescribe CR opioids for CNMP. All three TPB constructs were significant predictors of physicians' willingness to prescribe: A ($\beta = 0.45$), SN ($\beta = 0.21$), and PBC ($\beta = 0.22$). Attitude was the most significant determinant of physicians' willingness to prescribe. A majority of the physicians ($n = 179$) were willing to prescribe CR opioids for CNMP (Nwokeji, 2007).

The intentions of hospital nurses to work with computers was investigated using an expanded TPB model (Shoham & Gonen, 2008). The dependent variable was the nurse's behavioral intention toward working with computers. Most (60%) of the nurses were less than 40 years old (range: 20-65 years), were staff nurses (72%), had 10 or less years of working experience (62%) and were female (100%). The authors examined the model by running path analysis using Lisrel software. The study results showed that age, participation in a computer course, access to a computer, job and department in which the nurse worked did not directly predict intention. The strongest predictor of behavioral intention was A (nursing: $\beta = 0.30$; and general: $\beta = 0.20$, $p < 0.001$). Nurses had a positive attitude toward use of computers (general attitude: mean = 71.55%, SD = 17.82; nursing attitudes: mean = 67.53, SD = 12.21). The final model which included additional predictor variables (threat, challenge, departmental climate, organizational climate, innovativeness and self-efficacy) explained 49 percent of the variance in behavioral intention. The study did not report the regression coefficients for SN and PBC.

Bercher and colleagues conducted a study utilizing the TPB to determine the attitudes of U.S. paramedics toward performing home hazard inspections as an added everyday task (Bercher, 2008). A total of 202 paramedics from 37 states participated in the study. The average age of the paramedics was 38 years. Most respondents were male (74%), white (94%) and worked in small towns (34%) and for a fire department (42%). Using multiple regression, the study found that attitude toward the behavior ($\beta = 0.66$, $p < 0.001$), and PBC ($\beta = 0.23$, $p < 0.001$) were significant predictors of the intention to perform home injury prevention inspections. The model explained 57.5 percent of the variance in intention. SN was not a significant predictor of intention ($p > 0.05$). The study concluded that paramedics support home injury prevention inspections (Bercher, 2008).

Hart and Morris conducted a TPB-based cross-sectional study to explore factors that facilitate or hinder professionals from screening patients for poststroke depression (Hart & Morris, 2008). A total of 75 U.K. HCPs comprising doctors (10.7%),

psychologists (9.3%), nurses (34.7%), physiotherapists (12.0%) and others (33.3%) completed a postal questionnaire. Most of the respondents were female (86.7%) and worked full time (69.3%). The respondents had favorable attitudes toward screening patients for poststroke depression (mean = 18.57, SD = 2.94; possible range: 3-21) and positive SN (mean = 8.20, SD = 3.25; possible range: 2-14). Direct measures of A ($r = -0.03$, $p > 0.01$) and PBC ($r = -0.09$, $p > 0.01$) did not significantly predict intentions to screen. However, SN ($r = 0.36$, $p < 0.01$), past behavior (screening in the past month) ($r = 0.69$, $p < 0.01$), and screening policy ($r = 0.48$, $p < 0.01$) were significant predictors of screening intention (Hart & Morris, 2008). The study found that the major barriers to screening were time pressure and concerns about screening tests.

The literature search also yielded two studies pertaining to HCPs' reporting behavior (Feng & Wu, 2005; Randall & Gibson, 1991) (Table 3.3).

Table 3.3: Studies Using the TPB to Predict HCPs' Reporting Intentions

Study Author (s), Year	**Behavior**	**Sample**	**Beta Weights for A-I**	**Beta Weights For SN-I**	**Beta Weights For PBC-I**	**Intention**
Randall and Gibson, 1991	Report the healthcare professional	116 nurses	$\beta = 0.67^{***}$	$\beta = 0.22^{***}$	$\beta = 0.05$ (NS)	$R^2 = 0.61$
Feng and Wu, 2005	Report child abuse (severe cases)	1362 registered nurses	$\beta = 0.31^{**}$	$\beta = 0.15^{**}$	$\beta = 0.12^{**}$	$R^2 = 0.91$
Feng and Wu, 2005	Report child abuse (less severe cases)	1362 registered nurses	$\beta = 0.26^{**}$	$\beta = 0.06^{**}$	$\beta = 0.07^{**}$	$R^2 = 0.85$

A-I = Attitude-Intention
SN-I = Subjective norm-Intention
PBC-I = Perceived behavioral control-Intention
NS= not significant
*p < 0.05, **p < 0.01, ***p < 0.001.

Randall and Gibson (1991) conducted a study using the TPB to explain ethical decision making among 116 nurses. Nurses were provided with scenarios that depicted inadequate patient care and asked if they would report the health professionals responsible for the situation. Using regression analysis, the authors found that A (β = 0.67, $p < 0.001$), and SN (β = 0.22, $p < 0.001$) were significant predictors of intention while PBC was not a significant predictor (β = 0.05, p = 0.41). Overall, the TPB constructs explained 61 percent of the variance in intention to report the healthcare professional. In addition, the study found that nurses were less likely to report a mistake (52%) than incompetence (72%) (p = 0.002).

Feng and Wu (2005) conducted a study to identify the main predictors of nurses' intention to report suspected child abuse in Taiwan using an extended TPB model which added a knowledge construct (Feng & Wu, 2005). The authors ran separate models for severe and also for less severe cases. A total of 1,362 nurses working in 39 hospitals and involved in caring for children, participated in the study. A majority of respondents were female (98.7%), unmarried (62.7%), and childless (70.4%) and had a mean age of 30.5 (SD = 6.01) years. All three TPB constructs significantly predicted intention to report severe as well as less severe cases. In addition to the TPB constructs, the authors found that knowledge independently predicted intention (β = 0.71, $p < 0.01$) and was the strongest predictor of intention in the model (Table 3.4).

Table 3.4: Predictors of Intention to Report Child Abuse (n = 1,362)

Predictors of Intention to Report Suspected Child Abuse	**Models**	
	Severe (β)	**Less severe (β)**
Knowledge	0.71	0.71
Subjective norm	0.15	0.06
Attitude	0.31	0.26
Perceived behavioral control	0.12	0.07

All predictors were significant ($p < 0.01$).
Source: Feng and Wu (2005), p. 344.

SN and PBC were stronger predictors of intention to report child abuse in severe cases than in the less severe cases of child abuse. Nurses found it more socially acceptable to report severe child abuse cases than less severe cases. The extended TPB model explained 91 percent and 85 percent of the variance in intention to report severe and less severe cases, respectively. The authors noted that most nurses did not perceive themselves to have strong control over reporting suspected child abuse; reporting child abuse was not mostly up to them (Feng & Wu, 2005).

In all three cases that investigated reporting behavior, attitude was a stronger predictor of intentions than both SN and PBC. In addition, SN was significant in all three cases. Interestingly, the three models explained high variance in behavioral intentions (range: 61% - 91%).

In addition to the above mentioned studies, the literature search yielded five studies that used the TPB in studying pharmacists' behavior (Table 3.5).

Table 3.5: Studies Using the TPB to Predict Pharmacists' Intentions

Study Author (s), Year	**Behavior**	**Sample (N)**	**Correlation Coefficient (r)/ Beta Weights for A-I**	**Correlation Coefficient (r)/ Beta Weights For SN-I**	**Correlation Coefficient (r)/ Beta Weights For PBC-I**	**Intention**
Mashburn et al., 2003	Provide sterile syringes to intravenous drug users	135 Texas community pharmacists	$\beta = 0.658^{**}$	$\beta = 0.200^{***}$	NS	$R^2 = 0.74$
Walker et al., 2004	Treatment of vaginal candidiasis with non-prescription medicines	76 Scottish community pharmacists	$\beta = 0.28^{*}$	NS	NS	$R^2 = 0.19$
Herbert et al. 2006	Provide Medicare medication therapy management services	203 Iowa pharmacists	$\beta = 0.19^{**}$	$\beta = 0.41^{***}$	$\beta = 0.27^{***}$	$R^2 = 0.63^{+}$
Pradel et al., 2007	Pediatric asthma counseling	98 Maryland community pharmacists	$r = 0.37^{*}$	$r = 0.33^{*}$	$r = 0.51^{*}$	NA
Saengcharoen et al., 2008	Dispensing of antibiotics for upper respiratory infections	656 Thai community pharmacists	$\beta = 0.89^{*}$	$\beta = 0.07^{*}$	$\beta = 0.03$ (NS)	NA

A-I = Attitude-Intention; SN-I= Subjective norm-Intention; PBC-I = Perceived behavioral control-Intention

$^{+}$adjusted R^2; NS = Not significant

$^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$, NA = not available.

Mashburn and colleagues (2003) conducted a study to examine the factors predicting Texas community pharmacists' willingness to provide sterile syringes to known or suspected intravenous drug users (IDUs). The study used the TPB constructs (A, SN and PBC) and recent past behavior (RPB) to predict pharmacists' willingness to provide sterile syringes. A total of 176 Texas community pharmacists participated in the study. The average age of the respondents was 48.6 years (SD = 12.46, range: 26-78 years). Most (59.5%) respondents were male, Caucasians (79.7%), and staff pharmacists (44.4%), and worked in chain pharmacies mainly in urban or suburban areas (78.9%). The study found that most respondents were not willing to provide sterile syringes to known or suspected IDUs. Study participants held negative attitudes toward the provision of sterile syringes and perceived themselves as having some control over the provision of sterile syringes. The study results supported the TPB model. The study results showed that A ($\beta = 0.66$, $p = 0.001$) and subjective norm ($\beta = 0.20$, $p = 0.001$) were significant predictors of willingness. PBC was not a significant predictor of willingness ($\beta = 0.08$, $p = 0.133$).

Walker and colleagues (2004) applied the TPB to examine Scottish community pharmacists' attitudes, beliefs and intentions to supply non-prescription antifungals for the treatment of vulvovaginal candidiasis. A majority of respondents were female (64.5%), and employee pharmacists (58%) and worked full time (83%). The study results showed that pharmacists had a positive attitude (2, range: 0 - 3; measured on the scale -3 to +3), negative subjective norm (-2, range: -3 to +3), and positive PBC (2, range: -3 to +3). Only A significantly predicted behavioral intention ($\beta = 0.28$, $p < 0.05$). The regression weights for SN and PBC were not reported in the study. The TPB constructs explained 19 percent of the variance in behavioral intention (Walker et al., 2004).

Using the TPB, Herbert and colleagues (2006) published a study that predicted the behavioral intention of Iowa community pharmacists to provide Medicare medication therapy management services (MTMS). A majority of pharmacists were male (57.6%),

worked for independent pharmacies (50.2%), and had 21 or more years of experience (51.3%). Multivariate linear regression analysis showed that all the TPB constructs independently and significantly predicted the intent ($p < 0.05$). SN was the strongest predictor of intent ($\beta = 0.41$, $p < 0.001$), followed by PBC ($\beta = 0.27$, $p < 0.001$) and attitude ($\beta = 0.19$, $p = 0.002$). Pharmacists faced substantial barriers in implementing MTMS such as lack of support staff, computer support and time. The independent variables in the model accounted for 63.2 percent of the variation in intent (Herbert, Urmie, Newland, & Farris, 2006).

A cross-sectional study was conducted to explore the factors that influence community pharmacists' pediatric asthma counseling in Maryland from September 2002 through March 2003 (Pradel, Obeidat, & Tsoukleris, 2007). A mail survey was sent to 399 community pharmacists and 98 responded for a 25 percent response rate. Most respondents reported that it was important to provide asthma counseling to children (54%) or caregivers (68%), although only a few reported counseling the children (27%) or the parent (47%). Lack of time, lack of parent's interest, and lack of placebo devices useful for demonstrating the inhalation technique were some of the barriers to counseling that were cited by pharmacists. Intention to counsel significantly predicted the provision of counseling to children or caregivers ($p < 0.05$). Attitude ($r = 0.37$, $p < 0.05$), subjective norm ($r = 0.33$, $p < 0.05$), and perceived difficulty ($r = 0.51$, $p < 0.05$) were significantly correlated with intention (Pradel, Obeidat, & Tsoukleris, 2007). The study did not provide the variance in intention and behavior that was explained by the model.

Saengcharoen and colleagues (2008) studied the factors influencing dispensing of antibiotics for upper respiratory infections (URI) among Southern Thai community pharmacists. In Thailand, practicing pharmacists can legally dispense antibiotics without a prescription. Most of the 656 respondents were female (59.6%), and young (age range: 30-39 years, 54.8%), and had less than 10 years working experience (Saengcharoen et al., 2008). Most pharmacists had an unfavorable attitude toward antibiotics use for URI

(mean = 2.61, SD = 2.00) and did not intend to dispense antibiotics (mean = 2.35, SD = 1.85). Using structural equation modeling (SEM) to run the TPB model, the study found that attitude ($\beta = 0.89$, $p < 0.05$) and subjective norm ($\beta = 0.07$, $p < 0.05$) were significant predictors of intention. PBC ($\beta = 0.03$, $p > 0.05$) did not significantly predict intention to dispense antibiotics without a prescription. The authors suggested that the weak influence of subjective norm on intention to dispense antibiotics may be explained by the low professional interaction between pharmacists (Saengcharoen et al., 2008). The variance in intention and behavior that was explained by the model was not reported in the study. The final model had acceptable fit statistics [root mean square error of approximation (RMSEA) = 0.054, standardized root mean square residual (SRMR) = 0.056, Tucker-Lewis Index (TLI) = 0.97 and comparative fit index (CFI) = 0.98].

3.3.1 Other Predictors of Intention

Other constructs have been added to the TPB model in research studies. The additional constructs that have been found to increase the predictive power of the TPB model include past behavior (Sheeran, Norman and Armitage, 2000)(Hart & Morris, 2008), self-efficacy (Armitage & Conner, 1999; Ko et al., 2004), demographic factors, practice factors (Coleman, 2003; Fried, DeVore, & Dailey, 2001; Hart & Morris, 2008; Ko et al., 2004; Shoham & Gonen, 2008) and perceived moral obligation (Randall & Gibson, 1991; Werner & Mendelsson, 2001). The role of demographic and practice factors, past behavior and perceived moral obligation will be explored further owing to their potential relevance to this study.

3.3.1.1 Past Reporting Behavior

Past behavior (PB), the frequency with which a behavior has been performed in the past, is a good predictor of future action (Ajzen, 2002b). According to the TRA and

TPB, the effect of prior behavior on future behavior is fully mediated by intention and PBC. However, empirical research has found that the relationship between prior and future behavior is not fully mediated by the TRA and TPB constructs (Ajzen, 1991; Albarracin et al., 2001; Bagozzi, 1981). In previous studies, the addition of PB improved the prediction of behavioral intentions over and above the TRA and TPB constructs (Herbert et al., 2006; Leone, Perugini, & Ercolani, 1999; Mashburn et al., 2003; Millstein, 1996; Nwokeji, 2007; Quine & Rubin, 1997; Schaalma, Kok, & Peters, 1993; Walker, Grimshaw, & Armstrong, 2001). For example, in a study of Texas family physicians' willingness to prescribe long-acting opioid analgesics for patients with chronic nonmalignant pain, Nwokeji (2007) found that the addition of recent past behavior (RPB) to the TPB model significantly increased the explanatory power from 49 percent to 58 percent (R^2 change = 0.09). RPB was the strongest predictor of intention in the final model ($\beta = 0.38$, $p < 0.001$). Millstein (1996) found that PB was the single best predictor of future behavior of physicians ($R^2 = 0.42$, $p < 0.001$). Mashburn also found that RPB contributed significantly to the prediction of Texas community pharmacists' willingness to provide sterile syringes to intravenous drug users (Mashburn et al., 2003). The PB construct is important in predicting intentions and behaviors and warrants consideration in studies of HCPs including pharmacists.

Nwokeji (2007) found that the inclusion of RPB resulted in a reduction in the regression weights of A ($\beta = 0.33$), SN ($\beta = 0.16$), and PBC ($\beta = 0.13$) compared to A ($\beta = 0.45$), SN ($\beta = 0.21$), and PBC ($\beta = 0.22$) prior to adding RPB. In another study, the addition of past behavior to the model resulted in the attitude construct becoming statistically insignificant ($\beta = 0.14$, $p > 0.05$), and the PBC ($\beta = 0.24$, $p < 0.05$) becoming statistically significant (Walker, Grimshaw, & Armstrong, 2001). The addition of PB was associated with a lessened effect of intentions on behavior (Bagozzi, 1981). PB was also reported to be correlated with PBC and to influence individuals' beliefs about their control over a situation (Albarracin & Wyer, 2000; Sutton, McVey, & Glanz, 1999).

However, not all studies in the literature support this important role of past behavior in predicting intentions (Herbert et al., 2006). For example, Herbert and colleagues (2006) found that past participation in care-based services did not significantly predict pharmacists' intention to provide Medicare MTMS ($\beta = 0.21$, $p = 0.061$). These results may be explained by the way past participation was operationalized in the study. The article did not provide details on how past participation was operationalized in the study (Herbert et al., 2006).

3.3.1.2 Demographic and Practice Factors

According to the TRA and TPB, demographic factors (age, gender, education, working experience among others) are postulated to have no direct influence on intention and behavior (Sutton, McVey, & Glanz, 1999). These are said to influence attitude, subjective norm and PBC (Ajzen, 1991). In many studies on HCPs, demographic and practice factors did not independently and directly predict intentions (Herbert et al., 2006; Sable et al., 2006; Shoham & Gonen, 2008; Werner & Mendelsson, 2001). In Shoham and Gonen's (2008) study, age, job and department in which the nurse worked did not directly predict intention to work with computers. In another study, the pharmacists' gender, years of practice, practice setting and degree did not significantly predict intentions ($p > 0.05$) (Herbert et al., 2006).

However, in Coleman's (2003) study, three demographic and organizational variables were significant predictors of discussion: prescriptions written per day ($\beta = -0.169$, $p = 0.001$), hours worked per day ($\beta = 0.116$, $p = 0.023$) and working in a non-chain pharmacy ($\beta = 0.139$, $p = 0.011$). In another study, demographic variables (e.g., age, years of professional experience, years of working in the study hospital) independently predicted intention over and above the TPB constructs; nurses who were novice, younger, and with less professional experience had a more positive intention to

care for SARS patients (Ko et al., 2004). Also hours of employment significantly predicted self-assessment among Maryland Dental Hygienists (Fried, DeVore, & Dailey, 2001).

An important practice factor is knowledge about reporting ADEs. Feng and Wu (2005) found that knowledge was the strongest predictor of Taiwanese nurses' intentions to report child abuse. However, Sable and colleagues (2006) found that knowledge (score on a knowledge quiz) did not independently predict emergency contraception prescribing intentions. Coleman and Ko and colleagues also reported that knowledge did not significantly predict intentions ($p > 0.05$) (Coleman, 2003; Ko et al., 2004).

Although there are conflicting results on the role and effect of demographic and practice factors on intention and behavior, gender, ethnicity, knowledge, years in practice (experience), hours worked per day and primary practice setting merit further consideration.

3.3.1.3 Perceived Moral Obligation

The addition of a perceived moral obligation (PMO) construct to the TPB significantly increased the prediction of intentions (Gorsuch & Ortberg, 1983; Randall & Gibson, 1991; Werner & Mendelsson, 2001). The key features of moral situations are: a) importance—the choice and its consequences is viewed by the person as being significant and not trivial; b) immunity from deliberate change; and c) form of moral pressure—appeals to respect the rules as important in themselves (Hart, 1961). The importance of PMO has been reported to vary by situation. The PMO construct is a strong predictor in morally relevant situations and is not a strong predictor of intentions in nonmoral situations and vice-versa (Gorsuch & Ortberg, 1983). For example, PMO was reported to be a stronger predictor of intentions than A and SN in moral situations (Gorsuch & Ortberg, 1983; Schwartz & Tessler, 1972).

Summary and Review of the Studies

The above studies confirm the effectiveness of the TPB in predicting HCPs' intentions. The TPB model explained a wide range of HCPs' behaviors including delivering preventive services, using gloves, adhering to hand hygiene recommendations, reporting child abuse, and working with computers among others. The TPB's constructs—attitude, subjective norm, and perceived behavioral control—are good predictors of HCPs' behavioral intentions. The relative contributions of each of the constructs varied by behavior, study population and situation. As observed by Godin and Kok (1996), overall, the TPB was found to be a good framework to explain and predict intentions of HCPs' behaviors. The variance in intention accounted for by the models ranged from 16 percent to 91 percent across the studies.

A was the strongest predictor of behavioral intentions in most (n = 11) (Bercher, 2008; Feng & Wu, 2005; Ko et al., 2004; Mashburn et al., 2003; Meyer, 2002; Nwokeji, 2007; Randall & Gibson, 1991; Saengcharoen et al., 2008; Shoham & Gonen, 2008; Walker et al., 2004) of the TPB studies reviewed (n = 19). Note: Feng and Wu (2005) reported two studies. Most of these studies were on behaviors that are performed in private and which did not significantly involve or impact others. This is similar to Quine and Rubin (1997) who found that A is more important than normative beliefs in cases where the behavior is performed in private.

SN was the strongest predictor in four studies (Hart & Morris, 2008; Herbert et al., 2006; O'Boyle, Henly, & Larson, 2001; Walker, Grimshaw, & Armstrong, 2001). In these studies, the behavior involved or impacted others. SN was statistically significant in all the studies (n = 13) that reported the regression weights or correlation coefficients (r).

In the studies reviewed, PBC added significantly to the explanation and prediction of intention of most studies (n = 10). The addition of PBC improved prediction of intention, thus confirming that the PBC construct is an important construct for explaining

intention of HCPs. PBC was the strongest predictor in three studies (Levin, 1999; Millstein, 1996; Pradel, Obeidat, & Tsoukleris, 2007) (see Tables 3.2, 3.3, 3.5).

Given the usefulness of the TPB in explaining HCPs' (including pharmacists') decision making processes, the TPB may be useful for predicting pharmacists' intentions to report serious ADEs. There is a need for more research to examine the healthcare providers' (pharmacists) decision-making processes to better predict ADE reporting intentions and behaviors.

3.5 OBJECTIVES OF THE STUDY

The aim of the study is to use the TPB to better understand the factors related to pharmacists' reporting of serious ADEs in Texas.

The objectives of the study are to:

1. Identify pharmacists' beliefs concerning reporting of serious ADEs;
2. Explore the utility of the TPB model constructs (A, SN, PBC) in predicting pharmacists' intention to report serious ADEs;
3. Determine the contribution of the PBC construct to the prediction of pharmacists' intention to report serious ADEs beyond A and SN constructs;
4. Determine if the past reporting behavior (PRB) construct contributes toward the prediction of pharmacists' intention to report serious ADEs over and above the TPB constructs;
5. Determine if PMO significantly increases the explanatory power of the regression model compared to only using the A + SN + PBC to explain pharmacists' intention to report serious ADEs;
6. Determine if the pharmacists' A, SN or PBC toward reporting serious ADEs differs by practice characteristics and demographic factors; and

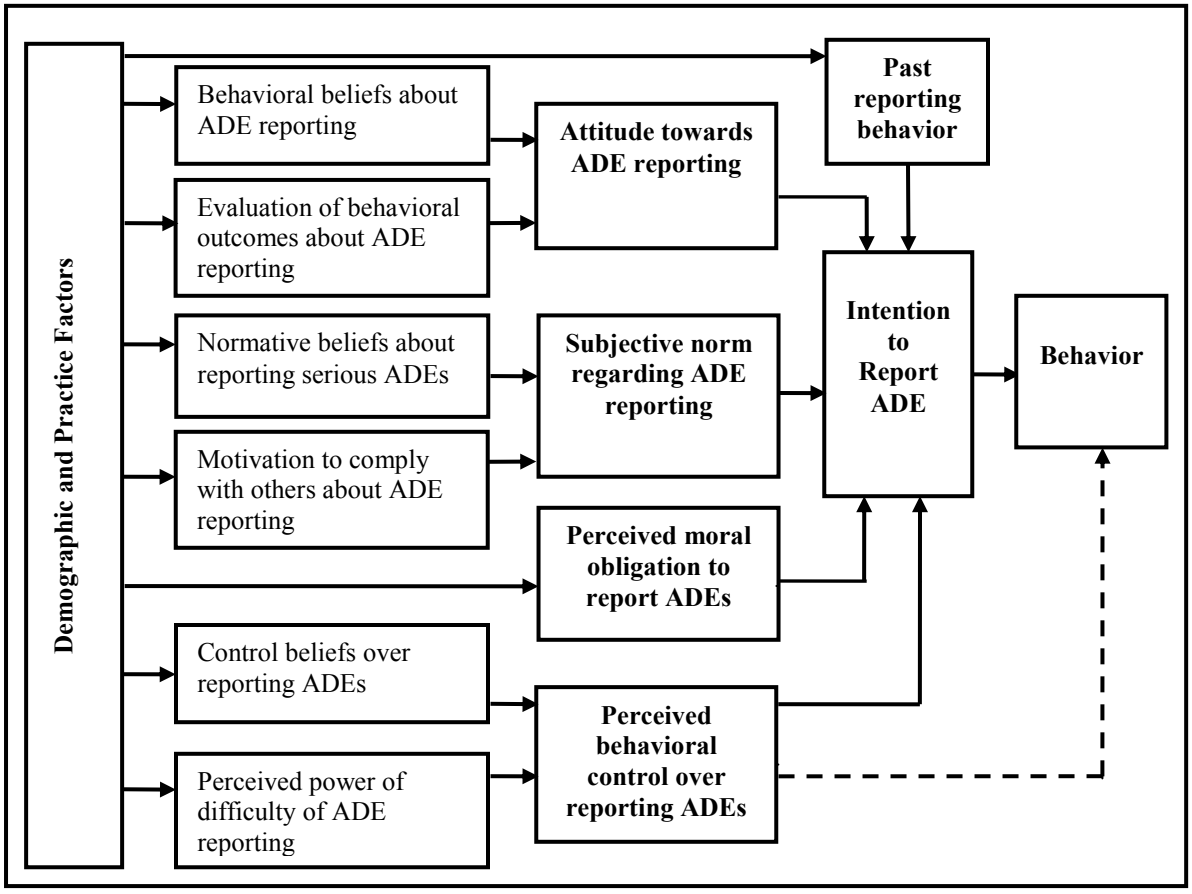
7. Recommend strategies for increasing the reporting rates of serious ADEs by Texas pharmacists.

3.6 THEORETICAL FRAMEWORK

A theoretical model will be employed to examine and predict pharmacists' intention to report serious ADEs. The TRA and TPB have been used extensively and successfully in the past to explain and predict healthcare professionals' intentions and behaviors. Many of the behaviors are not under the healthcare professional's complete volitional control. An accurate prediction of intentions requires an assessment of the extent to which the healthcare professional can exercise control over the behavior in question. This can be achieved by adding the PBC to the TRA. Thus, the TPB will be used to predict pharmacists' intention to report serious ADEs.

In addition to the three key TPB constructs (A, SN, and PBC), the study model includes three additional variables (1. PMO, 2. PRB and 3. demographic and practice factors) (Figure 3.3). Past behavior was found to help improve the ability to predict many health-related intentions and behaviors (Burak 1994, Leone, Perugin and Ercolani 1999, Sheeran, Norman and Armitage 2000). Similarly, PMO was also found to independently increase the variance in intention that is explained (Randall & Gibson, 1991; Werner & Mendelsson, 2001). Finally, a number of demographic and practice variables (gender, age, workload, knowledge and years of experience) have been found to independently predict HCPs' intentions (Coleman, 2003; Ko et al., 2004; Yedidia, Berry, & Barr, 1996).

Figure 3.3: The Conceptual Model of the Study



This study model postulates that pharmacists should intend to report serious ADEs if they have positive attitudes toward ADE reporting, are motivated to comply with referent others perceived as supporting the behavior, have reported serious ADEs in the past, consider themselves to be morally obliged to report serious ADEs and are able (through resources, knowledge and opportunity) to carry out the behavior.

3.7 STUDY HYPOTHESES

H1: Favorable attitude (A) is a positive and significant predictor of intention to report serious ADEs controlling for SN and PBC.

H2: SN supporting ADE reporting is a positive and significant predictor of intention to report serious ADEs controlling for A and PBC.

H3: Strong PBC is a positive and significant predictor of intention to report serious ADEs controlling for A and SN.

H4: A + SN + PBC constructs explain a significant amount of variance in pharmacists' intention to report serious ADEs.

H5: PBC significantly increases the explanatory power of the regression model compared to only using A + SN to explain pharmacists' intention.

H6: PRB significantly increases the explanatory power of the regression model compared to only using the A + SN + PBC to explain pharmacists' intention to report serious ADEs.

H7: PMO significantly increases the explanatory power of the regression model compared to only using the A + SN + PBC to explain pharmacists' intention to report serious ADEs.

$H_0$8: There is no significant difference in A to report serious ADEs by gender.

$H_0$9: There is no significant difference in SN regarding reporting serious ADEs by gender.

$H_0$10: There is no significant difference in PBC over reporting serious ADEs by gender.

$H_0$11: There is no significant relationship between A to report serious ADEs and pharmacists' years of experience.

$H_0$12: There is no significant relationship between SN to report serious ADEs and pharmacists' years of experience.

$H_0$13: There is no significant relationship between PBC to report serious ADEs and pharmacists' years of experience.

$H_0$14. There is no significant difference in A toward ADE reporting by pharmacists' primary setting (community-independent, community-multiple/chain, hospital-independent, hospital-multiple/chain, other).

$H_0$15: There is no significant difference in SN regarding ADE reporting by pharmacists' primary setting (community-independent, community-multiple/chain, hospital-independent, hospital-multiple/chain, other).

$H_0$16: There is no significant difference in PBC over ADE reporting by pharmacists' primary setting (community-independent, community-multiple/chain, hospital-independent, hospital-multiple/chain, other).

$H_0$17. There is no significant relationship between the pharmacists' number of hours worked and A toward ADE reporting.

$H_0$18: There is no significant relationship between the pharmacists' number of hours worked and SN regarding ADE reporting.

$H_0$19: There is no significant relationship between the pharmacists' number of hours worked and PBC over ADE reporting.

$H_0$20: There is no significant difference in A toward reporting serious ADEs by the pharmacists' race/ethnicity.

$H_0$21: There is no significant difference in SN regarding reporting serious ADEs by the pharmacists' race/ethnicity.

$H_0$22: There is no significant difference in PBC over reporting serious ADEs by the pharmacists' race/ethnicity.

$H_0$23. There is no significant relationship between the pharmacists' knowledge of ADE reporting and A toward ADE reporting.

$H_0$24: There is no significant relationship between the pharmacists' knowledge of ADE reporting and SN regarding ADE reporting.

$H_0$25: There is no significant relationship between the pharmacists' knowledge of ADE reporting and PBC over ADE reporting.

CHAPTER FOUR: RESEARCH METHODOLOGY

4.1 STUDY DESIGN

This study utilized a nonexperimental cross-sectional design and employed a self-report mail data collection survey instrument. A mail survey was chosen over telephone and face-to-face interviews for various reasons. A mail survey is anonymous, convenient, requires the least amount of resources, is less sensitive to interviewer biases, and does not require immediate and rushed decision-making from the respondents (Nakash, Hutton, Jorstad-Stein, Gates, & Lamb, 2006; Salant & Dillman, 1994). In addition, a mail questionnaire is able to reach a widely dispersed sample (Diamantopoulos, Schlegelmilch, & Webb, 1991). These advantages make it a very attractive data collection technique in pharmacy research.

The study data were analyzed primarily using multiple regression. The analyses statistically estimated the regression coefficients associated with the study variables in the model.

4.2 SAMPLE FRAME

This study's population of interest is all (active) Texas pharmacists. Texas pharmacists, like all other pharmacists, can report serious adverse drug events (ADEs) that they encounter to the FDA. The study used the current list of registered pharmacists in the state of Texas provided by the Texas State Board of Pharmacy (TSBP). The list comprises the name, license status (e.g., active), sex, race, and primary employment of all Texas pharmacists. The TSBP list had 25,177 registered pharmacists as of April 30th, 2009.

4.2.1 Inclusion and Exclusion Criteria

Pharmacists who were currently active had a realistic chance of being familiar with ADE reporting. Only active Texas pharmacists were included in the study. It was assumed that pharmacists who had an opportunity to contact patients (e.g., involved in direct patient care) were familiar enough with ADEs to form an impression of ADE reporting. As a result, only pharmacists working in community (government, independent and multiple/chain) and hospital (government and non-government) pharmacies were included in the study. Included pharmacists were not required to have reported ADEs in the past. Only pharmacists who were resident in the state of Texas were included. All non-active Texas pharmacists and those residing or practicing in other states were excluded from this study.

4.2.2 IRB Procedures

Two applications were sent to and approved by The University of Texas at Austin's Institutional Review Board (IRB) for this project. The first part of the study (focus groups) received expedited IRB approval and the second part comprising the mail survey received exempt approval.

4.3 SAMPLE SIZE DETERMINATION

Sample size determination is the a priori mathematical process of determining the number of subjects to be studied (Last, 1995). Determination of the sample size is a critical step of study design. To determine the sample size needed to meet the goals of the study, an a priori power estimation was conducted using G*Power version 3.0.10 software (Erdfelder, Faul, & Buchner, 1996). The software calculated the a priori sample size (N) based on the provided significance level (α), power level ($1-\beta$), number of predictors and the estimated (to-be-detected) population effect size. The effect size for

this study was estimated by a computed average of all the effect sizes from the studies that used the TPB to investigate the intentions of healthcare professionals (HCPs). An average of 14 studies' effect sizes in predicting intention was calculated [(0.27 + 0.15 + 0.74 + 0.56 + 0.35 + 0.49 + 0.49 + 0.58 + 0.61 + 0.91 +0.85 + 0.74 + 0.19 + 0.63)/14 = 0.54] and was used as the estimate of the population effect size. With respect to the regression model, the effect size of 0.54 means that the independent variables in the model explained 54 percent of the variability in the dependent variable (mostly intention). The value of R-squared lies between zero (0) and one (1). The alpha level of significance for all statistical tests was set at $\alpha = 0.05$, the statistical analyses' power was set at 0.80 and the number of predictors was set at five (5). The G*power software determined that the total sample size for the study should be 56.

At least 10 subjects are required per predictor variable in multiple regression analysis (Elliott & Woodward, 2007). Given that the study had five predictor variables (attitude, subjective norm, perceived behavioral control, perceived moral obligation and past behavior), a minimum of 50 subjects was needed. This was achieved by the calculated sample size of 56.

Low response rates are a challenge in mail surveys among HCPs (Nakash et al., 2006; Sibbald, Addingtonhall, Brenneman, & Freeling, 1994). Low response rates, especially in the cases where respondents and non responders differ with respect to the outcome under study, reduce the validity of the study, the representativeness of the sample (introduce bias) and the effective sample sizes (Armstrong, White, & Saracci, 1995; Nakash et al., 2006; Schulz & Grimes, 2002). The major factors influencing response to mail surveys among HCPs include increased paper work, type of population surveyed, investigating agency, questionnaire length, lack of interest in the study area and lack of time (Armstrong & Ashworth, 2000; Ashworth, 2001; Goyder, 1982; Heberlein & Baumgartner, 1978; Sibbald et al., 1994). Different response rates were obtained from studies involving HCPs. For example, a mean response rate of 61 percent was reported by

a review of published studies among doctors (Sibbald et al., 1994) and prescription event monitoring studies found average response rates of 50 to 70 percent (Mann, 2000).

Many pharmacists do not respond to mail surveys. Studies of pharmacists using the mail survey found response rates ranging from 46 to 89 percent (Katz, Draugalis, & Lai, 1995; Wright-De Aguero, Weinstein, Jones, & Miles, 1998). Several studies have used mail surveys among Texas pharmacists and obtained varied response rates (Brown, 1998; Brown, Barner, & Shah, 2005; Brown, Cantu, Corbell, & Roberts, 2007; Griggs & Brown, 2007; Mashburn et al., 2003; O'Donnell, Brown, & Dastani, 2006; Olson & Lawson, 1996) (see Table 4.1). These studies' response rates provide an indication of this study's expected response rate. Considering that response rates obtained by two of these studies seem to be outliers (Griggs & Brown, 2007; Olson & Lawson, 1996), this study used a median of these seven studies' response rates of 36 percent.

Table 4.1: Response Rates Achieved in Studies Involving Pharmacists in Texas

Author and Year	**Topic**	**Response Rates (%)**
Olson and Lawson, 1996	Relationship between hospital pharmacists' job satisfaction and involvement in clinical activities.	58.4
Brown, 1998	Use of alternative therapies and their impact on compliance: perceptions of community pharmacists in Texas.	39.6
Mashburn, Brown, Shepherd, Wilson, Barner and Marxwell, 2003	Using the theory of planned behavior to predict Texas community pharmacists' willingness to provide sterile syringes to known or suspected intravenous drug users.	35.1
Brown, Barner and Shah, 2005.	Community pharmacists' actions when patients use complementary and alternative therapies with medications.	27.0
O'Donnell, Brown and Dastani, 2006	Barriers to counseling patients with obesity: A study of Texas community pharmacists.	35.2
Brown, Cantu, Corbell and Roberts, 2007	Attitudes and interests of pharmacists regarding independent pharmacy ownership.	36.0
Griggs and Brown, 2007	Texas community pharmacists' willingness to participate in pharmacist-initiated emergency contraception.	51.0

The sample size was adjusted to take into consideration the low response rates. The adjusted sample size was calculated as the ratio of the number of responses needed and the expected response rate.

Adjusted sample size = number of responses needed / expected response rate

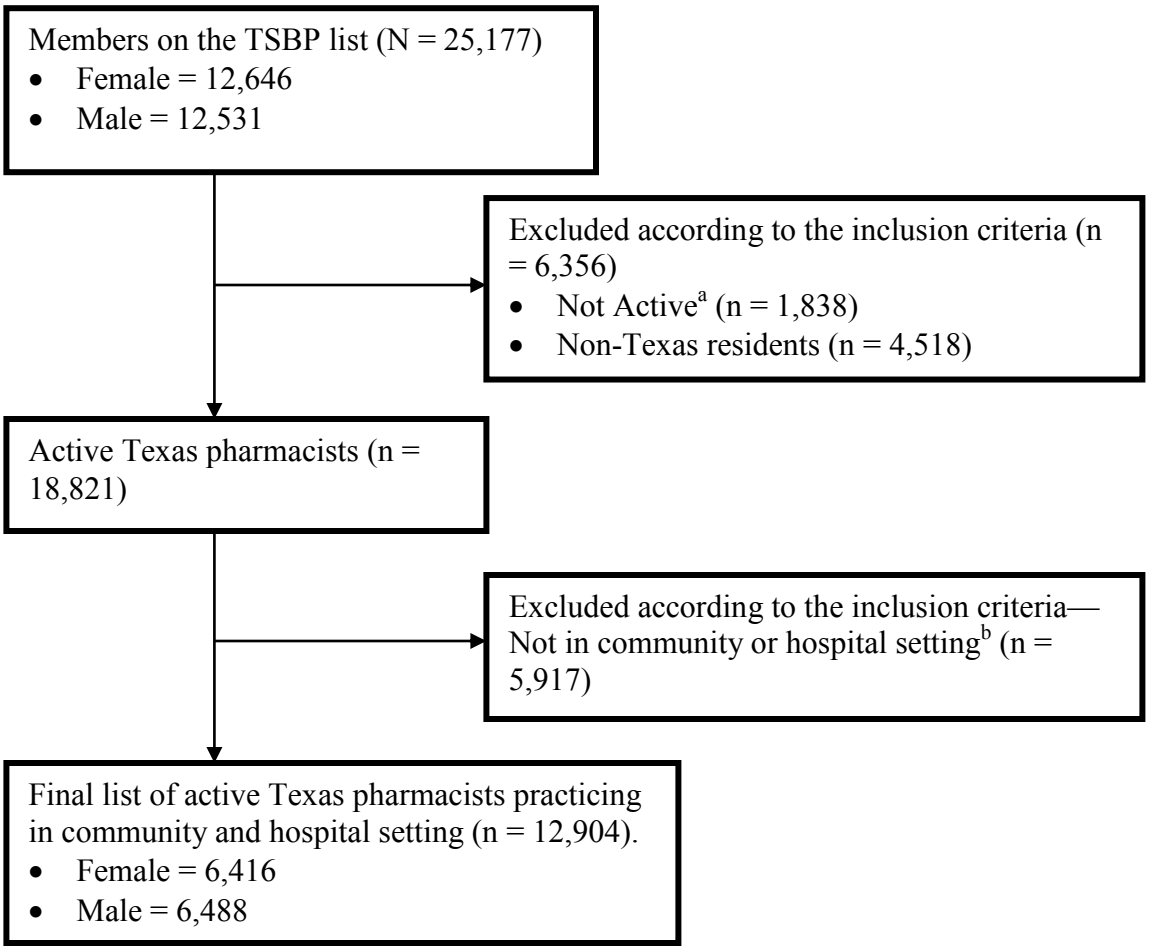
The adjusted sample size was calculated to be 56/0.36, N = 156. Thus, at least 200 questionnaires were to be distributed to achieve 56 responses. This adjusted sample size is meant to accommodate for anticipated missing data and unreturned questionnaires. Given that we had resources for a larger sample and to counter for an unexpected low response rate, we increased the sample size to 1,500.

4.4 SAMPLING

The TSBP list had a total of 25,177 names. The flow chart below shows the numbers of pharmacists who were excluded from the study and the reasons for their exclusion (Figure 4.1). The Statistical Package for the Social Sciences software was used to select the sample from the TSBP list. From 12,904 active Texas pharmacists practicing in community and hospital settings, 1,500 pharmacists (potential participants) were selected through simple random sampling[6]. A majority of the 1,500 pharmacists were female (n = 772, 51.5%), and worked in the community setting (n = 1,043, 69.5%). A total of 1,500 survey packets were mailed out.

6 Prior to sampling, the TSBP list was sorted alphabetically using first names of the members. This was done in order to eliminate systematic ordering by year of licensure. The original TSBP list was sorted according to the license number of the members.

Figure 4.1: Flowchart of Pharmacist/Respondent Selection



[a] Applicant (n = 30), delinquent (n = 286), inactive (n = 1343), probation (n = 125), restricted (n = 9), retired (n = 8), revoked (n = 21), surrendered (n = 3), and suspended (n = 13).
[b] Comprised of those serving in armed services, HMO, home health, mail service, manufacturer or wholesaler, nuclear, other, sterile pharmaceutical (n = 3,637) and unknown (n = 2,280).

4.5 Independent and Dependent Variables

The dependent variable for the study is the pharmacists' intention to report serious ADEs. For this study, intention to report serious ADEs was defined as the degree of likelihood to report serious ADEs to the FDA through the MedWatch program. The independent variables are attitude (A), perceived behavioral control (PBC), subjective

norm (SN), past reporting behavior (PRB), perceived moral obligation (PMO) and demographic and practice factors (Table 4.2). PRB and PMO were included in the model as direct predictors of intention. These are defined below.

Table 4.2: Definitions of the Independent Variables

Independent Variable	**Definition**
Attitude toward reporting serious ADEs	The degree of positive or negative value placed on reporting serious ADEs by pharmacists.
Perceived behavioral control over reporting serious ADEs	The perceived ease or difficulty of reporting serious ADEs and confidence in the ability to implement the reporting plans.
Subjective norm	Pharmacists' perception of social pressure to report serious ADEs.
Perceived moral obligation	An individual's self assessment of the level of moral obligation to report serious ADEs.
Past reporting behavior	The frequency with which ADE reporting (the behavior) has been performed in the past.
Demographic and practice factors	The personal factors and practice characteristics of the pharmacists.

4.6 STUDY INSTRUMENT DEVELOPMENT

The study instrument was developed in two stages. The first stage involved conducting qualitative studies with a convenience sample of Texas pharmacists. A total of 13 pharmacists participated in two (2) different focus group discussions to share their views and experiences with ADE reporting. In the second stage, the instrument to measure pharmacists' attitudes, subjective norm, perceived behavioral control, past reporting behavior, perceived moral obligation and intention to report serious ADEs was developed, pilot tested and administered to a sample of pharmacists. The survey instrument has 94 items (see Appendix B).

4.6.1 Focus Groups Discussions

In line with Ajzen and Fishbein (1980), preliminary/elicitation studies or focus groups were conducted to identify behavioral, perceived control and normative beliefs. Two focus groups were held in Austin. During the elicitation studies, the researcher conducted audiotaped interviews with a convenience sample of practicing Texas pharmacists. The first focus group was attended by Texas pharmacists attending graduate school at The University of Texas at Austin. The Capital Area Pharmacists' Association (CAPA) leadership helped to recruit members to participate in the second focus group. Each focus group had the minimum of 6-8 volunteers recommended in the literature (Patton 1990, Fowler 1993). The second focus group participants were given a $25.00 gift card for participating. All potential focus group participants were informed of the time, date and location of the focus group through a letter (see Appendix C). They were also sent e-mail reminders the night before the meetings. All focus group participants signed an informed consent form (see Appendix D).

The focus group was conducted to: a) determine the advantages and disadvantages of reporting serious ADEs by pharmacists; b) identify the individuals and groups who would approve or would not approve pharmacists reporting serious ADEs; and c) determine the factors that would make it easier or more difficult for pharmacists to report serious ADEs to the FDA. The purpose, length and rules of the focus group were explained to all focus group volunteers. The following open-ended questions, adapted from Montano and Kasprzyk (2002), were used in the focus groups (see Appendix E).

1. What do you think are some of the advantages associated with pharmacists reporting serious ADEs to the FDA?
2. What do you think are some of the disadvantages associated with pharmacists reporting serious ADEs to the FDA?
3. Are there any individuals or groups who would approve pharmacists reporting serious ADEs to the FDA?

4. Are there any individuals or groups who would not approve pharmacists reporting serious ADEs to the FDA?
5. What do you think would make it easier to report serious ADEs to the FDA?
6. What do you think would make it more difficult to report serious ADEs to the FDA?

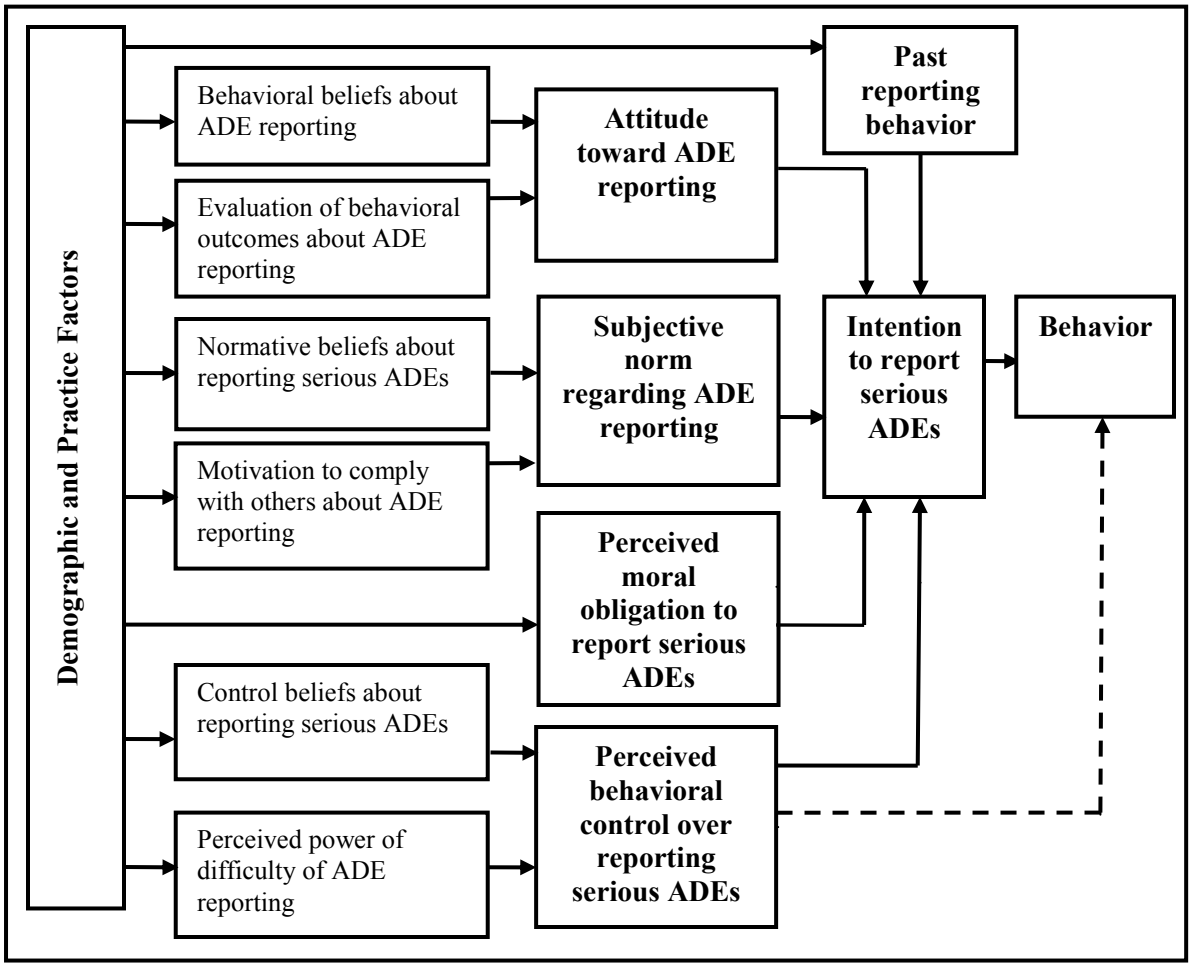
During the focus groups, the moderator guided the discussion using the outline of open-ended questions contained in the focus group interview guide (Appendix E). The moderator probed for details and asked follow-up questions to elicit more discussion. Each focus group lasted approximately one hour. A content analysis was performed on the basis of the written transcriptions of the focus groups. The data were coded in order to facilitate the search for patterns and themes within the data.

The important behavioral outcomes and referents were identified. As recommended by Ajzen and Fishbein (1980), the beliefs gathered from the elicitation study were formatted to create an instrument that was later used in the mail survey.

4.6.2 Measurement of Study Variables

Elaborate measurement techniques for the components of the TPB and guidelines for measurement and questionnaire construction exist (Ajzen, 2002). All study variables were constructed based on the TPB guidelines (Ajzen & Fishbein, 1980). In addition to demographic and practice characteristics, the study examined attitude (A), subjective norm (SN), perceived behavioral control (PBC), past reporting behavior (PRB), perceived moral obligation (PMO) and behavioral intention (BI) variables (Figure 4.2). These variables are discussed below.

Figure 4.2: The Conceptual Model



4.6.2.1 Predictor Variables

The study's predictor variables comprise the three TPB constructs (A, SN and PBC), PRB and PMO. The three TPB constructs were measured through both direct and indirect measures. Although the indirect and direct measures of the same construct are measured in different ways, there should be a positive and strong correlation between them (Ajzen, 2002; Montano & Kasprzyk, 2002). Direct and indirect measures are expected to be correlated since they both serve as indicators of the same underlying latent construct (Ajzen, 2002). The direct measures of the TPB constructs are stronger predictors of intention than indirect measures (Montano & Kasprzyk, 2002). Indirect

measures help researchers to understand the main drivers of behavior or "why people hold certain attitudes, subjective norms, and perceptions of behavioral control" (Ajzen, 2002, p. 8) that can be targeted by interventions. The study used seven-point Likert-type scales to measure the strength of behavioral beliefs and evaluations of the importance of behavioral beliefs. The corresponding evaluations of the behavioral, normative and control measures were measured as suggested by Ajzen and Fishbein (1980).

The A, SN, and PBC items in this study were developed based on the findings from the focus group and on TPB recommendations (Ajzen, 2002).

1) Attitude

Direct Measure of Attitude

The direct measure of pharmacists' attitude toward reporting serious ADEs was measured through a single multi-part item. The item measured the pharmacists' overall evaluation of the behavior. The strength of attitude was assessed using a bipolar semantic differential scales anchored by worthless (-3) and valuable (+3), unpleasant (-3) and pleasant (+3), bad (-3) and good (+3), unenjoyable (-3) and enjoyable (+3), and harmful (-3) and beneficial (+3). The total score from these five items represents the pharmacist's overall positive or negative feeling toward reporting serious ADEs.

Q. For me to report serious ADEs to the FDA each time I come across them is

worthless: _3_:_-2_:_-1_:_0_:_1_:_2_:_3_: valuable

unpleasant: _3_:_-2_:_-1_:_0_:_1_:_2_:_3_: pleasant

bad: _3_:_-2_:_-1_:_0_:_1_:_2_:_3_: good

unenjoyable: _3_:_-2_:_-1_:_0_:_1_:_2_:_3_: enjoyable

harmful: _3_:_-2_:_-1_:_0_:_1_:_2_:_3_: beneficial

Indirect Measure of Attitude

The indirect measures of attitude were measured as a function of: a) behavioral beliefs (**b)**, and b) outcome evaluations (**e)** (Ajzen & Fishbein, 1980). The eight (8) modal salient beliefs identified from the focus groups constitute the items. Each behavioral belief item was rated using a bipolar semantic differential scale anchored by extremely unlikely (+1) and extremely likely (+7). For example, a salient belief of increased risk of malpractice looked as shown below.

Q. My reporting of serious ADEs to the FDA whenever I encounter them will increase my risk of malpractice.

extremely unlikely: _3_:_-2_:_-1_:_0_:_1_:_2_:_3_: extremely likely

A similar but separate scale was used to measure the outcome evaluation (the consequences) (**e).** Each of the evaluative outcomes and attributes associated with the respective behavioral belief was measured and rated using a semantic differential scale anchored by extremely bad (+1) and extremely good (+7). For example, for the salient belief, the corresponding outcome evaluation looked as shown below.

Q. Increased risk of malpractice is…

extremely bad: _1_:_2_:_3_:_4_:_5_:_6_:_7_: extremely good

For each respondent, the behavioral belief (**b**) and outcome evaluation (**e**) scores were multiplied. The attitude score was determined by summing these cross-products for all referents for each respondent. Higher absolute scores indicate that the respondents have more favorable attitude towards reporting serious ADEs to the FDA.

$A = \sum b_i e_i$
a = attitude towards the object of behavior
b_i = belief about the object's attributes or about the behavior's consequences
e_i = evaluation of attributes or consequences

2) Subjective Norm

Similar to A, SN was measured through both direct and indirect measures.

Direct Measures of Subjective Norm

The direct subjective norm was assessed by a three-item scale. The pharmacists rated their agreement with three statements using a 7-point bipolar scale ranging from -3 to +3. The total possible scores ranged from -9 to +9.

Q. Most people who are important to me think that
I should: _3_:_2_:_1_:_0_:_-1_:_-2_:_-3_: I should not
report serious ADEs that I encounter to the FDA.

Q. The people in my life whose opinions I value would
approve: _3_:_2_:_1_:_0_:_-1_:_-2_:_-3_: disapprove
my reporting of serious ADEs that I encounter to the FDA.

Q. The pharmacists whose opinions I value
report: _3_:_2_:_1_:_0_:_-1_:_-2_:_-3_: do not report
serious ADEs to the FDA.

Indirect Measures of Subjective Norm

The indirect subjective norm was assessed using two sub-scales: normative beliefs (**n**) and motivation to comply with each referent (**m**). The pharmacists' salient referents were obtained from the focus groups data. Pharmacists were asked to indicate the likelihood that the specified referents, who are important to them, would approve or disapprove of their reporting behavior. The strength of the normative beliefs was measured using a 7-point semantic differential scale ranging from extremely unlikely (+1) to extremely likely (+7). For example, the normative belief question pertaining to physicians was asked as follows.

Q. "How likely is it that physicians would think that you should report serious ADEs to the FDA?"

extremely unlikely: _1_:_2_:_3_:_4_:_5_:_6_:_7_: extremely likely

The pharmacists' level of motivation to comply with each referent was assessed using a 7-point semantic differential scale ranging from extremely unlikely (+1) to extremely likely (+7). The following question was asked.

Q. "Generally speaking, how likely are you to do what the physicians want you to do when it comes to ADE reporting?"

extremely unlikely: _1_:_2_:_3_:_4_:_5_:_6_:_7_: extremely likely

For each respondent, the normative belief and motivation to comply scores were multiplied. The subjective norm (indirect measures) was determined by summing these cross-products for all referents for each respondent. Higher scores indicate that the referents have greater influence on the pharmacists.

$SN = \sum n_i m_i$

SN = subjective norm
n_i = normative belief about reporting ADEs
m_i = motivation to comply with the referent

3) Perceived Behavioral Control

Direct Measure of Perceived Behavioral Control (PBC)

PBC refers to the pharmacist's perception of the ease or difficulty of undertaking the behavior (reporting serious ADEs) (Ajzen, 1991). Pharmacists were asked to rate their perceived control over reporting serious ADEs to the FDA. The study used two items to directly measure the PBC over reporting serious ADEs. The PBC items were measured using a 7-point bipolar semantic differential scale anchored by -3 (e.g., strongly disagree) and +3 (e.g., strongly agree). The scores from the two items were then summed. The total possible score ranged from -6 to +6. Higher scores indicate pharmacists have greater confidence in their capability to report serious ADEs to the FDA. The following questions were used.

Q. How much control do you believe you have over reporting serious ADEs that you encounter to the FDA?

no control: _-3_:_-2_:_-1_:_0_:_1_:_2_:_3_: complete control

Q. It is mostly up to me whether or not I report serious ADEs to the FDA.

strongly disagree: _-3_:_-2_:_-1_:_0_:_1_:_2_:_3_: strongly agree

Indirect Measures of Perceived Behavioral Control

Two subscales were used to measure the pharmacists' indirect PBC over ADE reporting: control beliefs (**c**), and perceived power (**p**). The pharmacists' salient control beliefs reflect the main factors likely to inhibit or facilitate their reporting of serious

ADEs to the FDA. Pharmacists were asked to rate how much a specific factor would make it easy or difficult for them to report serious ADEs to the FDA. All the control items were measured using a 7-point bipolar semantic differential scale anchored by extremely difficult (+1) and extremely easy (+7). For example, the following question on the lack of time factor was asked of respondents to measure their control beliefs.

Q. "Will the lack of time make it easy or difficult for you to report serious ADEs that you encounter to the FDA?"

extremely difficult: _1_:_2_:_3_:_4_:_5_:_6_:_7_: extremely easy

The pharmacists' perceived power indicates how much control they (pharmacists) believe they have over reporting serious ADEs that they encounter to the FDA. Perceived power was measured using a 7-point bipolar scale anchored on no control (+1) and complete control (+7). For example, the following question on the lack of time factor was asked.

Q. "How much control do you feel you have over the lack of time when it comes to reporting serious ADEs to the FDA?"

no control:_1_:_2_:_3_:_4_:_5_:_6_:_7_: complete control

For each respondent, the control belief (**c**) and perceived power (**p**) scores were multiplied. The PBC score for each respondent was determined by summing these cross-products across the number of factors as shown below. Higher absolute PBC scores indicate that the pharmacists perceive themselves to have more control over reporting serious ADEs.

$$PBC = \sum c_i p_i$$

PBC = perceived behavioral control
c_i = the control belief toward the factor
p_i = the perceived power of a particular control factor to facilitate or inhibit ADE reporting.

4) Past Reporting Behavior

Given the importance of past behavior in explaining significant variance in behavioral intention, the past reporting behavior (PRB) construct was included in this study. The PRB measure was developed based on similar measures used in previous studies (Mashburn et al., 2003; Millstein, 1996; Nwokeji, 2007). PRB was measured using two dichotomous questions where respondents were required to make a choice between two response alternatives: 1 = no, and 2 = yes. A total score was obtained by summing the scores from these two items. Higher scores indicate higher PRB. Below are the two questions that were used to measure PRB.

Q. Have you ever reported any ADEs to the FDA through MedWatch?

Q. Have you reported any ADEs to the FDA through MedWatch in the previous 12 months?

5) Perceived Moral Obligation

The study also included PMO as an additional determinant of intentions given that moral values may influence pharmacists' behavioral intention to report serious ADEs. The ability of PMO to predict pharmacists' reporting intention was assessed using a single item adapted from Randall and Gibson (1991) and Gorsuch and Ortberg (1983). The item was measured using a bipolar Likert response scale anchored by 1 = strongly disagree and 7 = strongly agree. The single item is shown below.

Q. I believe I have a moral obligation to report serious ADEs that I will encounter to the FDA.

6) Demographic and Practice Characteristics

Given the importance of demographic factors and practice characteristics in influencing pharmacists' beliefs, evaluation of behavioral outcomes, motivation to comply with others, perceived power of difficulty of ADE reporting, PRB, and PMO, the following eleven demographic and practice variables were collected and examined.

- Gender (male/female);
- Age (year of birth);
- Ethnic/racial background (African American/non-Hispanic black, American Indian or Alaska Native, Asian American/Pacific Islander, Caucasian/non-Hispanic white, Mexican American/Hispanic, or other;
- Practice experience (in years);
- Current job title at primary place of employment (pharmacy owner/partner, pharmacy manager/supervisor, clinical pharmacist, staff pharmacist, relief pharmacist, or other);
- Practice setting at primary place of employment (community—independent, community—multiple/chain [3 or more pharmacies under common ownership], hospital—independent, hospital—multiple/chain [3 or more pharmacies under common ownership], or other);
- Practice location (urban, suburban or rural);
- Average number of hours worked per week;
- Average number of hours per week spent dispensing medication;

- Pharmacist workload (average number of prescriptions or medication orders dispensed per day); and
- Knowledge of ADE reporting (the study used nine questions as shown below).

Pharmacists Knowledge of ADE Reporting

Nine (9) dichotomous questions were used to measure the pharmacists' knowledge and awareness of ADE reporting and drug safety issues. The questions below cover the goals, procedures and expectations from MedWatch. Respondents were required to make a choice between two response alternatives: 0 = false and 1 = true. The correct answer for the first eight questions is shaded. For question nine (9), no response is shaded because there was no correct or wrong answer for this question. An individual's total score was obtained by summing his/her scores on the first eight items. This score was then converted to a percentage. Higher scores indicate higher knowledge of ADE reporting.

1. All ADEs, irrespective of severity, should be reported to the FDA (True/False).
2. Pharmacists should report serious ADEs even if they are uncertain that the product caused the event (True/False).
3. Pharmacists should report serious ADEs even if they do not have all the details (e.g., complete patient history and demographic data) (True/False).
4. All serious ADEs are known before a drug is marketed (True/False).
5. The FDA does not disclose the ADE reporter's identity in response to a request from the public (True/False).

6. Pharmacists can report ADEs to the FDA anonymously (True/False).
7. Adverse experiences with cosmetics and special nutritional products (e.g., dietary supplements, infant formulas) may be reported to the FDA (True/False).
8. One case reported by a pharmacist does not contribute much to knowledge on drug risks (True/False).
9. I have adequate knowledge on ADE reporting (e.g., what to report and how to report) (True/False).

4.6.2.2 Outcome Variable

Intention to Report Serious ADEs

The pharmacists' intention to report serious ADEs to the FDA was measured using three items. The items asked pharmacists to indicate the extent to which they will try, plan or intend to report serious ADEs that they will encounter to the FDA. The strength of the intention was measured on a 7-point bipolar Likert-type scale anchored by 1 (e.g., extremely unlikely) and 7 (e.g., extremely likely). The total possible scores ranged from 3 to 21. Higher total scores represent a higher intention to report serious ADEs.

Q. I intend to report serious ADEs that I will encounter to the FDA.
extremely unlikely: _1_:_2_:_3_:_4_:_5_:_6_:_7_: extremely likely

Q. I will try to report serious ADEs that I will encounter to the FDA.
definitely true: _1_:_2_:_3_:_4_:_5_:_6_:_7_: definitely false

Q. I plan to report serious ADEs that I will encounter to the FDA.
strongly disagree: _1_:_2_:_3_:_4_:_5_:_6_:_7_: strongly agree

The behavioral intention was calculated as the weighted sum of A, SN, PBC, PMO and PRB using multiple regression analysis. Each of the regression coefficients in the equation was calculated using multiple regression analysis.

$$BI = B_0 + B_1 (A) + B_2 (SN) + B_3 (PBC) + B_4 (PRB) + B_5 (PMO) + E_i$$

BI = Behavioral intention
A = Attitude
SN = Subjective norm
PBC = Perceived behavioral control
PRB = Past reporting behavior
PMO = Perceived moral obligation
B_{1-5} = Unstandardized regression weights
B_0 = Constant
E_i = Error term

4.7 PILOT TESTING

The developed instrument was pilot tested on a convenience sample of Texas pharmacists. As suggested by Polit and Beck (2004), the questionnaire was pre-tested to achieve the following: a) identify parts of the instrument package that are difficult for subjects to read or understand; b) identify any questions that participants may find objectionable; and c) determine if the measures yield data with sufficient variability. In addition, the pilot test was also used to assess the face and content validity of the instrument. Twelve pharmacists consisting of nine (9) community and three hospital pharmacists were asked to complete a questionnaire and then to give feedback and comments on the clarity and relevance of items. Pilot test participants were asked to recommend item word modifications as needed and to make a judgment on the extent to which the scales represented the domain concept. All participants were asked to record and report the time it took them to complete the survey. Respondents took an average of 10 minutes to complete the survey instrument.

The responses from the pilot test were coded and analyzed. The reliability of the instrument was measured by Cronbach's alpha—a measure of internal consistency—using the pilot test responses. Cronbach's alphas were calculated for all scales with 3 or more items. The calculated internal consistency or Cronbach's alpha are given in Table 4.3. Cronbach's alpha values less than 0.60 are deemed not acceptable (Robinson, Shaver, & Wrightsman, 1991). All the calculated Cronbach alphas were greater or equal to 0.70. Overall, the instrument appeared to have acceptable reliability.

Table 4.3: Reliability of Direct Measures Based on Pilot Test Results

Scales	**Number of Items**	**Cronbach's Alpha**
Attitude (direct measure)	5	0.70
Subjective norm (direct measure)	3	0.79
Perceived behavioral control (direct measure)[a]	2	-
Intention	3	0.84
Past behavior [a]	2	-

[a] No reliability estimates were calculated for scales with less than 3 items

Appropriate modifications were made to the survey instrument based on the participants' feedback during pilot testing. Based on the feedback from the pilot test, the following changes were made to the survey instrument:

- The questions were re-ordered. The section on attitude was placed ahead of the intention section. The order of the two past reporting behavior items was swapped.
- Some questions including the attitude item pertaining to 'taking too much time' were re-phrased.
- The counterbalancing of the positive and negative endpoints in the direct attitude scale which had been designed to counteract possible response sets was eliminated.

After these refinements, the survey instrument was ready for distribution.

4.8 MAIL SURVEY DATA COLLECTION PROCEDURES

For the mail survey, data collection included distributing the study materials and sending out follow-up materials and letters to the potential respondents as described below. First, the study materials consisting of a cover letter and the questionnaire were mailed to the potential respondents. The cover letter highlighted the objectives of the study, assured the respondents of confidentiality and anonymity of individual responses and requested the respondents' participation in the study. Through the cover letter, respondents were offered an aggregate summary of responses as an incentive for participation in the study. Participants were given two weeks to complete and return the questionnaire. A copy of the cover letter is in Appendix F.

Second, a second mailing of the questionnaires together with a follow-up cover letter were distributed to the sample 21 days after the initial mailing. The mailings were sent to the entire sample given the anonymous responses. A copy of the follow-up cover letter can be found in Appendix F.

4.9 DATA CLEANING

Data were cleaned and prepared for analysis. The process addressed three fundamental aspects vis-à-vis outliers, violation of assumptions (nonnormality), and missing values as described below. First, outliers were identified and analyzed. For all non-dichotomous variables/items, z-scores were calculated and those items with z-values greater than +3.29 or less than -3.29 were identified and examined ($p < 0.001$). Those considered valid were retained and those that were considered invalid were considered outliers and were substituted with the median value.

Second, given that multiple regression assumes that all the variables are multivariate normally distributed, the data were assessed for nonnormality. Skew and kurtosis statistics were calculated and used to test for nonnormality. Skew greater than |2|

and kurtosis greater than |7| were considered serious violations of the assumption (Curran, West, & Finch, 1996). Scatterplots and histograms of studentized residuals between all independent variables with the dependent variable were made to test the violation of assumptions of linearity and normality.

Third, the study assessed the missing values and the pattern of these values. Pair-wise and list-wise deletion was used if data were missing. The study also compared data on key variables (Intention, A, SN, PBC, PRB, PMO) between those with at least one missing response and those without.

4.10 DATA ANALYSIS

The data from the questionnaires were coded and inputted into the Statistical Package for Social Sciences (SPSS)® for Windows version 14.0 for analysis (SPSS inc, Chicago Illinois, 2005). The acceptable level of significance for all analyses was $p < 0.05$. Several analyses were conducted in this study including descriptive statistics, correlation analyses, t-tests, analysis of variance (ANOVA) and multiple regression.

Descriptive Statistics

Means, frequency distributions and standard deviations were calculated for all demographic and study variables (interval data) (BI, A, SN, PBC, PMO, PRB and demographic and practice characteristics). Frequencies and percentages of all categorical data (e.g., gender, race, practice setting) were obtained.

Correlation Analyses

Pearson correlation coefficients were calculated to show the correlation between the main variables in the conceptual model (BI, A, SN, PBC, PRB and PMO).

Correlations between direct and indirect measures of each of the TPB's independent constructs (A, SN and PBC) were also computed and compared.

T-Test Analyses

Independent t-tests were applied to compare A, SN, and PBC among male and female pharmacists, and among intenders and non-intenders. To compare intenders and non-intenders, the following procedures were taken. All responses of one (1) to three (3) on any of the three intention items were re-corded with a minus one (-1) for that item. All responses between a five and a seven on any of these three items were re-coded with positive one (+1) for that item. Those who marked a four on any of the three intention items were re-coded with a zero for that item. For each respondent, the dummy codes (-1s, 0s and +1s) were added together across the three intention items. This composite score was then used to categorize respondents into intenders (e.g., positive total score), non-intenders (e.g., negative total score) and neither intenders nor non-intenders (had a total score of zero).

Analysis of Variance (ANOVA)

ANOVA was conducted to assess the mean differences in A, SN, PBC and intention across the study's polytomous categorical variables (e.g., ethnicity, and pharmacists' primary setting).

Multiple Regression Analyses

Multiple (linear) regression analysis and hierarchical regression were used to regress behavioral intention on the TPB constructs (A, SN and PBC), PMO, and PRB. Multiple regression analysis was used to determine the predictors of Texas pharmacists' intention to report serious ADEs. Separate equations were run for direct and indirect measures of the TPB predictors. It is important to note that multiple regression does not

infer causality. Attributing causality is an issue of study design and not statistical analysis.

The study used generalized linear models to compare responses for each item and for all domains. If significant differences were detected, the least squares mean post hoc test was used to determine significant pair-wise differences.

The use of regression analysis is theoretically justified if the data satisfies four assumptions. Linear regression analysis assumes the following:

- Linearity: there is a linear relationship between the dependent and independent variables. Scatterplots or partial regression plots for the dependent and independent variables were assessed for systematic patterning among the residuals to evaluate the linearity of the data. The existence of a pattern in the plot may suggest that the relationship between the plotted variables is non-linear.
- No multicollinearity: there is no serial correlation or the independent variables are not highly correlated with each other. The values of correlation coefficients of the variables, tolerance, and variance inflation factors were used to test this criterion. Multicollinearity is a significant problem in cases where correlation coefficients exceed 0.75 (Graphpad Instat, 1990). Tolerance is the proportion of variance in the independent variable in question that is not explained by its association with other predictor variables. “A tolerance value close to 1.00 means that you are safe in including that variable, whereas a value close to 0 shows that you run the risk of multicollinearity, possibly no solution, by including this variable” (Hays, 1994, pp. 722, 723). Tolerance values range from zero to one. Variance Inflation Factors (VIF) are inverses of tolerance. VIF ranges from 1 to infinity. Higher values of VIF indicate there is a multicollinearity problem. As a rule of thumb, VIF greater than 10 raises concern about multicollinearity (Myers, 1990).

- Normality of the distribution of errors: the residuals[7] or errors are normally distributed around each predicted value of the dependent variable. The distribution of residual values was evaluated by inspecting histograms and normal probability plots. Histograms that differ markedly from a normal distribution raise concern.
- Homoscedasticity (constant variance) of errors: the variances and standard deviations of the errors are constant for all the independent variables. This assumption was assessed by examining the scatterplots of residuals versus predicted values.

Reliability

Measures with low reliabilities "lead to an underestimate of the relations among the theory's constructs and of its predictive validity" (Ajzen, 2002, p. 4). The reliability of all the multiple-item scales in the instrument was measured by Cronbach's alpha, a measure of internal consistency. These scales include intention to report ADEs, A (direct measures only), and SN (direct measures only). Cronbach's alpha values less than 0.60 are deemed not acceptable (Robinson, Shaver, & Wrightsman, 1991).

4.11 OBJECTIVES, HYPOTHESIS TESTS AND CORRESPONDING STATISTICAL ANALYSES

Table 4.4 provides the objectives, hypotheses and statistical tests used in this study.

[7] Residuals are the difference between the predicted value of the dependent variable and the obtained value of the dependent variable.

Table 4.4: Study Objectives, Hypotheses and Statistical Tests

Objectives	**Hypotheses**	**Statistical Model**	**Statistical Test**
Objective 1	Identify pharmacists' beliefs concerning reporting of serious ADEs.		Descriptive statistics: means and SDs
Objective 2	To explore the utility of the TPB model constructs (A, SN, PBC) in predicting pharmacists' intention to report serious ADEs.		
	H1: Favorable attitude (A) is a positive and significant predictor of intention to report serious ADEs controlling for SN and PBC.	$BI = B_0 + B_1(Ad) + B_2(SNd) + B_3(PBCd)$ $BI = B_0 + B_1(Ai) + B_2(SNi) + B_3(PBCi)$	Multiple regression, R^2, F-test, T-test
	H2: SN supporting ADE reporting is a positive and significant predictor of intention to report serious ADEs controlling for A and PBC.	$BI = B_0 + B_1(Ad) + B_2(SNd) + B_3(PBCd)$ $BI = B_0 + B_1(Ai) + B_2(SNi) + B_3(PBCi)$	Multiple regression, R^2, F-test, T-test
	H3: Strong perceived behavioral control (PBC) is a positive and significant predictor of intention to report serious ADEs controlling for A and SN.	$BI = B_0 + B_1(Ad) + B_2(SNd) + B_3(PBCd)$ $BI = B_0 + B_1(Ai) + B_2(SNi) + B_3(PBCi)$	Multiple regression, R^2, F-test, T-test
	H4: A + SN + PBC constructs explain a significant amount of variance in pharmacists' intention to report serious ADEs.	$BI = B_0 + B_1(Ad) + B_2(SNd) + B_3(PBCd)$ $BI = B_0 + B_1(Ai) + B_2(SNi) + B_3(PBCi)$	Multiple regression, R^2, F-test
A = attitude, SN = subjective norm, PBC = perceived behavioral control; i = indirect measure, d = direct measure, ADE = adverse drug event, SD = standard deviation, B_{0-3} = unstandardized regression coefficients.			

Table 4.4: Study Objectives, Hypotheses and Statistical Tests

Objectives	**Hypotheses**	**Statistical Model**	**Statistical Test**
Objective 3	To determine the contribution of the PBC construct to the prediction of pharmacists' intention to report serious ADEs beyond A and SN constructs.		
	H5: PBC significantly increases the explanatory power of the regression model compared to only using A + SN to explain pharmacists' intention.	$BI = B_0 + B_1(Ad) + B_2(SNd) + B_3(PBCd)$ $BI = B_0 + B_1(Ai) + B_2(SNi) + B_3(PBCi)$	Hierarchical regression, R^2, F-test
Objective 4	To determine if the past reporting behavior (PRB) construct contributes toward the prediction of pharmacists' intention to report serious ADEs over and above the TPB constructs.		
	H6: PRB significantly increases the explanatory power of the regression model compared to only using the A + SN + PBC to explain pharmacists' intention to report serious ADEs.	$BI = B_0 + B_1(Ad) + B_2(SNd) + B_3(PBCd) + B_4$ (PRB) $BI = B_0 + B_1(Ai) + B_2(SNi) + B_3(PBCi) + B_4$ (PRB)	Hierarchical regression, R^2, F-test
Objective 5	To determine if PMO significantly increases the explanatory power of the regression model compared to only using the A + SN + PBC to explain pharmacists' intention to report serious ADEs.		
	H7: PMO significantly increases the explanatory power of the regression model compared to only using the A + SN + PBC to explain pharmacists' intention to report serious ADEs.	$BI = B_0 + B_1(Ad) + B_2(SNd) + B_3(PBCd) + B_4$ (PMO) $BI = B_0 + B_1(Ai) + B_2(SNi) + B_3(PBCi) + B_4$ (PMO)	Hierarchical regression, R^2, F-test
A = attitude, SN = subjective norm, PBC = perceived behavioral control; i = indirect measure, d = direct measure, PRB = past reporting behavior, PMO = perceived moral obligation, ADE = adverse drug event, and $B_{0\text{-}3}$ = unstandardized regression coefficients.			

Table 4.4: Study Objectives, Hypotheses and Statistical Tests

Objectives	Hypotheses	Statistical Model	Statistical Test
Objective 6	To determine if the pharmacists' A, SN or PBC toward reporting serious ADEs is related to practice characteristics and demographic factors.		
Gender	$H_0$8: There is no significant difference in A to report serious ADEs by gender.	Ad = B_0 + B_1 (gender) Ai = B_0 + B_1 (gender)	T-test
	$H_0$9: There is no significant difference in SN regarding reporting serious ADEs by gender.	SNd = B_0 + B_1 (gender) SNi = B_0 + B_1 (gender)	T-test
	$H_0$10: There is no significant difference in PBC over reporting serious ADEs by gender.	PBCd = B_0 + B_1 (gender) PBCi = B_0 + B_1 (gender)	T-test
Years experience	$H_0$11: There is no relationship between A to report serious ADEs and pharmacists' years of experience.	Ad = B_0 + B_1 (years experience) Ai = B_0 + B_1 (years experience)	Correlation
	$H_0$12: There is no significant relationship between SN to report serious ADEs and pharmacists' years of experience.	SNd = B_0 + B_1 (years experience) SNi = B_0 + B_1 (years experience)	Correlation
	$H_0$13: There is no significant relationship between PBC to report serious ADEs and pharmacists' years of experience.	PBCd = B_0 + B_1 (years experience) PBCi = B_0 + B_1 (years experience)	Correlation
Practice setting	$H_0$14. There is no significant difference in A toward ADE reporting by pharmacists' primary practice setting.	Ad = B_0 + B_1 (practice setting) Ai = B_0 + B_1 (practice setting)	ANOVA
	$H_0$15: There is no significant difference in SN regarding ADE reporting by pharmacists' primary practice setting.	SNd = B_0 + B_1 (practice setting) SNi = B_0 + B_1 (practice setting)	ANOVA
	$H_0$16: There is no significant difference in PBC over ADE reporting by pharmacists' primary practice setting.	PBCd = B_0 + B_1 (practice setting) PBCi = B_0 + B_1 (practice setting)	ANOVA
A = attitude, SN = subjective norm, PBC = perceived behavioral control; I = indirect measure, d = direct measure, ADE = adverse drug event, $B_{0\text{-}1}$ = unstandardized regression coefficients, ANOVA = analysis of variance.			

Table 4.4: Study Objectives, Hypotheses and Statistical Tests

Objectives	**Hypotheses**	**Statistical Model**	**Statistical Test**
Hours worked	$H_0$17. There is no significant relationship between the pharmacists' number of hours worked and A toward ADE reporting.	Ad = B_0 + B_1 (hours worked) Ai = B_0 + B_1 (hours worked)	Correlation
	$H_0$18: There is no significant relationship between the pharmacists' number of hours worked and SN regarding ADE reporting.	SNd = B_0 + B_1 (hours worked) SNi = B_0 + B_1 (hours worked)	Correlation
	$H_0$19: There is no significant relationship between the pharmacists' number of hours worked and PBC over ADE reporting.	PBCd = B_0 + B_1 (hours worked) PBCi = B_0 + B_1 (hours worked)	Correlation
Race/ethnicity	$H_0$20: There is no significant difference in A toward ADE reporting by pharmacists' race/ethnicity.	Ad = B_0 + B_1 (race/ethnicity) Ai = B_0 + B_1 (race/ethnicity)	ANOVA
	$H_0$21: There is no significant difference in SN regarding ADE reporting by pharmacists' race/ethnicity.	SNd = B_0 + B_1 (race/ethnicity) SNi = B_0 + B_1 (race/ethnicity)	ANOVA
	$H_0$22: There is no significant difference in PBC over ADE reporting by pharmacists' race/ethnicity.	PBCd = B_0 + B_1 (race/ethnicity) PBCi = B_0 + B_1 (race/ethnicity)	ANOVA
Knowledge	$H_0$23. There is no significant relationship between the pharmacists' knowledge of ADE reporting and A toward ADE reporting.	Ad = B_0 + B_1 (knowledge) Ai = B_0 + B_1 (knowledge)	Correlation
	$H_0$24: There is no significant relationship between the pharmacists' knowledge of ADE reporting and SN regarding ADE reporting.	SNd = B_0 + B_1 (knowledge) SNi = B_0 + B_1 (knowledge)	Correlation
	$H_0$25: There is no significant relationship between the pharmacists' knowledge of ADE reporting and PBC over ADE reporting.	PBCd = B_0 + B_1 (knowledge) PBCi = B_0 + B_1 (knowledge)	Correlation
A = attitude, SN = subjective norm, PBC = perceived behavioral control; I = indirect measure, d = direct measure, ADE = adverse drug event, $B_{0\text{-}1}$ = unstandardized regression coefficients, ANOVA = analysis of variance.			

4.12 LIMITATIONS

There are several limitations associated with this study.

1. The study did not validate the respondents' responses with the actual ADE reports. This task is impossible given the anonymity of the study's respondents and of the ADE reports and ADE reporting in general.
2. Good quality serious ADE reports are necessary for a proper evaluation of drug safety signals. Poor quality reports or those with missing information may be of little value in efforts to improve patient safety and the quality of patient care. This notwithstanding, this study does not consider the quality of the reports submitted by the pharmacists.
3. The problem of social desirability response bias which is "the tendency of some individuals to misrepresent their responses consistently by giving answers that are congruent with prevailing social values" (Polit and Beck, p.359) cannot be completely ruled out in the study. Also given the sensitivity of the topic, it may be that some respondents gave socially desirable answers.
4. The use of a structured questionnaire/data collection instrument does not allow respondents sufficient opportunity to qualify their responses. The use of an unstructured or loosely structured data collection tool/method may give the study even more depth. However, respondents got an opportunity to make open-ended comments on the survey instrument. Further studies employing qualitative methods may be needed to further explore pharmacists' intention to report serious ADEs.
5. Other important variables influencing pharmacists' ADE reporting might not be included in the TPB (e.g., cues to action in the Health Belief Model). Also, belief-based and direct measures do not perfectly measure the underlying, latent variable (Ajzen, 2002).

6. Causality influences cannot be explicitly made in this study. This is so because the study used a nonexperimental research design with a cross-sectional data collection and did not control for all appropriate confounding variables. However, this nonexperimental model, with hypothesized causal relationships guided by the theory and prior research, seems plausible/suitable.
7. This cross-sectional study assessed the effects of the independent variables in explaining intention at the time of data collection. This may provide a poor prediction and understanding of pharmacists' reporting behavior. Ideally, a prospective study design with the predictors and intention measured at one time and behavior measured at a later time point, is recommended.

4.13 SUMMARY

This chapter focuses on the research methods that were used for this study. It outlines the research design and the procedures that were used to develop the instrument and the steps that were taken in pilot testing and checking the reliability of the questionnaire. The chapter also describes the procedures for data collection (sampling, distribution of the instrument) and data analysis (objectives, hypotheses and statistical analyses).

CHAPTER FIVE: RESULTS

This chapter describes the main findings of the study. The first section details the findings from the two focus groups followed by the results of the mail survey. Internal consistency of the scale items and descriptive statistics of study constructs are presented. The multivariate analyses of data are described and a summary of hypothesss tests is detailed.

5.1 FOCUS GROUP RESULTS

A total of 13 Texas pharmacists participated in two focus groups. The first focus group was conducted at The University of Texas College of Pharmacy and was attended by six (6) practicing pharmacists. The second focus group was conducted during the monthly meeting of the Capital Area Pharmacists Association (CAPA) in Austin with seven (7) CAPA members. The focus groups lasted approximately an hour each. The pharmacists who participated in the first focus group were provided lunch. CAPA members who volunteered to participate in the second study were offered a $25 gift card as an incentive for participating. The focus groups identified the pharmacists' behavioral, normative and control beliefs that underpin their intention to report serious ADEs. Emerging themes were identified through content analyzing the focus group participants' responses to the study questions. The key words and phrases of all the three belief-based categories were tallied and their frequencies were ranked (Tables 5.1, 5.2, and 5.3).

5.1.1 Behavioral Beliefs

A total of 11 behavioral beliefs were identified from the responses of focus group participants (Table 5.1). Nine of the 13 pharmacists believed that reporting serious ADEs to the FDA was time consuming. Six pharmacists believed that reporting serious ADEs to the FDA educates others about drug risks. In addition, results of the focus groups showed

that pharmacists believed that reporting provided them little benefit/reward, compromises their relationship with physicians, increases the risk of malpractice, improves patient safety, breaks their trust with their patients and disrupts the normal workflow (Table 5.1). The eight most commonly mentioned behavioral beliefs were used to construct the indirect attitude measures. This number is in line with the recommended minimum of five to nine belief items (Ajzen & Fishbein, 1980). In addition, information contained in items 9-11 was likely reflected in other items already included. These items (9-11) did not have as much support from the focus groups as the other items.

Table 5.1: Behavioral Belief Items (n = 13 Pharmacists)

Item	**Frequency**
Time consuming (to gather facts, to report)	9
Educates others about drug risks (e.g., increases knowledge and information about drugs)	6
Little benefit gained from reporting (e.g., reporting is not rewarding, no compensation)	5
Compromise the relationship one has with physicians and other HCPs	4
Increase risk of malpractice/legal liability	4
Improves patient safety	4
Breaks trust with patient and changes patient care	3
Disrupts the normal workflow	3
Make sure that another patient does not have the same experience	2
Results in call from pharmacy board	1
To have the information centralized	1

5.1.2 Normative Beliefs

The main normative beliefs identified from the focus group responses are given in Table 5.2. A total of 15 categories of normative beliefs were identified. The pharmacists believed that physicians would approve and disapprove of their reporting of serious ADEs to the FDA. The other salient social norms were patients, drug manufacturers, pharmacy associations, family/spouses, the FDA, pharmacy managers, colleagues, and

hospitals or hospital groups. A total of nine most commonly mentioned individuals and groups were included as indirect subjective norm measures (Table 5.2).

Table 5.2: Normative Belief Items (n = 13 Pharmacists)

Item	Frequency
Physicians (physician groups and individual physicians)	10
Patients	7
Drug manufacturers	6
Pharmacy associations (APhA, ASHP, ACCP, CAPA)	4
My family/spouse/significant others	4
Food and Drug Administration (FDA)	4
Pharmacy managers	3
Other pharmacists	3
Hospitals and hospital groups	3
Medicare and Medicaid budget officers	2
Lawyers	2
Third party payers (PBMs)	1
Texas State Board of Pharmacy	1
Pharmacy technicians	1
Centers for Medicare and Medicaid Services (CMS)	1

5.1.3 Control Beliefs

The focus group participants cited many factors that they believed would make it easier or more difficult for them to report serious ADEs to the FDA (Table 5.3). Pharmacists believed that not having the patient's complete medical history made it difficult for them to report serious ADEs (n = 12). Also, a majority of the participants (n = 10) believed that lack of time made it difficult for them to report serious ADEs. The other major control beliefs identified by the participants are pharmacists awareness of ADE reporting (e.g., MedWatch program), streamlining the MedWatch form and reporting process, lack of employer support of ADE reporting, lack of some form of personal benefit (e.g., reward or compensation), ADE reporting not being part of normal workflow, increased patient counseling, patient awareness of drug risks, pharmacists

being drug experts and lack of clarity on the definition of ADEs to be reported (Table 5.3). Eleven of the most commonly cited control belief items were used to construct the indirect perceived behavioral control (PBC) measure in the instrument. Although this was two more than the nine recommended by Ajzen and Fishbein (Ajzen & Fishbein, 1980), the focus group participants were passionate about these two extra items. In addition, lack of clarity on reportable ADEs has been consistently found to be a barrier to reporting ADEs in the literature (Eland et al., 1999; Green et al., 2001; Hasford et al., 2002; Martin et al., 1998).

Table 5.3: Control Belief Items (n = 13 Pharmacists)

Item	Frequency
I don't have the patient's complete medical history	12
Lack of time (busy, no time)	10
Pharmacists awareness of ADE reporting (e.g., MedWatch program)	7
Streamlining the MedWatch form and reporting process (having a simpler form)	6
Lack of employer support of ADE reporting (not a priority in the business model)	5
Lack of some form of benefit (e.g., reward or compensation)	5
ADE reporting not part of the normal workflow and routine	4
Increased patient counseling (spending time with patients, getting better information, telling patients what's happening)	4
Patient awareness of drug risks (e.g., ADEs) and their role in post marketing surveillance (PMS)	4
Pharmacists being the drug experts	4
Lack of clarity on the definition of ADEs to be reported	3
No access to the web at work	3
Difficulty in pinpointing the drug causing the ADEs	2
Fear of possible malpractice suit/legal action	2
We do not see serious ADEs	2
Apathetic patients	1
Do not want to have anything to do with ADE reporting	1
Having the pharmacist accessible to patients	1
Increased feedback from patients	1
More pharmacists	1
My knowledge of the ADE in question	1
Not going to contribute significantly to the literature	1
Patient and consumer advocacy of ADE reporting	1
Perspective of the pharmacist's role with respect to reporting	1
Pharmacist burnout	1
Prioritize ADE reporting	1
To publish case reports	1

The survey instrument was consists of 94 items, 69 of which measure the TPB constructs as shown in Table 5.4.

Table 5.4: Number of Survey Items by Each of the TPB Constructs

Construct	Beliefs	Number of Items	Questionnaire Number
Attitude – indirect	Behavioral beliefs Outcome evaluation	8 8	1a-h 2a-h
Intention		3	3-5
Attitude – direct		5	6a-e
Subjective norm - indirect	Normative beliefs Motivation to comply	9 9	7a-i 8a-i
Subjective Norm - direct		3	9-11
Perceived behavioral control – indirect	Control beliefs Perceived power	11 11	13a-k 14a-k
Perceived behavioral control – direct		2	15-16

5.2 SURVEY RESPONSE RATES

Data were collected using a self-administered mail survey between May and July 2009. Surveys together with a cover letter were mailed to 1,500 practicing Texas pharmacists. The sample comprised 772 (51.5%) female and 728 (48.5%) male pharmacists. A total of 70 letters were returned undeliverable after the first and second mail outs. Therefore, 1,430 letters were considered delivered. A total of 399 surveys were received via mail by July 31st for a 27.9 percent response rate (399/1,430). Five responses received after the 31st July were excluded from the study. In addition, six respondents indicated that they had retired, one indicated that he/she was not willing to participate (returned an uncompleted survey), one indicated that she was not currently working and 14 surveys were incomplete (e.g., had more than 20% missing responses). Thus, 377 usable responses were obtained, yielding a usable response rate of 26.4 percent (377 complete/1,430 delivered).

5.3 DATA PREPARATION AND CLEANING

The data were entered into SPSS and prepared and screened for data analysis. Data preparation and screening focused on checking the adherence of the data to distributional assumptions (normality) and also investigated the existence of outliers and missing data.

5.3.1 Non-normality

Skew and kurtosis values of all variables were calculated and plotted using SPSS. Non-normality was defined as having skew > |2| and kurtosis > |7|. The distributions of all the interval level variables did not exceed the skew and kurtosis thresholds of > |2| and > |7|, respectively. All the interval level variables were considered normally distributed.

5.3.2 Outliers

To identify outliers, the z-scores of all the variables were computed and examined. All the non-dichotomous variables with a z-score less than -3.29 or greater than +3.29 were identified and examined. Some of these values were considered valid and thus were retained. However, a total of thirteen univariate outliers that met the criteria (z value > 3.29 or < -3.29) were considered to be invalid and thus were considered to be outliers. All these outliers pertained to the average number of prescriptions/medication orders dispensed per day variable. These values were substituted with the median value (average number of prescriptions/medication orders dispensed) for similar cases. Similar cases were defined as those cases with similar values on the following variables: type of practice setting and area/setting of primary place of employment. The old and new values for the 13 cases are shown in Table 5.5.

Table 5.5: Case Numbers, and Old and New Values of the Outliers

Case Number*	Old Value	New Value
387	7200	250
375	6000	135
125	3000	200
19	2100	200
121	1600	150
32	1200	234
182	800	180
211	800	127.50
235	700	200
18	700	150
353	600	200
262	600	200
175	600	123.75

* All cases pertained to the average number of prescriptions/medication orders dispensed variable.

5.3.3 Missing Data

Data were missing in 150 instances across all 94 variables and all the 377 respondents. Thus, there were 0.40 missing responses for each respondent. Incomplete data involved 74 respondents (20%). One respondent had 13 missing items (Table 5.6).

Table 5.6: Distribution of Missing Responses by Respondents (n = 377)

Number of Missing Responses	Number of Respondents	Percent
0	303	80.4
1	51	13.5
2	7	1.9
3	5	1.3
4	4	1.1
5	3	0.8
8	1	0.3
9	2	0.5
13	1	0.3
Total	**377**	**100**

The variables with the highest frequency of missing values responses were "average number of prescriptions/medication orders dispensed" (n = 14) and "year of birth" (age, n = 11 missing responses).

We compared data on the key study variables (intention, A, SN, PBC, PRB, and PMO) between those with at least one missing response and those without. The analysis showed no differences between those with missing information and those without missing information.

5.4 INTERNAL CONSISTENCY

Reliability estimates of all the direct measure scales with at least 3 items were computed and examined. The intention scale had a high reliability coefficient of 0.95. The attitude (0.75) and subjective norm (0.81) scales were also internally consistent with Cronbach alpha scores greater than 0.60 (see Table 5.7).

Table 5.7: Reliability Analysis of Direct Measures Study Scales

Scale	Number of Items	Cronbach Alpha
Attitude (direct measure)	5	0.75
Subjective norm (direct measure)	3	0.81
Perceived behavioral control (direct measure)[a]	2	0.71
Intention	3	0.95
Past reporting behavior [a]	2	0.37
Perceived moral obligation[b]	1	-
Knowledge[c]	9	0.41

[a] Spearman's rho correlation was computed instead of reliability estimates for scales with less than 3 items but more than one item.
[b] No reliability estimates could be calculated.
[c] Kuder-Richardson's ρ was calculated as the items were dichotomous.

5.5 PHARMACISTS' DEMOGRAPHIC FACTORS AND PRACTICE CHARACTERISTICS

The pharmacists' demographic factors and practice characteristics data were computed and examined. A brief description of these results is provided below:

5.5.1 Demographic Factors

A majority of respondents were male (n = 199, 52.9%), with an average age of 51.46 (SD = 12.69) years, ranging from 27 to 86 years. A majority of the pharmacists were Caucasian (n = 262, 70.2%). Table 5.8 depicts the age, gender, and ethnicity of the respondents.

Table 5.8: Age, Gender and Ethnicity of the Respondents

Variable	Frequency (%)	Mean (SD)
Age (years; n=366) [a]		51.46 (12.69)
Gender (n=376) [a]		
Male	199 (52.9)	
Female	177 (47.1)	
Race/Ethnicity (n=373)[a]		
Caucasian/non-Hispanic white	262 (70.2)	
Asian-American/Pacific Islander	37 (9.9)	
Mexican-American/Hispanic	33 (8.8)	
African American/non-Hispanic Black	27 (7.2)	
Other [b]	11 (2.9)	
American-Indian or Alaska native	3 (0.8)	

[a] N is less than 377 because of missing responses.
[b] The eleven pharmacists who indicated the 'Other' category for their ethnicity were as follows: Spanish (1), Anglo-white Caucasian (1), Czech-German (1), and Asian (3). Five respondents who checked the 'Other' category did not specify their ethnicity.

5.5.2 Practice Characteristics

The average number of years of experience of the respondents was 24.98 (SD = 13.12) years. Pharmacists worked an average of 38.43 (SD = 10.61) hours per week and spent an average of 30.79 (SD = 14.80) hours per week dispensing medication/interacting with patients (Table 5.9). Pharmacists dispensed an average of 174.67 (SD = 119.72) prescriptions/medication orders per day. Respondents were primarily staff pharmacists (42.4%) and pharmacy managers (27.1%). One hundred and fifty nine respondents practiced in the community-multiple/chain setting (42.2%). Eighty percent of the respondents worked in urban and suburban areas while 20 percent worked in rural areas.

Table 5.9: Practice Characteristics of the Respondents

Variable	Frequency (%)	Mean (SD)
Years of experience (n=375)		24.98 (13.0)
Hours worked per week (n=375)		38.43 (10.6)
Hours per week dispensing medication/interacting with patients (n=373)		30.79 (14.8)
Number of prescriptions/medication orders dispensed per day (n=363)		174.67 (119.7)
Current job title at primary place of employment (n=377)		
Staff pharmacist	160 (42.4)	
Pharmacy manager	102 (27.1)	
Pharmacy owner/Partner	44 (11.7)	
Clinical pharmacist	37 (9.8)	
Relief pharmacist	24 (6.4)	
Other [a]	10 (2.7)	
Area/setting of primary place of employment (n=375)		
Urban	175 (46.7)	
Suburban	126 (33.6)	
Rural	74 (19.7)	
Practice setting (n=377)		
Community—multiple/chain	159 (42.2)	
Community—independent	74 (19.6)	
Hospital—multiple/chain	58 (15.4)	
Hospital—independent	44 (11.7)	
Other [b]	42 (11.1)	

[a] Ten pharmacists indicated 'Other' category for their current job title, including pharmacy informatics (n = 2), consultancy (n = 2), general manager, clinical pharmacy coordinator (n = 2), assistant pharmacy manager, pharmacist-in-charge and vice-president.

[b] Forty two pharmacists indicated 'Other' category for their practice setting. Government hospital was the most common 'Other' practice setting. Other settings specified by the respondents include Veterans Affairs, community health center/clinic, home infusion, long term care, army/military, county hospital/clinic, surgery center, city health department, mail order, research, worksite pharmacy, home health care and correctional managed care. Four respondents who checked the other category did not specify their practice setting.

5.6 KNOWLEDGE SCORES

Less than 75 percent of the respondents got items 1, 3 and 6 correct (Table 5.10). The lowest pass rate was achieved for the first item with 43.3 percent of pharmacists responding that all ADEs irrespective of severity should be reported to the FDA, whereas MedWatch stipulates that only serious ADEs should be reported. About 35 percent of pharmacists did not know that they could report serious ADEs even if they did not have all the details (complete patient history and demographic data) (item 3). Thirty percent of the pharmacists did not know that they could anonymously report ADEs to the FDA. The highest pass rate was achieved for item four (4) with 361 (96.0%) respondents knowing that not all serious ADEs are known before a drug is marketed. None of the items had a 100 percent pass rate. A majority of the respondents (n = 247, 65.7%) considered themselves to have inadequate knowledge about ADE reporting (e.g., what to report and how to report).

Table 5.10: Pharmacists with Correct Responses on Knowledge Items

Item	N	Number (%) with correct responses
1. All ADEs, irrespective of severity, should be reported to the FDA [false].	374	212 (56.7)
2. Pharmacists should report serious ADEs even if they are uncertain that the product caused the event [true].	376	298 (79.3)
3. Pharmacists should report serious ADEs even if they do not have all the details (e.g., complete patient history and demographic data) [true].	376	244 (64.9)
4. All serious ADEs are known before a drug is marketed [false].	376	361 (96.0)
5. The FDA does not disclose the ADE reporter's identity in response to a request from the public [true].	370	295 (79.7)
6. Pharmacists can report ADEs to the FDA anonymously [true]	370	259 (70.0)
7. Adverse experiences with cosmetics and special nutritional products (e.g., dietary supplements, infant formulas) may be reported to the FDA [true].	374	308 (82.4)
8. One case reported by a pharmacist does not contribute much to knowledge on drug risks [false].	375	287 (76.5)

[=correct answer]

5.7 Theory of Planned Behavior Constructs

The study measured the following theory of planned behavior (TPB) constructs: A, SN, PBC and intention. The independent variables were measured using both direct and indirect measures. In addition, the study measured PRB and PMO.

5.7.1 Intention

Intention was measured using three items. The means for these items were 5.16 (SD = 1.51), 5.44 (SD = 1.42) and 5.27 (SD = 1.50) (possible range: 1-7; Table 5.11). Two hundred and sixty four (70.0%) pharmacists indicated that they were likely to intend to report serious ADEs that they encounter to the FDA, while 49 respondents (13.0%) said that they were unlikely to intend to report. Three hundred pharmacists (79.6%) agreed that they will try to report serious ADEs that they encounter to the FDA, while

276 (73.2%) indicated that they planned to report serious ADEs that they encounter to the FDA (Table 5.11). The three items were summed to form an aggregate intention score with a mean of 15.87 (SD = 4.22) (possible range: 3 - 21). This score suggests that the respondents moderately likely to intend to report serious ADEs that they encounter to the FDA.

Table 5.11: Mean and Frequency Distribution of Intention (n = 377)

Items	**Mean**	**SD**	**Frequency Distribution of Responses (%)**						
			Extremely unlikely (1)	**2**	**3**	**Neither likely nor unlikely (4)**	**5**	**6**	**Extremely likely (7)**
1. I intend to report serious ADEs that I will encounter to the FDA.	5.16	1.51	9 (2.4)	17 (4.5)	23 (6.1)	64 (17.0)	85 (22.5)	101 (26.8)	78 (20.7)
			Strongly disagree (1)	**2**	**3**	**Neither agree nor disagree (4)**	**5**	**6**	**Strongly agree (7)**
2. I will try to report serious ADEs that I will encounter to the FDA.	5.44	1.42	7 (1.9)	14 (3.7)	12 (3.2)	44 (11.7)	93 (24.7)	111 (29.4)	96 (25.5)
3. I plan to report serious ADEs that I will encounter to the FDA.	5.27	1.50	6 (1.6)	21 (5.6)	15 (4.0)	59 (15.6)	91 (24.1)	92 (24.4)	93 (24.7)
Overall mean	**15.87**	**4.22**							

5.7.2 Attitude (Direct and Indirect Measures)

The direct measure of attitude was measured using five (5) items (score: -3 to +3). The respondents believed that reporting serious ADEs to the FDA was valuable (mean = 1.83, SD = 1.26, n = 328), neither pleasant nor unpleasant (mean = 0, SD = 1.41, n = 148), good (mean = 1.37, SD = 1.49, n = 262), unenjoyable (mean = -0.24, SD = 1.40, n = 127) and beneficial (mean = 1.67, SD = 1.45, n = 281) (Table 5.12). Thirty two (8.5%), 22 (5.9%), and 21 (5.6%) respondents believed that reporting serious ADEs to the FDA was worthless, bad, and harmful, respectively. The attitude scores on the five items were summed to form a composite attitude score (direct measure). The attitude scores had a mean of 4.62 (SD = 4.92, possible range: -15 to +15) and they ranged from -12 to +15. Overall, pharmacists had a moderately favorable attitude (direct measure) towards reporting serious ADEs to the FDA.

The indirect attitude construct was measured using eight items (range: 1-7, 4 = neutral). On average, pharmacists felt that reporting serious ADEs to the FDA educates others about drug risks (mean = 5.53, SD = 1.22), and improves patient safety (mean = 5.80, SD = 1.12). Pharmacists also believed that reporting was personally beneficial/rewarding to the pharmacist (mean = 4.96, SD = 1.56), time consuming (mean = 5.06, SD = 1.55) and disrupted the normal workflow (mean = 4.55, SD = 1.65). Respondents did not believe that reporting serious ADEs to the FDA increased the risk of malpractice (mean = 3.70, SD = 1.62), compromised their relationship with physicians (mean = 3.40, SD = 1.49), and broke trust with patients (mean = 2.85, SD = 1.57) (Table 5.13).

The pharmacists rated all eight outcomes with three of them being rated as being good: educates others about drug risks (mean = 6.02, SD = 1.03), personally beneficial/rewarding to the pharmacist (mean = 5.28, SD = 1.30), and improves patient safety (mean = 6.07, SD = 0.97). They rated the rest of the outcomes as being bad:

increases risk of malpractice (mean = 3.45, SD = 1.53), compromises relationship with physicians (mean = 3.33, SD = 1.39), breaks trust with patients (mean = 3.05, SD = 1.53), disrupts the normal workflow (mean = 3.60, SD = 1.57) and time consuming to report (mean = 3.71, SD = 1.66) (Table 5.14).

The product of behavioral beliefs and behavioral outcome evaluations was computed after reverse coding all the negatively worded items. The means for each product item are given in Table 5.15. The product of the item "Reporting serious ADEs to the FDA will improve patient safety" and its behavioral outcome evaluation had the highest mean (mean = 35.77, SD = 10.57) (Table 5.15). The overall mean for all the eight product means was 24.45 (SD = 6.73) ranging from 9 to 46 (possible range: 1 – 49, neutral = 16), indicating that pharmacists had marginally favorable A towards reporting serious ADEs to the FDA.

Table 5.12: Mean and Frequency Distribution of A Direct Measures

Q. I feel that reporting serious ADEs to the FDA each time I encounter them is:

				Frequency Distribution of Responses (%)						
Items	**N**	**Mean**	**SD**	**Worthless (-3)**	**-2**	**-1**	**0**	**1**	**2**	**Valuable (3)**
1. Worthless—valuable	376	1.83	1.26	3 (0.8)	7 (1.9)	12 (3.2)	26 (6.9)	71 (18.9)	119 (31.6)	138 (36.7)
				Unpleasant (-3)	**-2**	**-1**	**0**	**1**	**2**	**Pleasant (3)**
2. Unpleasant—pleasant	374	0.00	1.41	23 (6.1)	25 (6.7)	65 (17.4)	148 (39.6)	58 (15.5)	37 (9.9)	18 (4.8)
				Bad (-3)	**-2**	**-1**	**0**	**1**	**2**	**Good (3)**
3. Bad—good	374	1.37	1.49	9 (2.4)	9 (2.4)	14 (3.7)	80 (21.4)	55 (14.7)	103 (27.5)	104 (27.8)
				Unenjoyable (-3)	**-2**	**-1**	**0**	**1**	**2**	**Enjoyable (3)**
4. Unenjoyable—enjoyable	374	-0.24	1.40	33 (8.8)	38 (10.2)	56 (15.0)	153 (40.9)	55 (14.7)	31 (8.3)	8 (2.1)
				Harmful (-3)	**-2**	**-1**	**0**	**1**	**2**	**Beneficial (3)**
5. Harmful—beneficial	376	1.67	1.45	9 (2.4)	7 (1.9)	5 (1.3)	64 (17.0)	48 (12.8)	104 (27.4)	139 (37.0)
Overall mean		**4.62**	**4.92**							

Table 5.13: Mean and Frequency Distribution of Behavioral Beliefs

Q. How likely do you think the following outcomes will be if you report serious ADEs to the FDA?

				Frequency Distribution of Responses (%)						
Items	**N**	**Mean**	**SD**	**Extremely unlikely (1)**	**2**	**3**	**Neither likely not unlikely (4)**	**5**	**6**	**Extremely likely (7)**
1. educates others about drug risks	377	5.53	1.22	4 (1.1)	8 (2.1)	14 (3.7)	18 (4.8)	130 (34.5)	119 (31.6)	84 (22.3)
2. personally beneficial/ rewarding to the pharmacist	377	4.96	1.57	18 (4.8)	14 (3.7)	16 (4.2)	87 (23.1)	94 (24.9)	78 (20.7)	70 (18.6)
3. improves patient safety	377	5.80	1.12	2 (0.5)	4 (1.1)	7 (1.9)	26 (6.9)	90 (23.9)	136 (36.1)	112 (29.7)
4. increases risk of malpractice	377	3.70	1.62	46 (12.2)	56 (14.9)	38 (10.1)	133 (35.3)	52 (13.8)	34 (9.0)	18 (4.8)
5. compromises relationship with physicians	377	3.40	1.49	38 (10.1)	84 (22.3)	60 (15.9)	124 (32.9)	37 (9.8)	23 (6.1)	11 (2.9)
6. breaks trust with patients	377	2.85	1.57	89 (23.6)	98 (26.0)	54 (14.3)	88 (23.3)	23 (6.1)	15 (4.0)	10 (2.7)
7. disrupts the normal workflow	377	4.55	1.65	21 (5.6)	32 (8.5)	32 (8.5)	83 (22.0)	101 (26.8)	58 (15.4)	50 (13.3)
8. time consuming to report	377	5.06	1.55	13 (3.4)	19 (5.0)	18 (7.4)	43 (11.4)	113 (30.0)	93 (24.7)	68 (18.0)

Table 5.14: Mean and Frequency Distribution of Behavioral Outcome Evaluations

Q. **How good or bad do you feel each of the following outcomes would be if you reported serious ADEs to the FDA?**

				Frequency Distribution of Responses (%)						
Items	**N**	**Mean**	**SD**	**Extremely bad (1)**	**2**	**3**	**Neither likely not unlikely (4)**	**5**	**6**	**Extremely good (7)**
1. educates others about drug risks	376	6.02	1.03	-	2 (0.5)	2 (0.5)	27 (7.2)	81 (21.5)	106 (28.2)	158 (42.0)
2. personally beneficial/ rewarding to the pharmacist	376	5.28	1.30	4 (1.1)	3 (0.8)	14 (3.7)	94 (25.0)	90 (23.9)	88 (23.4)	83 (22.1)
3. improves patient safety	376	6.07	0.97	-	-	5 (1.3)	21 (5.6)	72 (19.1)	122 (32.4)	156 (41.5)
4. increases risk of malpractice	373	3.45	1.53	55 (14.7)	59 (15.8)	35 (9.4)	152 (40.8)	43 (11.5)	17 (4.6)	12 (3.2)
5. compromises relationship with physicians	375	3.33	1.39	50 (13.3)	58 (15.5)	62 (16.5)	157 (41.9)	26 (6.9)	15 (4.0)	7 (1.9)
6. breaks trust with patients	376	3.05	1.53	82 (21.8)	69 (18.4)	48 (12.8)	132 (35.1)	22 (5.9)	16 (4.3)	7 (1.9)
7. disrupts the normal workflow	376	3.60	1.57	46 (12.2)	36 (9.6)	92 (24.5)	114 (30.3)	45 (12.0)	21 (5.6)	22 (5.9)
8. time consuming to report	376	3.71	1.66	40 (10.6)	47 (12.5)	91 (24.2)	91 (24.2)	47 (12.5)	32 (8.5)	28 (7.4)

Table 5.15: Mean and Standard Deviation of the Product of Behavioral Belief and Behavioral Outcome Evaluation Scores

Behavioral Beliefs and Outcome Evaluation	**N**	**Mean**	**SD**
1. Reporting serious ADEs to the FDA will educate others about drug risks	376	33.98	10.95
2. Reporting serious ADEs to the FDA is personally beneficial/rewarding to the pharmacist	376	27.50	12.87
3. Reporting serious ADEs to the FDA will improve patient safety	376	35.77	10.57
4. Reporting serious ADEs to the FDA will increase risk of malpractice	373	20.72	11.80
5. Reporting serious ADEs to the FDA will compromise relationship with physicians	375	22.53	11.21
6. Reporting serious ADEs to the FDA will break trust with patients	376	26.50	12.69
7. Reporting serious ADEs to the FDA will disrupt the normal workflow	376	15.59	9.90
8. Reporting serious ADEs to the FDA is time consuming	376	13.02	8.85
Overall mean	**376**	**24.45**	**6.73**

Note: The belief and behavioral outcome evaluation ratings for items 4 to 8 were first reverse coded before being multiplied.

5.7.3 Subjective Norm (Direct and Indirect Measures)

The direct measure of subjective norm was measured through three (3) items (score: -3 to +3). The average SN across these three items was 5.65 (SD = 2.99) ranging from -5 to +9. Three hundred and eight (81.9%) pharmacists believed that most people who were important to them thought that they should report serious ADEs that they encounter to the FDA (mean = 1.83, SD = 1.15), while 64 (17.0%) were neutral. Three hundred and forty two (91.0%) pharmacists believed that the people in their lives whose opinions they valued would approve their reporting of serious ADEs that they encounter to the FDA (mean = 2.19, SD = 0.99). A majority of pharmacists (n = 298, 79.2%) also believed that the pharmacists whose opinions they valued report serious ADEs to the FDA (mean = 1.62, SD = 1.34) (Table 5.16).

The indirect measure of SN was measured using nine (9) items (range: 1-7, 4 = neutral). On average, pharmacists believed that physicians (mean = 4.97, SD = 1.53), patients (mean = 5.76, SD = 1.32), drug manufacturers (mean = 4.37, SD = 1.91), the Food and Drug Administration (mean = 6.02, SD = 1.32), pharmacy associations (mean = 5.71, SD = 1.37), family/spouse/significant others (mean = 5.08, SD = 1.52), pharmacy managers/bosses (mean = 5.09, SD = 1.49), hospitals or hospital groups (mean = 5.26, SD = 1.37), and other pharmacists (mean = 5.23, SD = 1.30) were likely to think that they should report serious ADEs to the FDA (Table 5.17). The largest number of pharmacists (n = 320, 85.3%) believed that the FDA was likely to think that they should report serious ADEs.

When it came to reporting ADEs to the FDA, a majority of pharmacists were likely to do what physicians (mean = 5.12, SD = 1.43, n = 243), patients (mean = 5.59, SD = 1.26, n = 319), drug manufacturers (mean = 4.56, SD = 1.65, n = 190), the FDA (mean =5.63, SD = 1.30, n = 320), pharmacy associations (mean = 5.25, SD = 1.26, n = 306), family/spouses/significant others (mean = 5.13, SD = 1.49, n = 228), pharmacy

managers/bosses (mean = 5.43, SD = 1.39, n = 249), hospitals or hospital groups (mean = 5.12, SD = 1.39, n = 262) and other pharmacists (mean = 5.16, SD = 1.33, n = 274) would want them to do (Table 5.18).

The mean indirect SN scores were high, indicating a favorable subjective norm (mean = 28.75, SD = 9.38; range: 2 – 29, possible range: 1 – 49, neutral =16). The FDA appeared to be the most influential with respect to reporting serious ADEs (had the highest mean of 34.82, SD = 12.16), while drug manufacturers appeared to be the least influential with the least mean SN of 21.55 (SD = 13.83) (Table 5.19). The overall mean of 28.75 indicates that the referents had moderate influence on the pharmacists' when it comes to reporting serious ADEs to the FDA.

Table 5.16: Mean and Frequency Distribution of SN Direct Measure

				Frequency Distribution of Responses (%)						
Items	**N**	**Mean**	**SD**	**I should not (-3)**	**-2**	**-1**	**0**	**+1**	**+2**	**I should (+3)**
1. Most people who are important to me think that… report serious ADEs that I encounter to the FDA	376	1.84	1.15	1 (0.3)	1 (0.3)	2 (0.5)	64 (17.0)	55 (14.6)	114 (30.3)	139 (37.0)
				Disapprove (-3)	**-2**	**-1**	**0**	**+1**	**+2**	**Approve (+3)**
2. The people in my life whose opinions I value would…my reporting of serious ADEs that I encounter to the FDA.	376	2.19	0.99	1 (0.3)	-	1 (0.3)	32 (8.5)	36 (9.6)	126 (33.5)	180 (47.9)
				Do not report (-3)	**-2**	**-1**	**0**	**+1**	**+2**	**Report (+3)**
3. The pharmacists whose opinion I value…serious ADEs to the FDA	375	1.62	1.34	5 (1.3)	9 (2.4)	2 (0.5)	62 (16.5)	69 (18.4)	109 (29.1)	119 (31.7)
Overall mean	**375**	**5.65**	**2.99**							

Table 5.17: Mean and Frequency Distribution of Normative Beliefs

Q. How likely is it that each of the following groups or individuals would think that you should report serious ADEs to the FDA?

				Frequency Distribution of Responses (%)						
Items	**N**	**Mean**	**SD**	**Very unlikely (1)**	**2**	**3**	**Neither likely nor unlikely (4)**	**5**	**6**	**Very likely (7)**
1. Physicians	377	4.97	1.53	13 (3.4)	18 (4.8)	17 (4.5)	86 (22.8)	98 (26.0)	75 (19.9)	70 (18.6)
2. Patients	377	5.76	1.32	6 (1.6)	5 (1.3)	8 (2.1)	39 (10.3)	79 (21.0)	100 (26.5)	140 (37.1)
3. Drug manufacturers	375	4.37	1.91	41 (10.9)	34 (9.1)	42 (11.2)	68 (18.1)	72 (19.2)	53 (14.1)	65 (17.3)
4. Food and Drug Administration	375	6.02	1.32	4 (1.1)	7 (1.9)	5 (1.3)	39 (10.4)	47 (12.5)	78 (20.8)	195 (52.0)
5. Pharmacy associations	377	5.71	1.37	7 (1.9)	4 (1.1)	8 (2.1)	52 (13.8)	73 (19.4)	91 (24.1)	142 (37.7)
6. Family/spouse/significant others	377	5.08	1.52	13 (3.4)	8 (2.1)	11 (2.9)	117 (31.0)	74 (19.6)	61 (16.2)	93 (24.7)
7. Pharmacy managers/bosses	377	5.09	1.49	10 (2.7)	13 (3.4)	21 (5.6)	84 (22.3)	84 (22.3)	91 (24.1)	74 (19.6)
8. Hospitals or hospital groups	376	5.26	1.37	7 (1.9)	4 (1.1)	18 (4.8)	85 (22.6)	85 (22.6)	96 (25.5)	81 (21.5)
9. Other pharmacists (colleagues/peers)	377	5.23	1.30	6 (1.6)	8 (2.1)	8 (2.1)	81 (21.5)	112 (29.7)	91 (24.1)	71 (18.8)

Table 5.18: Mean and Frequency Distribution of Motivation to Comply

Q. Generally speaking, how likely are you to do what the following individuals or groups would want you to do when it comes to ADE reporting?

				Frequency Distribution of Responses (%)						
Items	**N**	**Mean**	**SD**	**Extremely unlikely (1)**	**2**	**3**	**Neither likely nor unlikely (4)**	**5**	**6**	**Extremely likely (7)**
1. Physicians	374	5.12	1.43	12 (3.2)	5 (1.3)	11 (2.9)	100 (26.7)	91 (24.3)	79 (21.1)	76 (20.3)
2. Patients	373	5.59	1.26	6 (1.6)	1 (0.3)	8 (2.1)	55 (14.7)	89 (23.9)	109 (29.2)	105 (28.2)
3. Drug manufacturers	374	4.56	1.66	28 (7.5)	15 (4.0)	30 (8.0)	113 (30.2)	78 (20.9)	54 (14.4)	56 (15.0)
4. Food and Drug Administration	374	5.64	1.30	6 (1.6)	3 (0.8)	7 (1.9)	56 (15.0)	77 (20.6)	109 (29.1)	116 (31.0)
5. Pharmacy associations	375	5.25	1.36	7 (1.9)	3 (0.8)	13 (3.5)	98 (26.1)	84 (22.4)	84 (22.4)	86 (22.9)
6. Family/spouse/significant Others	375	5.13	1.49	13 (3.5)	4 (1.1)	12 (3.2)	116 (30.9)	65 (17.3)	77 (20.5)	88 (23.5)
7. Pharmacy managers/bosses	375	5.43	1.39	9 (2.4)	6 (1.6)	8 (2.1)	68 (18.1)	83 (22.1)	103 (27.5)	98 (26.1)
8. Hospitals or hospital groups	375	5.13	1.39	9 (2.4)	7 (1.9)	13 (3.5)	99 (26.4)	91 (24.3)	83 (22.1)	73 (19.5)
9. Other pharmacists (colleagues/ peers)	373	5.15	1.33	9 (2.4)	6 (1.6)	8 (2.1)	92 (24.7)	105 (28.2)	89 (23.9)	64 (17.2)

Table 5.19: Mean and Standard Deviation of the Product of Normative Beliefs and Motivation to Comply Scores

Normative Beliefs and Motivation to Comply	**N**	**Mean**	**SD**
1. Physicians	374	26.43	12.57
2. Patients	373	32.93	11.99
3. Drug manufacturers	372	21.55	13.83
4. Food and Drug Administration	372	34.82	12.16
5. Pharmacy associations	375	30.98	12.67
6. Family/spouse/significant others	375	27.31	13.30
7. Pharmacy managers/bosses	375	28.77	12.71
8. Hospitals or hospital groups	374	28.07	12.51
9. Other pharmacists (colleagues/peers)	373	27.94	11.78
Overall mean	**365**	**28.75**	**9.38**

5.7.4 Perceived Behavioral Control (Direct and Indirect Measures)

The direct PBC construct was measured through two (2) items (score: -3 to +3). A majority of pharmacists (n = 319, 85.1%) believed that it was mostly up to them whether or not they report serious ADEs to the FDA (mean = 1.83, SD = 1.51) and that they had control over reporting serious ADEs that they encounter to the FDA (n = 317, 84.8%, mean = 1.71, SD = 1.46) (Table 5.20). The overall mean PBC score was high (mean = 3.54, SD = 2.69) indicating a positive and high control over reporting serious ADEs (possible/actual range: -6 to +6, 0 = neutral) (Table 5.20).

The indirect PBC construct was measured through eleven (11) items (range = 1-7, 4 = neutral). Pharmacists believed that a complete patient medical history (n = 204, mean = 4.41, SD = 1.92), improved awareness of ADE reporting (n = 269, mean = 5.03, SD = 1.25), a streamlined MedWatch form and reporting process (n = 319, mean = 5.61, SD = 1.24), employer support of ADE reporting (n = 291, mean = 5.42, SD = 1.28), some type of reward or compensation for reporting serious ADEs (n = 136, mean = 4.54, SD = 1.31), ADE reporting as a part of the normal workflow (n = 270, mean = 5.14, SD = 1.47), increased patient counseling (spending more time with patients) (n = 245, mean = 4.94, SD = 1.56), awareness of drug risks by patients (n = 261, mean = 5.09, SD = 1.25), being a drug expert (n = 297, mean = 5.44, SD = 1.17), and clear knowledge of what constitutes a reportable ADE (e.g., definition) (n = 319, mean = 5.71, SD = 1.20) will make it easy for them to report serious ADEs that they encounter to the FDA. A majority of pharmacists (n = 304, mean = 2.55, SD = 1.34) believed that lack of time will make it difficult for them to report serious ADEs that they encounter to the FDA (Table 5.21).

Pharmacists believed that they did not have control over having a complete patient medical history (mean = 3.30, SD = 1.81), lack of time (mean = 2.99, SD = 1.49), a streamlined MedWatch form and reporting process (mean = 3.42, SD = 1.77), employer support of ADE reporting (mean = 3.75, SD = 1.79), some type of reward or

compensation (mean = 2.67, SD = 1.61) and having ADE reporting as a part of the normal workflow (mean = 3.62, SD = 1.68). Pharmacists however believed that they had control over improved awareness of ADE reporting (mean = 4.43, SD = 1.45), increased patient counseling (mean = 4.17, SD = 1.67), awareness of drug risks by patients (mean = 4.27, SD = 1.52), being a drug expert (mean = 5.31, SD = 1.28), and having a clear knowledge of what constitutes a reportable ADE (e.g., definition) (mean = 4.85, SD = 1.54) (Table 5.22).

The overall mean PBC score (indirect measure) was high (mean = 20.18, SD = 6.59; range: 5–45) (possible range: 1 – 49, neutral = 16) indicating that pharmacists perceived themselves as having more control of reporting serious ADEs to the FDA (Table 5.23).

Table 5.20: Mean and Frequency Distribution of PBC Direct Measures

				Frequency Distribution of Responses (%)						
Items	**N**	**Mean**	**SD**	**Strongly disagree (-3)**	**-2**	**-1**	**0**	**+1**	**+2**	**Strongly agree (+3)**
1. It is mostly up to me whether or not I report serious ADEs to the FDA.	375	1.83	1.51	13 (3.5)	8 (2.1)	11 (2.9)	24 (6.4)	50 (13.3)	106 (28.3)	163 (43.5)
	N	**Mean**	**SD**	**No control (-3)**	**-2**	**-1**	**0**	**+1**	**+2**	**Complete control (+3)**
2. How much control do you believe you have over reporting serious ADEs that you encounter to the FDA?	374	1.71	1.46	12 (3.2)	7 (1.9)	10 (2.7)	28 (7.5)	71 (19.0)	108 (28.9)	138 (36.9)
Overall mean	**375**	**3.54**	**2.69**							

Table 5.21: Mean and Frequency Distribution of Control Beliefs

Q. How easy or difficult will the following factors make it for you to report serious ADEs that you encounter to the FDA?

				Frequency Distribution of Responses (%)						
Items	**N**	**Mean**	**SD**	**Extremely difficult (1)**	**2**	**3**	**Neither easy nor difficult (4)**	**5**	**6**	**Extremely easy (7)**
1. a complete patient medical history	376	4.41	1.92	38 (10.1)	44 (11.7)	40 (10.6)	50 (13.3)	69 (18.4)	79 (21.0)	56 (14.9)
2. lack of time	377	2.55	1.34	92 (24.4)	107 (28.4)	105 (27.9)	45 (11.9)	13 (3.4)	9 (2.4)	6 (1.6)
3. improved awareness of ADE reporting	374	5.03	1.25	3 (0.8)	13 (3.5)	22 (5.9)	67 (17.9)	140 (37.4)	86 (23.0)	43 (11.5)
4. a streamlined MedWatch form and reporting process	376	5.61	1.24	3 (0.8)	10 (2.7)	8 (2.1)	36 (9.6)	89 (23.7)	138 (36.7)	92 (24.5)
5. employer support of ADE reporting	375	5.42	1.28	6 (1.6)	3 (0.8)	15 (4.0)	58 (15.5)	97 (25.9)	115 (30.7)	81 (21.6)
6. some type of reward or compensation	376	4.54	1.31	11 (2.9)	8 (2.1)	14 (3.7)	207 (55.1)	47 (12.5)	49 (13.0)	40 (10.6)
7. ADE reporting as a part of the normal workflow	377	5.14	1.47	7 (1.9)	17 (4.5)	30 (8.0)	51 (13.5)	99 (26.3)	104 (27.6)	69 (18.3)
8. increased patient counseling	377	4.94	1.56	16 (4.2)	17 (4.5)	26 (6.9)	73 (19.4)	84 (22.3)	103 (27.3)	58 (15.4)

Table 5.21: Mean and Frequency Distribution of Control Beliefs

Q. How easy or difficult will the following factors make it for you to report serious ADEs that you encounter to the FDA?

				Frequency Distribution of Responses (%)						
Items	**N**	**Mean**	**SD**	**Extremely difficult (1)**	**2**	**3**	**Neither easy nor difficult (4)**	**5**	**6**	**Extremely easy (7)**
9. awareness of drug risks by patients	375	5.09	1.25	4 (1.1)	7 (1.9)	23 (6.1)	80 (21.3)	112 (29.9)	103 (27.5)	46 (12.3)
10. being a drug expert	377	5.44	1.17	5 (1.3)	1 (0.3)	8 (2.1)	66 (17.5)	93 (24.7)	138 (36.6)	66 (17.5)
11. clear knowledge of what constitutes a reportable ADE (e.g., definition)	375	5.71	1.20	3 (0.8)	4 (1.1)	9 (2.4)	40 (10.7)	79 (21.1)	131 (34.9)	109 (29.1)

Table 5.22: Mean and Frequency Distribution of Perceived Power Over Reporting ADEs

Q. How much control do you feel you have over the following factors when it comes to reporting serious ADEs to the FDA?

				Frequency Distribution of Responses (%)						
Items	**N**	**Mean**	**SD**	**No Control (1)**	**2**	**3**	**Neither complete control nor no control (4)**	**5**	**6**	**Complete control (7)**
1. a complete patient medical history	375	3.30	1.81	86 (22.9)	57 (15.2)	63 (16.8)	59 (15.7)	65 (17.3)	26 (6.9)	19 (5.1)
2. lack of time	376	2.99	1.49	63 (16.8)	92 (24.5)	98 (26.1)	61 (16.2)	42 (11.2)	9 (2.4)	11 (2.9)
3. improved awareness of ADE reporting	375	4.43	1.45	8 (2.1)	26 (6.9)	64 (17.1)	92 (24.5)	106 (28.3)	41 (10.9)	38 (10.1)
4. a streamlined MedWatch form and reporting process	377	3.42	1.77	77 (20.4)	49 (13.0)	59 (15.6)	95 (25.2)	49 (13.0)	25 (6.6)	23 (6.1)
5. employer support of ADE reporting	377	3.75	1.79	59 (15.6)	42 (11.1)	53 (14.1)	100 (26.5)	58 (15.5)	34 (9.0)	31 (8.2)
6. some type of reward or compensation	374	2.76	1.61	138 (36.9)	38 (10.2)	26 (7.0)	140 (37.4)	18 (4.8)	6 (1.6)	8 (2.1)
7. ADE reporting as a part of the normal workflow	376	3.62	1.68	53 (14.1)	52 (13.8)	63 (16.8)	92 (24.5)	70 (18.6)	24 (6.4)	22 (5.9)
8. increased patient counseling	377	4.17	1.67	31 (8.2)	38 (10.1)	60 (15.9)	63 (16.7)	107 (28.4)	49 (13.0)	29 (7.7)
9. awareness of drug risks by patients	377	4.27	1.52	24 (6.4)	27 (7.2)	52 (13.8)	89 (23.6)	112 (29.7)	50 (13.3)	23 (6.1)

Table 5.22: Mean and Frequency Distribution of Perceived Power Over Reporting ADEs

Q. How much control do you feel you have over the following factors when it comes to reporting serious ADEs to the FDA?

				Frequency Distribution of Responses (%)						
Items	**N**	**Mean**	**SD**	**No Control (1)**	**2**	**3**	**Neither complete control nor no control (4)**	**5**	**6**	**Complete control (7)**
10. being a drug expert	377	5.31	1.28	6 (1.6)	3 (0.8)	15 (4.0)	72 (19.1)	102 (27.1)	106 (28.1)	73 (19.4)
11. clear knowledge of what constitutes a reportable ADE (e.g., definition)	377	4.85	1.54	13 (3.4)	17 (4.5)	38 (10.1)	75 (19.9)	94 (24.9)	84 (22.3)	56 (14.9)

Table 5.23: Mean and Standard Deviation of the Product of Control Belief and Perceived Power Over Reporting ADEs

Control Beliefs and Perceived Power Over Reporting	**N**	**Mean**	**SD**
1. a complete patient medical history	374	15.74	12.08
2. lack of time	376	8.62	7.54
3. improved awareness of ADE reporting	372	23.02	10.58
4. a streamlined MedWatch form and reporting process	376	19.44	11.86
5. employer support of ADE reporting	375	20.88	12.20
6. some type of reward or compensation	374	12.71	8.90
7. ADE reporting as a part of the normal workflow	376	19.35	11.85
8. increased patient counseling (spending more time with patients)	377	21.64	11.94
9. awareness of drug risks by patients	375	22.49	11.01
10. being a drug expert	377	29.69	10.96
11. clear knowledge of what constitutes a reportable ADE (e.g., definition)	375	28.37	11.98
Overall mean	**377**	**21.96**	**6.59**

5.7.5 Correlations Among TPB Constructs

Tables 5.24 and 5.25 show the correlations among the TPB direct measure constructs and indirect measure constructs, respectively. Among the direct and indirect measure TPB constructs, SN had the highest correlation with intention.

Table 5.24: Correlations of the TPB Direct Measure Constructs

TPB Constructs	Intention	Attitude Direct	Subjective Norm Direct	PBC Direct
Intention Direct	1.000			
Attitude Direct	0.420**	1.000		
Subjective Norm Direct	0.549**	0.455**	1.000	
PBC Direct	0.199**	0.186**	0.293**	1.000

** Correlation is significant at the 0.01 level

Table 5.25: Correlations of the TPB Belief-Based Constructs

TPB Constructs	Intention	Attitude Indirect	Subjective Norm Indirect	PBC Indirect
Intention	1.000			
Attitude Indirect	0.331**	1.000		
Subjective Norm Indirect	0.434**	0.407**	1.000	
PBC Indirect	0.471**	0.416**	0.516**	1.000

** Correlation is significant at the 0.01 level

A Pearson correlation showed a significant positive correlation of large strength between the direct and indirect measures of SN ($r = 0.544$, $n = 375$, $p < 0.001$). There was a positive and significant correlation between the direct and indirect measures of A ($r = 0.396$, $n = 376$, $p < 0.001$) and PBC ($r = 0.288$, $n = 375$, $p < 0.001$) (Table 5.26).

Table 5.26: Correlation Between Direct and Indirect TPB Measures

TPB Constructs	**Attitude (Indirect)**	**Subjective norm (Indirect)**	**Perceived behavioral control (Indirect)**
Attitude (Direct)	0.396**		
Subjective norm (Direct)		0.544**	
Perceived behavioral control (Direct)			0.288**

** Statistically significant ($p < 0.001$).

5.8 Past Reporting Behavior

A majority of the respondents (n = 256, 67.9%) had never reported any ADEs to the FDA through MedWatch, while 352 (93.4%) had not reported any ADEs in the previous 12 months. Only 25 respondents (6.6%) had reported ADEs to the FDA through MedWatch in the previous 12 months. Many respondents (n = 168, 44.6%) indicated that they had encountered reportable ADEs in their practice in the past. One hundred and eight respondents (28.6%) indicated that they did not know whether they had encountered any reportable ADEs in their practice in the past (Table 5.27).

Table 5.27: Past Reporting Behavior (n = 377)

Item	Frequency (%)
Ever reported an ADE to the FDA through MedWatch	
Yes	121 (32.1)
No	256 (67.9)
Reported any ADEs to the FDA through MedWatch in the previous 12 months	
Yes	25 (6.6)
No	352 (93.4)
Encountered any reportable ADEs in the past	
Yes	168 (44.6)
No	101 (26.8)
Don't know	108 (28.6)

5.9 Perceived Moral Obligation

Perceived moral obligation (PMO) was measured using a single item on a 1-to-7 bipolar Likert response scale anchored by strongly disagree and strongly agree. The mean PMO score was 5.90 (SD = 1.27). A majority (n = 324; 86.2%) of the respondents agreed that they had a moral obligation to report serious ADEs that they encounter to the FDA (Table 5.28).

Table 5.28: Perceived Moral Obligation (n = 376)

Scale	Frequency (%)
7 (strongly agree)	156 (41.2)
6	111 (29.5)
5	58 (15.4)
4 (neither agree nor disagree)	34 (9.0)
3	10 (2.7)
2	3 (0.8)
1 (strongly disagree)	5 (1.3)

5.10 HYPOTHESIS TESTING RESULTS

Data analyses were conducted using multiple regression, t-test, analysis of variance (ANOVA) and correlation analysis. A summary of the results of the hypotheses tests is provided below.

H1: Favorable attitude (A) is a positive and significant predictor of intention to report serious ADEs controlling for SN and PBC.

Multiple regression analysis was run with A, SN and PBC being the independent variables and intention as the dependent variable. Separate models were run for direct measure constructs and the belief-based (i.e., indirect) independent constructs. Both the direct and indirect measure attitude were (statistically) significant and positive predictors of intention to report serious ADEs after controlling for SN and PBC (B = 0.190, $p < 0.001$ and B = 0.009, p = 0.030, respectively) (Table 5.29). Therefore, **H1** was supported.

Table 5.29: Results of Multiple Regression Analysis for the TPB Constructs

PREDICTOR VARIABLE	B	SE	Beta (β)	t	p
Direct Measures					
Constant	11.302	0.408		27.73	<0.001
Attitude	0.190	0.041	0.221	4.64	<0.001
Subjective norm	0.620	0.069	0.438	8.95	<0.001
PBC	0.044	0.070	0.028	0.64	0.526
N = 374 pharmacists F = 63.60, df = 3, 370, $p < 0.001$, R = 0.583, $R^2 = 0.340$, Adjusted $R^2 = 0.335$					
Indirect Measures					
Constant	7.531	0.780		9.66	<0.001
Attitude	0.009	0.004	0.108	2.18	0.030
Subjective norm	0.011	0.003	0.227	4.30	<0.001
PBC	0.017	0.004	0.318	6.00	<0.001
N = 374 pharmacists F = 49.92, df = 3, 370 , $p < 0.001$, R = 0.537, $R^2 = 0.288$, Adjusted $R^2 = 0.282$					

Dependent variable = Intention, B = Unstandardized coefficients, Beta = Standardized coefficients, SE = Standard error

Since the belief-based attitude measure significantly predicted intention to report serious ADEs to the FDA, the behavioral beliefs, outcome evaluations and products for those who intend to report and those who do not intend to report were compared[8] (Tables 5.30, 5.31, and 5.32). Forty-five respondents were categorized as non-intenders, 35 were categorized as neither intenders nor non-intenders (were excluded from analysis), and 297 were categorized as intenders. When comparing intenders and non-intenders—using indirect measures—intenders had higher mean A (mean = 25.37, SD = 6.52) than non-intenders (mean = 21.01, SD = 7.13) ($t = -4.122$, $df = 339$, $p < 0.001$).

Intenders had significantly higher mean A scores than non-intenders on the following: educates others about drug risks, personally beneficial/rewarding to the pharmacist, and improves patient safety ($p < 0.05$) (Table 5.30). Non-intenders had significantly higher means on the items of reporting serious ADEs "disrupts the normal workflow" and "time consuming to report" serious ADEs than intenders ($p < 0.05$) (Table 5.30).

[8] As described in Chapter Four (page 130), all the respondents who marked from a one to a three on any of the three intention items were considered non-intenders for that item (re-coded with a -1). All responders who marked between a five and a seven on any of these three items were considered intenders for that item (re-coded with a +1). Those who coded a four on any of the three intention items were considered to be neither intenders nor non-intenders (for that item) and were re-coded with a zero. For each respondent, the dummy codes (-1s, 0s and +1s) were added together across the three intention items. This composite score was then used to categorize respondents into intenders (e.g., positive total score), non-intenders (e.g., had a negative total score) and neither intenders nor non-intenders (had a total score of zero).

Table 5.30: Behavioral Beliefs About Reporting Serious ADEs by Intenders and Non-Intenders

Behavioral Beliefs	**Means for Non-Intenders (SD) (n = 45)**	**Means for Intenders (SD) (n = 297)**	**t-test [a] (p-value)**
1. educates others about drug risks	4.91 (1.47)	5.68 (1.14)	-4.034 (p<0.001)
2. personally beneficial/rewarding to the pharmacist	4.49 (1.66)	5.10 (1.49)	-2.517 (p=0.012)
3. improves patient safety	5.24 (1.19)	5.94 (1.05)	-4.095 (p<0.001)
4. increases risk of malpractice	3.87 (1.82)	3.67 (1.62)	0.734 (p=0.463)
5. compromises relationship with physicians	3.71 (1.34)	3.35 (1.52)	1.492 (p=0.137)
6. breaks trust with patients	2.87 (1.53)	2.79 (1.57)	0.288 (p=0.773)
7. disrupts the normal workflow	5.40 (1.42)	4.39 (1.67)	3.858 (p<0.001)
8. time consuming to report	5.78 (1.36)	4.90 (1.54)	3.628 (p<0.001)

The respondents who were neutral on intention to report serious ADEs were excluded from the analysis.

[a] Equal variances were assumed in the t-test for equality of means. The Levene's test of equality of variance was not significant ($p > 0.05$) for all eight items.

Scale: 1 = very unlikely; 4 = neither unlikely nor likely; 7 = very likely; possible range: 1 to 7.

When comparing the mean behavioral outcome evaluations about reporting serious ADEs between intenders and non-intenders, intenders were more likely to believe that reporting serious ADEs educates others about drug risks, is personally beneficial/rewarding to the pharmacist, and improves patient safety ($p < 0.05$) (Table 5.31).

Table 5.31: Behavioral Outcome Evaluations About Reporting Serious ADEs by Intenders and Non-intenders

Outcome Evaluations	**Means for Non-Intenders (SD) (n)**	**Means for Intenders (SD) (n)**	**t-test (p-value)**
a. educates others about drug risks	5.49 (1.20) (n=45)	6.14 (0.96) (n=296)	-3.470* (p=0.001)
b. personally beneficial/rewarding to the pharmacist	4.71 (1.31) (n=45)	5.39 (1.25) (n=296)	-3.362 (p=0.001)
c. improves patient safety	5.58 (1.12) (n=45)	6.20 (0.87) (n=296)	-3.590* (p=0.001)
d. increases risk of malpractice	3.73 (1.62) (n=45)	3.35 (1.55) (n=293)	1.534 (p=0.126)
e. compromises relationship with physicians	3.38 (1.59) (n=45)	3.29 (1.40) (n=295)	0.393 (p=0.695)
f. breaks trust with patients	3.04 (1.58) (n=45)	3.00 1.56 (n=296)	0.165 (p=0.869)
g. disrupts the normal workflow	3.67 (2.02) (n=45)	3.58 (1.50) (n=296)	0.262* (p=0.794)
h. time consuming to report	3.93 (2.18) (n=45)	3.69 (1.58) (n=296)	0.734* (p=0.467)

The respondents who were neutral on intention were excluded from the analysis.
*Equal variances were not assumed in the t-test for equality of means. The Levene's test of equality of variance was statistically significant ($p < 0.05$).
Scale: 1 = extremely bad; 4 = neither good nor bad; 7 = extremely good; possible mean range: 1 to 7.

When comparing the mean product of behavioral outcome evaluations and behavioral beliefs about reporting serious ADEs between intenders and non-intenders, intenders were more likely to believe that reporting serious ADEs educates others about drug risks, is personally beneficial/rewarding to the pharmacist, and improves patient safety ($p < 0.05$) (Table 5.32).

Table 5.32: Product of Behavioral Beliefs and Outcome Evaluations About Reporting Serious ADEs by Intenders and Non-Intenders

Behavioral Beliefs x Outcome Evaluations	**Means for Non-Intenders (SD) (n)**	**Means for Intenders (SD) (n)**	**t-test (p-value)**
a. educates others about drug risks	28.13 (12.32) (n=45)	35.34 (10.26) (n=296)	-3.733* (p<0.001)
b. personally beneficial/rewarding to the pharmacist	22.27 (12.46) (n=45)	28.64 (12.54) (n=296)	-3.18 (p=0.002)
c. improves patient safety	29.82 (10.98) (n=45)	37.32 (9.79) (n=296)	-4.71 (p<0.001)
d. increases risk of malpractice	15.87 (12.17) (n=45)	13.53 (10.52) (n=293)	1.36 (p=0.175)
e. compromises relationship with physicians	13.60 (9.38) (n=45)	12.12 (9.62) (n=295)	0.965 (p=0.335)
f. breaks trust with patients	9.71 (8.60) (n=45)	9.30 (8.83) (n=296)	0.289 (p=0.773)
g. disrupts the normal workflow	20.60 (15.06) (n=45)	16.18 (10.39) (n=296)	1.90* (p=0.063)
h. time consuming to report	23.09 (15.68) (n=45)	18.44 (11.13) (n=296)	1.92* (p=0.061)

*Equal variances were not assumed in the t-test for equality of means. The Levene's test of equality of variance was statistically significant ($p < 0.05$). Equal variances were assumed for the rest of the items.
The respondents who were neutral on intention were excluded from the analysis.
Possible mean range: 1 to 49.

H2: SN supporting ADE reporting is a positive and significant predictor of intention to report serious ADEs controlling for A and PBC.

Table 5.29 indicates that both the direct (B = 0.620, p < 0.001) and indirect (B = 0.011, p < 0.001) SN measures were positive and significant predictors of intention, after controlling for A and PBC. Therefore, **H2** was supported. Overall, intenders (mean = 6.31, SD = 2.67) had higher SN (direct measure) than non-intenders (mean = 2.91, SD = 2.80) (t = -7.913, df = 339, p < 0.001). Intenders had higher mean SN scores than non-intenders on all three direct measure items (Table 5.33).

Table 5.33: Mean SN Between Intenders and Non-Intenders

Direct Measure Items	**Mean for Non-Intenders (SD), n**	**Means for Intenders (SD), n**	**t-test [a] (p-value)**
1. Most people who are important to me think that I should/should not report serious ADEs that I encounter to the FDA.	0.82 (1.11) 45	2.08 1.05 296	-7.445 <0.001
2. The people in my life whose opinions I value would approve/ disapprove my reporting of serious ADEs that I encounter to the FDA.	1.44 0.99 45	2.37 0.89 296	-6.399 <0.001
3. The pharmacists whose opinion I value report/do not report serious ADEs to the FDA.	0.64 1.42 45	1.87 1.23 295	-6.125 <0.001
Overall	**2.91** **(2.80)**	**6.31** **(2.67)**	**-7.913** **<0.001**

The respondents who were neutral on intention were excluded from the analysis.
[a] Equal variances were assumed in the t-test for equality of means. The Levene's test of equality of variance was not statistically significant for all items (p > 0.05).
Scale: -3 (e.g., disapproave) to +3 (e.g., approave), 0 = neutral.

Using indirect measures, overall intenders also had higher mean SN (mean = 30.24, SD = 9.17) than non-intenders (mean = 22.39, SD = 8.03) (t = -5.433, df = 338, p < 0.001). When comparing the normative belief mean scores between intenders and non-

intenders, intenders had significantly higher mean scores than non-intenders on all the nine salient referents (Table 5.34).

Table 5.34: Normative Beliefs About Reporting Serious ADEs by Intenders and Non-Intenders

Behavioral Beliefs	**Means for Non-Intenders (SD) (n)**	**Means for Intenders (SD) (n)**	**t-test [*] (p-value)**
1. Physicians	4.22 (1.72) 45	5.15 (1.47) 297	-3.858 (p<0.001)
2. Patients	5.02 (1.43) 45	5.91 (1.26) 297	-4.281 (p<0.001)
3. Drug manufacturers	3.33 (1.83) 45	4.55 (1.89) 296	-4.042 (p< 0.001)
4. Food and Drug Administration	5.49 (1.56) 43	6.14 (1.26) 297	-2.619* (p=0.012)
5. Pharmacy associations	4.96 (1.55) 45	5.91 (1.26) 297	-4.574 (p<0.001)
6. Family/spouse/significant Others	4.31 (1.86) 45	5.27 (1.44) 297	-3.326* (p=0.002)
7. Pharmacy managers/bosses	4.33 (1.61) 45	5.26 (1.42) 297	-3.978 (p<0.001)
8. Hospitals or hospital groups	4.78 (1.43) 45	5.39 (1.33) 296	-2.836 (p=0.005)
9. Other pharmacists (colleagues/peers)	4.18 (1.32) 45	5.46 (1.23) 297	-6.461 (p<0.001)

Respondents who were neutral on intention were excluded from the analysis.
[*]Equal variances were not assumed in the t-test for equality of means. The Levene's test of equality of variance was significant ($p < 0.05$).
Scale: 1 = very unlikely; 4 = neither unlikely nor likely; 7 = very likely; possible range: 1 to 7.

When comparing the mean motivation to comply about reporting serious ADEs between intenders and non-intenders, intenders were more likely to be motivated to comply with physicians, patients, drug manufacturers, FDA, pharmacy associations, family/spouses/significant others, hospital or hospital groups, and other pharmacists (colleagues/peers) ($p < 0.05$) (Table 5.35) than non-intenders. There was, however, no significant difference in mean motivation to comply between intenders and non-intenders on the influence of pharmacy managers/bosses and physicians ($p > 0.05$) (Table 5.35).

Table 5.35: Motivation to Comply With Referents Concerning Reporting Serious ADEs by Intenders and Non-intenders

Outcome Evaluations	**Means for Non-Intenders (SD) (n)**	**Means for Intenders (SD) (n)**	**t-test [a] (p-value)**
1. Physicians	4.80 (1.27) (n=45)	5.22 (1.47) (n=295)	-1.815 (p=0.070)
2. Patients	5.20 (1.24) (n=45)	5.68 (1.26) (n=293)	-2.358 (p=0.019)
3. Drug manufacturers	3.80 (1.66) (n=45)	4.70 (1.66) (n=294)	-3.399 (p=0.001)
4. Food and Drug Administration	4.93 (1.44) (n=45)	5.80 (1.24) (n=294)	-4.255 (p<0.001)
5. Pharmacy associations	4.38 (1.39) (n=45)	5.44 (1.32) (n=295)	-5.005 (p<0.001)
6. Family/spouse/significant Others	4.49 (1.56) (n=45)	5.23 (1.48) (n=295)	-3.116 (p=0.002)
7. Pharmacy managers/bosses	5.11 (1.45) (n=45)	5.54 (1.36) (n=295)	-1.946 (p=0.052)
8. Hospitals or hospital groups	4.56 (1.25) (n=45)	5.27 (1.40) (n=295)	-3.260 (p<0.001)
9. Other pharmacists (colleagues/peers)	4.47 (1.24) (n=45)	5.30 (1.33) (n=293)	-3.968 (p<0.001)

Respondents who were neutral on intention were excluded from the analysis.
[a] Equal variances were assumed in the t-test for equality of means. The Levene's test of equality of variance was not statistically significant ($p > 0.05$) for all the items.
Scale: 1 = extremely unlikely; 4 = neither likely nor unlikely; 7 = extremely likely; possible mean range: 1 to 7.

When comparing the mean product of normative beliefs and motivation to comply with referents concerning reporting serious ADEs between intenders and non-intenders, intenders were more likely to believe that referents expected them to report serious ADEs than did non-intenders ($p < 0.05$) (Table 5.36).

Table 5.36: Product of Normative Beliefs and Motivation to Comply Concerning Reporting Serious ADEs by Intenders and Non-Intenders

Beliefs x Outcome evaluations	**Means for Non-Intenders (SD) (n)**	**Means for Intenders (SD) (n)**	**t-test (p-value)**
1. Physicians	20.71 (11.61) (n=45)	27.93 (12.69) (n=295)	-3.594 (p<0.001)
2. Patients	27.20 (11.71) (n=45)	34.18 (11.95) (n=293)	-3.661 (p<0.001)
3. Drug manufacturers	14.13 (10.63) (n=45)	22.97 (14.13) (n=293)	-4.946* (p<0.001)
4. Food and Drug Administration	29.26 (12.16) (n=43)	36.21 (11.86) (n=294)	-3.578 (p<0.001)
5. Pharmacy associations	22.76 (11.30) (n=45)	32.96. (12.31) (n=295)	-5.233 (p<0.001)
6. Family/spouse/significant Others	21.51 (13.69) (n=45)	28.58 (13.26) (n=295)	-3.319 (p=0.001)
7. Pharmacy managers/bosses	23.76 (12.84) (n=45)	30.05 (12.64) (n=295)	-3.143 (p=0.002)
8. Hospitals or hospital groups	22.91 (11.58) (n=45)	29.48 (12.50) (n=294)	-3.314 (p=0.001)
9. Other pharmacists (colleagues/peers)	19.64 (8.86) (n=45)	29.82 (11.70) (n=293)	-6.841* (p<0.001)

*Equal variances were not assumed in the t-test for equality of means. The Levene's test of equality of variance was statistically significant ($p < 0.05$). Equal variances were assumed in the rest of the items.
Respondents who were neutral on intention were excluded from the analysis.
Possible mean range: 1 to 49.

H3: Strong perceived behavioral control (PBC) is a positive and significant predictor of intention to report serious ADEs controlling for A and SN.

The PBC (indirect measure) was a positive and statistically significant predictor of intention (B = 0.017, p< 0.001), but the direct PBC construct was not statistically significant (B = 0.044, p = 0.526) (Table 5.29). Therefore, **H3** was supported using belief-based measures but not supported using direct measures. Using indirect measures, intenders (overall) had higher mean PBC (mean = 21.61, SD = 7.12) than non-intenders (mean = 14.76, SD = 4.96) (t = -8.094, df = 74.69, p < 0.001). Since the belief-based PBC was a statistically significant predictor of intention to report serious ADEs to the FDA, Tables 5.37, 5.38, and 5.39 provide a comparison of the control beliefs, perceived power and products of control beliefs and perceived power between those who intend to report and those who do not intend to report.

Intenders had statistically significantly higher means than the non-intenders on nine of the 11 control beliefs (p < 0.05). The greatest mean difference between intenders and non-intenders was on the increased patient counseling item. Intenders were more likely to believe that they had control over a complete patient medical history, lack of time, a streamlined MedWatch form and reporting process, employer support of ADE reporting, ADE reporting as a part of the normal workflow, increased patient counseling, awareness of drug risks by patients, being a drug expert, and clear knowledge of what constitutes a reportable ADE than non-intenders. There were no statistically significant differences in the means for improved awareness of ADE reporting and some type of reward or compensation items (p > 0.05) (Table 5.37). However, intenders had significantly higher means on all perceived power items than non-intenders (p < 0.05) (Table 5.38).

Table 5.37: Control Beliefs About Reporting Serious ADEs by Intenders and Non-Intenders

Controls Beliefs (N)	**Means for Non-Intenders (SD) (n)**	**Means for Intenders (SD) (n)**	**t-test (p-value)**
a. a complete patient medical history	3.80 (1.83) (n=45)	4.62 (1.89) (n=296)	-2.715 (p=0.007)
b. lack of time	2.18 (1.23) (n=45)	2.65 (1.34) (n=297)	-2.221 (p=0.027)
c. improved awareness of ADE reporting	4.93 (1.27) (n=45)	5.16 (1.16) (n=295)	-1.217 (p=0.225)
d. a streamlined MedWatch form and reporting process	5.22 (1.36) (n=45)	5.77 (1.12) (n=296)	-2.966 (p=0.003)
e. employer support of ADE reporting	5.09 (1.29) (n=45)	5.59 (1.18) (n=295)	-2.600 (p=0.010)
f. some type of reward or compensation	4.73 (1.25) (n=45)	4.54 (1.31) (n=296)	0.944 (p=0.346)
g. ADE reporting as a part of the normal workflow	4.44 (1.75) (n=45)	5.34 (1.35) (n=297)	-3.297* (p=0.002)
h. increased patient counseling (spending more time with patients)	4.09 (1.65) (n=45)	5.18 (1.46) (n=297)	-4.558 (p<0.001)
i. awareness of drug risks by patients	4.47 (1.34) (n=45)	5.24 (1.22) (n=295)	-3.910 (p<0.001)
j. being a drug expert	5.09 (1.15) (n=45)	5.59 (1.09) (n=297)	-2.863 (p=0.004)
k. clear knowledge of what constitutes a reportable ADE (e.g., definition)	5.18 (1.27) (n=45)	5.85 (1.16) (n=295)	-3.603 (p<0.001)

*Equal variances were not assumed in the t-test for equality of means. The Levine's test for equality of variances was statistically significant ($p < 0.05$).
The respondents who were neutral were excluded from the analysis.
Scale: 1 = extremely difficult; 4 = neither easy nor difficult; 7 = extremely easy; possible mean range: 1 to 7.

Table 5.38: Perceived Power About Reporting Serious ADEs by Intenders and Non-Intenders

Perceived Power	**Means for Non-Intenders (SD) (n)**	**Means for Intenders (SD) (n)**	**t-test (p-value)**
a. a complete patient medical history	2.38 (1.30) (n=45)	3.50 (1.83) (n=295)	-5.075 (p<0.001)
b. lack of time	2.38 (1.35) (n=45)	3.14 (1.51) (n=296)	-3.197 (p=0.002)
c. improved awareness of ADE reporting	3.67 (1.19) (n=45)	4.65 (1.42) (n=295)	-4.401 (p<0.001)
d. a streamlined MedWatch form and reporting process	2.49 (1.39) (n=45)	3.59 (1.82) (n=297)	-4.727 (p<0.001)
e. employer support of ADE reporting	2.76 (1.57) (n=45)	3.94 (1.78) (n=297)	-4.203 (p<0.001)
f. some type of reward or compensation	2.16 (1.46) (n=45)	2.88 (1.64) (n=294)	-2.795 (p=0.005)
g. ADE reporting as a part of the normal workflow	2.73 (1.36) (n=45)	3.81 (1.70) (n=294)	-4.066 (p<0.001)
h. increased patient counseling (spending more time with patients)	3.18 (1.64) (n=45)	4.37 (1.63) (n=297)	-4.595 (p<0.001)
i. awareness of drug risks by patients	3.67 (1.52) (n=45)	4.42 (1.50) (n=297)	-3.144 (p=0.002)
j. being a drug expert	4.69 (1.49) (n=45)	5.51 (1.16) (n=297)	-4.234 (p<0.001)
k. clear knowledge of what constitutes a reportable ADE (e.g., definition)	4.18 (1.39) (n=45)	5.04 (1.51) (n=297)	-3.633 (p<0.001)

*Equal variances assumed in the t-test for equality of means. Equal variances were not assumed in the rest of the items.
The respondents who were neutral were excluded from the analysis.
Scale: 1 = no control; 4 = neither complete control nor no control; 7 = complete control; possible mean range: 1 to 7.

Intenders had significantly higher means on the products of control beliefs and perceived power on 10 of the 11 items ($p < 0.05$). There was, however, no statistically significant difference on the product for the item "some type of reward or compensation" ($p > 0.05$) (Table 5.39).

Table 5.39: Product of Control Beliefs and Perceived Power About Reporting Serious ADEs by Intenders and Non-Intenders to Report Serious ADEs

Control Beliefs x Perceived Power	**Means for Non-Intenders (SD) (n)**	**Means for Intenders (SD) (n)**	**t-test (p-value)**
a. a complete patient medical history	9.80 (8.08) (n=45)	17.25 (12.45) (n=294)	-5.298* (p<0.001)
b. lack of time	5.80 (5.46) (n=45)	9.40 (7.97) (n=296)	-3.847* (p<0.001)
c. improved awareness of ADE reporting	18.56 (7.88) (n=45)	24.58 (10.50) (n=293)	-3.693 (p<0.001)
d. a streamlined MedWatch form and reporting process	13.00 (7.52) (n=45)	20.90 (12.40) (n=296)	-5.951* (p<0.001)
e. employer support of ADE reporting	14.42 (10.18) (n=45)	22.37 (12.14) (n=295)	-4.749* (p<0.001)
f. some type of reward or compensation	10.56 (8.23) (n=45)	13.24 (9.19) (n=294)	-1.849 (p=0.065)
g. ADE reporting as a part of the normal workflow	12.24 (7.51) (n=45)	21.02 (12.07) (n=296)	-6.643 (p<0.001)
h. increased patient counseling (spending more time with patients)	13.71 (8.57) (n=45)	23.87 (11.25) (n=295)	-6.700* (p<0.001)
i. awareness of drug risks by patients	17.11 (9.05) (n=45)	23.87 (11.25) (n=295)	-3.847 (p<0.001)
j. being a drug expert	24.82 (10.67) (n=45)	31.46 (10.46) (n=297)	-3.956 (p<0.001)
k. clear knowledge of what constitutes a reportable ADE (e.g., definition)	22.29 (9.99) (n=45)	30.17 (11.85) (n=295)	-4.233 (p<0.001)

*Equal variances were not assumed in the t-test for equality of means. The Levene's test for equality of variances was statistically significant ($p < 0.05$).
The respondents who were neutral on intention were excluded from the analysis.
Possible mean range: 1 to 49.

H4: A + SN + PBC constructs explain a significant amount of variance in pharmacists' intention to report serious ADEs.

The direct and indirect A, SN and PBC measures together accounted for 34.0 and 28.8 percent of the variance in intention to report serious ADEs to the FDA, respectively (Table 5.29). Both the direct measure and belief-based models were statistically significant ($F = 63.60$, d.f. = 3, 370, $p < 0.001$ and $F = 49.92$, d.f. = 3, 370, $p < 0.001$). Therefore, **H4** was supported.

H5: PBC significantly increases the explanatory power of the regression model compared to only using A + SN to explain pharmacists' intention.

The direct A and SN measures together explained 34.0 percent of the variance in intention. The addition of PBC (direct measure) did not significantly increase the variance in intention explained (R^2 change = 0.001, F [1, 370] change = 0.404, $p = 0.526$). The regression coefficient for PBC (direct measure) was not statistically significant ($B = 0.044$, $p = 0.526$).

Using indirect measures, A and SN together statistically significantly explained 21.9 percent of the variance in intention [$F (2, 371) = 51.99$, $p < 0.001$]. The addition of an indirect measure PBC significantly added to the prediction of intention (R^2 change = 0.069, F [1, 370] change = 35.99, $p < 0.001$). The regression weight for the PBC indirect measure was statistically significant ($B = 0.017$, $p < 0.001$). Therefore, **H5** was supported for indirect measures but not for direct measures.

H6: PRB significantly increases the explanatory power of the regression model compared to only using the A + SN + PBC to explain pharmacists' intention to report serious ADEs.

The addition of PRB to direct measure constructs increased the proportion of variance in intention explained from 34.0 percent to 35.0 percent (R^2 change= 0.009, F [1, 369] change = 5.39, p = 0.021). The regression weight of the PRB construct was significant (B = 0.698, p = 0.021) (Table 5.40). The addition of PRB to the indirect A, SN and PBC measures also significantly increased the proportion of variance in intention explained from 28.8 percent to 30.1 percent (R^2 change = 0.013, F [1, 369] change = 6.93, p = 0.013). The regression coefficient of the PRB was also statistically significant (B = 0.823, p = 0.009). After the addition of PRB in the model, A became statistically insignificant (B = 0.007, p = 0.069). Therefore, **H6** was supported.

Table 5.40: Regression Coefficients After Adding the PRB to the TPB Constructs

PREDICTOR VARIABLE	B	SE	Beta (β)	t	p
Direct Measures					
(Constant)	14.015	1.237	-	11.33	<0.001
Attitude	0.184	0.041	0.215	4.53	<0.001
Subjective norm	0.600	0.069	0.424	8.65	<0.001
Perceived behavioral control	0.030	0.069	0.019	0.43	0.666
Past reporting behavior	0.698	0.301	0.100	2.32	0.021
N = 374, F = 49.61, df = 4, 369, p < 0.001, R = 0.591, R^2 = 0.350, Adjusted R^2 = 0.343					
Indirect Measures					
(Constant)	6.000	0.968	-	6.20	<0.001
Attitude	0.007	0.004	0.091	1.83	0.069
Subjective norm	0.011	0.003	0.229	4.36	<0.001
Perceived behavioral control	0.016	0.003	0.303	5.71	<0.001
Past reporting behavior	0.823	0.313	0.118	2.63	0.009
N = 374, F = 39.78, df = 4, 369, p < 0.001, R = 0.549, R^2 = 0.301, Adjusted R^2 = 0.294					

Dependent variable = Intention, B = Unstandardized coefficients, Beta (β) = Standardized coefficients, SE = Standard error.

H7: PMO significantly increases the explanatory power of the regression model compared to only using the A + SN + PBC to explain pharmacists' intention to report serious ADEs.

The addition of the PMO construct to the TPB constructs (A, SN and PBC) direct measures increased the proportion of variance in intention explained by the model from 34.0 percent to 37.6 percent. The change in R-squared was statistically significant (R^2 change = 0.036, F [1, 369] change = 21.21, $p < 0.001$). The regression coefficient of the PMO construct was statistically significant (B = 0.809, $p < 0.001$) (Table 5.41).

The addition of the PMO construct to indirect A + SN + PBC measures increased the proportion of variance in intention explained by the model from 28.8 percent to 36.9 percent. The change in R-squared was statistically significant (R^2 change= 0.081, F [1, 369] change = 47.17, $p < 0.001$). The PMO construct became the largest single predictor of intention and its regression coefficient was statistically significant (B = 1.074, $p < 0.001$) (Table 5.41). After the addition of PMO in the model, A became statistically insignificant (B = 0.005, p = 0.163). Therefore, **H7** was supported.

Table 5.41: Regression Coefficients After Adding the PMO to the TPB Constructs

PREDICTOR VARIABLE	B	SE	Beta	t	p
Direct Measures					
(Constant)	7.742	0.869		8.908	<0.001
Attitude	0.166	0.040	0.193	4.127	<0.001
Subjective norm	0.424	0.080	0.300	5.314	<0.001
Perceived behavioral control	0.045	0.068	0.029	0.671	0.503
Perceived moral obligation	0.809	0.176	0.244	4.605	<0.001
N = 374, F = 55.61, df = 4, 369, $p < 0.001$, R = 0.613, $R^2 = 0.376$, Adjusted $R^2 = 0.369$					
Indirect Measures					
(Constant)	3.697	0.923		4.005	<0.001
Attitude	0.005	0.004	0.066	1.396	0.163
Subjective norm	0.008	0.003	0.160	3.149	0.002
Perceived behavioral control	0.012	0.003	0.234	4.539	<0.001
Perceived moral obligation	1.074	0.156	0.324	6.868	<0.001
N = 374, F = 53.91, df = 4, 369, $p < 0.001$, R = 0.607, $R^2 = 0.369$, Adjusted $R^2 = 0.362$					

Dependent variable = Intention, B = Unstandardized coefficients, Beta = Standardized coefficients, SE = Standard error.

$H_0$8: There is no significant difference in A to report serious ADEs by gender.

An independent groups t-test showed no statistically significant difference in mean attitude scores (direct measures) between male (mean = 4.24, SD = 5.09, n = 199) and female (mean = 5.07, SD = 4.69, n = 177) pharmacists (t = -1.642, df = 374, p = 0.101). There was also no statistically significant difference in mean attitude scores (indirect measures) between male (mean = 24.02, SD = 6.90, n = 199) and female (mean = 24.96, SD = 6.52, n = 176) pharmacists (t = -1.349, df = 373, p = 0.178). Therefore, **$H_0$8** was confirmed.

$H_0$9: There is no significant difference in SN regarding reporting serious ADEs by gender.

An independent groups t-test showed no statistically significant difference in mean SN scores (direct measures) between male (mean = 5.57, SD = 3.0, n = 198) and female (mean = 5.78, SD = 2.96, n = 177) pharmacists (t = 0.694, df = 373, p = 0.488). However, using indirect measures, female pharmacists (mean = 29.85, SD = 9.32, n = 177) had significantly higher mean SN scores than male (mean = 27.83, SD = 9.35, n = 197) (t = -2.097, df = 372, p = 0.037). Therefore, **$H_0$9** was supported using direct measures but not supported using indirect measures.

$H_0$10: There is no significant difference in PBC over reporting serious ADEs by gender.

An independent groups t-test showed no statistically significant difference in mean PBC scores (direct measures) between male (mean = 3.43, SD = 2.64) and female (mean = 3.67, SD = 2.75) pharmacists (t = 0.865, df = 372, p = 0.388). In addition, using indirect measures, female pharmacists (mean = 20.91, SD = 7.11) had significantly higher mean PBC scores than male pharmacists (mean = 19.52, SD = 7.47) (t = -1.844, df = 374, p = 0.066). Therefore, **$H_0$10** was supported using both direct and indirect measures.

$H_0$11: There is no significant relationship between A to report serious ADEs and pharmacists' years of experience.

Attitude (direct measure) was not significantly correlated with the pharmacists' years of experience (r = -0.080, n = 375, p = 0.123). However, the indirect measure of attitude was significantly negatively correlated with the pharmacists' years of experience (r = -0.136, n = 374, p = 0.008). Pharmacists who had more years of experience had a less favorable attitude (indirect measures) towards reporting serious ADEs than those with

fewer years of experience. Therefore, **$H_0$11** was confirmed with direct measures but not confirmed with the indirect measures.

$H_0$12: There is no significant relationship between SN to report serious ADEs and pharmacists' years of experience.

A Pearson correlation showed no statistically significant correlation between SN (direct measures) and the pharmacists' years of experience ($r = -0.044$, $n = 374$, $p = 0.398$). However, the indirect SN measures was negatively and significantly correlated with the pharmacists' years of experience ($r = -0.164$, $n = 373$, $p = 0.001$). Pharmacists who had been in practice longer were more likely to think that the important others (indirect measures) did not support ADE reporting than those who had been in practice for fewer years. Therefore, **$H_0$12** was confirmed with the direct measures but not confirmed with the indirect measures.

$H_0$13: There is no significant relationship between PBC to report serious ADEs and pharmacists' years of experience.

A Pearson correlation showed no statistically significant relationship between PBC (direct measures) and the pharmacists' years of experience ($r = -0.012$, $n = 373$, $p = 0.821$). However, the indirect measures of PBC was negatively and significantly correlated with the pharmacists' years of experience ($r = -0.106$, $n = 375$, $p = 0.040$). Pharmacists with more years in practice perceived more constraints (indirect measures) to reporting serious ADEs than those with fewer years of practice. Therefore, **$H_0$13** was confirmed with the direct measures but not confirmed with the indirect measures.

$H_0$14. There is no significant difference in A toward ADE reporting by pharmacists' primary practice setting (community-independent, community-multiple/chain, hospital-independent, hospital-multiple/chain, and other).

A one-way ANOVA showed no significant difference in mean direct A towards reporting ADEs among pharmacists practicing in the five practice settings ($F = 1.932$, $df = 4, 372$; $p = 0.105$). However, using indirect measures, a one-way ANOVA showed a significant difference in mean A towards reporting serious ADEs among pharmacists practicing in the five practice settings ($F = 2.538$, $df = 4, 371$; $p = 0.04$). A Tukey's post hoc test showed that the mean for the hospital-multiple/chain group (mean = 26.72, SD = 7.10) was significantly higher than the mean for the community-independent group (mean = 23.23, SD = 7.30) at an alpha level of $p < 0.05$. No other between groups mean A scores were statistically significant. The means (SDs) and group sizes for the five groups are provided in Table 5.42. Therefore, **$H_0$14** was confirmed with direct measures but not with indirect measures.

Table 5.42: Mean Indirect A Scores by Type of Primary Practice Setting

Type of Primary Practice Setting	**N**	**Mean**	**Standard Deviation**
Hospital-Multiple/Chain	58	26.72	7.10
Hospital-Independent	44	25.07	6.06
Community-Multiple/Chain	158	24.10	6.21
Other	42	24.10	7.18
Community-Independent	74	23.23	7.30
Total	**376**	**24.45**	**6.73**

$H_0$15: There is no significant difference in SN regarding ADE reporting by pharmacists' primary practice setting (community-independent, community-multiple/chain, hospital-independent, hospital-multiple/chain, and other).

A one-way ANOVA showed no significant difference in mean direct SN ($F = 0.650$, $df = 4, 371$; $p = 0.627$) and indirect SN ($F = 1.685$, $df = 4, 370$; $p = 0.153$) toward reporting serious ADEs among pharmacists practicing in the five practice settings. Therefore, **$H_0$15** was confirmed.

$H_0$16: There is no significant difference in PBC over ADE reporting by pharmacists' primary practice setting (community-independent, community-multiple/chain, hospital-independent, hospital-multiple/chain, and other).

A one-way ANOVA showed no significant difference in mean direct ($F = 0.103$, $df = 4, 370$; $p = 0.981$) and indirect PBC over reporting serious ADEs ($F = 0.690$, $df = 4, 372$; $p = 0.599$) among pharmacists practicing in the five practice settings. Therefore, **$H_0$16** was confirmed.

$H_0$17. There is no significant relationship between the pharmacists' number of hours worked and A toward ADE reporting.

A Pearson correlation showed no significant relationship between A (direct measures) and the number of hours worked by the pharmacist per week ($r = 0.068$, $n = 375$, $p = 0.189$). However, for indirect measures, a Pearson correlation showed a statistically significant positive relationship between A and the number of hours worked by the pharmacist per week ($r = 0.157$, $n = 374$, $p = 0.002$). Thus, pharmacists who worked longer hours were more likely to have a favorable A toward reporting serious ADEs than those who worked less. Therefore, **$H_0$17** was supported using direct measures but not confirmed using indirect measures.

$H_0$18: There is no significant relationship between the pharmacists' number of hours worked and SN regarding ADE reporting.

Using direct measures, a Pearson correlation showed a statistically significant positive relationship between the number of hours worked by pharmacists and SN regarding ADE reporting ($r = 0.104$, $n = 374$, $p = 0.044$). Pharmacists who worked longer hours tended to have a more favorable SN towards ADE reporting than those who worked less hours. However, using indirect measures, a Pearson correlation showed no statistically significant relationship between the pharmacists' number of hours worked and SN regarding ADE reporting ($r = 0.045$, $n = 373$, $p = 0.390$). Therefore, **$H_0$18** was supported using indirect measures but not supported using direct measures.

$H_0$19: There is no significant relationship between the pharmacists' number of hours worked and PBC over ADE reporting.

A Pearson correlation showed no significant relationship between pharmacists' number of hours worked and PBC over ADE reporting using both direct ($r = 0.096$, $n = 373$, $p = 0.063$) and indirect ($r = 0.086$, $n = 375$, $p = 0.096$) measures. The number of hours worked was not related to the constraints that the pharmacists perceived. Therefore, **$H_0$19** was supported.

$H_0$20: There is no significant difference in A toward reporting serious ADEs by the pharmacists' ethnicity.

A one-way analysis of variance (ANOVA) showed a significant difference in mean direct A towards reporting serious ADEs by pharmacists' ethnicity ($F = 3.675$, $df = 5, 367$, $p = 0.003$). A Tukey's post-hoc test showed that the A for African American/non-Hispanic black group (mean = 7.04, SD = 5.77) was significantly more favorable than that of the Caucasian/non-Hispanic white group (mean = 4.10, SD = 4.84) at an alpha level of $p < 0.05$. There were no statistically significant differences between the means

for the American Indian or Alaska Native (mean = 1.67, SD = 1.35), Asian American/Pacific Islander (mean = 6.49, SD = 4.29), Mexican American/Hispanic (mean = 5.36, SD = 3.60) and other (mean = 2.91, SD = 4.81) groups.

However, using indirect measures, a one-way ANOVA showed no statistically significant difference in mean A towards reporting serious ADEs by the pharmacists' ethnicity (F = 0.560, df = 5, 366, p = 0.731). Therefore, **$H_0$20** was confirmed using indirect measures but not confirmed using direct measures.

$H_0$21: There is no significant difference in SN regarding reporting serious ADEs by the pharmacists' ethnicity.

A one-way ANOVA showed no statistically significant difference in mean direct SN (F = 2.050, df = 5, 366, p = 0.071) and indirect SN (F = 2.152, df = 5, 365, p = 0.059) regarding reporting serious ADEs by pharmacists' ethnicity. Therefore, **$H_0$21** was confirmed for both direct and indirect measures.

$H_0$22: There is no significant difference in PBC over reporting serious ADEs by the pharmacists' ethnicity.

A one-way ANOVA showed no statistically significant difference in mean direct PBC over reporting serious ADEs ratings by pharmacists' ethnicity (F = 1.431, df = 5, 365, p = 0.212). However, using indirect measures, a one-way ANOVA showed a statistically significant difference in mean PBC ratings toward reporting serious ADEs by pharmacists' ethnicity (F = 4.437, df = 5, 367, p = 0.001). A Tukey's post-hoc test showed that the African American/non Hispanic black group (mean = 24.53, SD = 9.47) had significantly higher perceived control than the Caucasian/non-Hispanic white group (mean = 19.24, SD = 6.57) at an alpha level of $p < 0.05$. The means for the American Indian or Alaska Native (mean = 26.97, SD = 17.66), Asian American/Pacific Islander (mean = 21.46, SD = 6.92) and the Mexican American/Hispanic (mean = 22.75, SD =

8.19) groups were not significantly different. Therefore, **$H_0$22** was confirmed using direct measures but not confirmed using indirect measures.

$H_0$23: There is no significant relationship between the pharmacists' knowledge of ADE reporting and A toward ADE reporting.

A Pearson correlation showed a statistically significant positive relationship between A toward ADE reporting and pharmacists' knowledge of ADE reporting for both direct ($r = 0.274$, $n = 376$, $p < 0.001$) and indirect ($r = 0.293$, $n = 375$, $p < 0.001$) measures. Pharmacists who had higher knowledge on ADE reporting had a more favorable A towards reporting serious ADEs to the FDA than those who had lower knowledge. Therefore, **$H_0$23** was not confirmed.

$H_0$24: There is no significant relationship between the pharmacists' knowledge of ADE reporting and SN regarding ADE reporting.

A Pearson correlation showed a statistically significant positive relationship between pharmacists' knowledge of ADE reporting and SN regarding ADE reporting for both direct ($r = 0.254$, $n = 375$, $p < 0.001$) and indirect ($r = 0.200$, $n = 374$, $p < 0.001$) measures. Pharmacists with higher knowledge of ADE reporting had higher SN than those with lower knowledge. Therefore, **$H_0$24** was not confirmed.

$H_0$25: There is no significant relationship between the pharmacists' knowledge of ADE reporting and PBC over ADE reporting.

A Pearson correlation showed a statistically significant positive relationship between the pharmacists' knowledge of ADE reporting and PBC over ADE reporting for both direct ($r = 0.220$, $n = 374$, $p < 0.001$) and indirect ($r = 0.343$, $n = 376$, $p < 0.001$) measures. Pharmacists with higher knowledge of ADE reporting had higher perceived control than those with lower knowledge. Therefore, **$H_0$25** was not confirmed.

5.11 ASSUMPTIONS OF MULTIPLE (LINEAR) REGRESSION ANALYSIS

The study examined the data to determine if it satisfied the assumptions for multiple (linear) regression analysis. Specifically, the investigation looked at the following four criteria: normality, homoscedasticity, linearity, and multicollinearity.

The normality of the distribution of errors was assessed by inspecting the histograms of residuals from the regression analysis (direct and indirect TPB constructs) (see Appendix G). The assumption was also assessed by inspecting and evaluating the normal probability plots (see Appendix H). The histograms show that the standardized residuals of the regression analysis had a normal distribution. The sample data was from a normal distribution given that most standardized residuals fell along the reference line on the normal probability plot (Appendix H). The plots showed that A, SN, and PBC (direct and indirect measures) were normally distributed (Appendix H).

The homoscedasticity of errors assumption was assessed by inspecting the scatterplot of standardized residuals against the regression standardized predicted values of the dependent variable (direct and indirect TPB constructs) (see Appendix I). The sample data did not violate the assumption of homoscedasticity of errors because the residuals were evenly scattered around zero (Appendix I).

The scatterplots of regression standardized residuals versus regression standardized predicted values (direct TPB and indirect TPB) were evaluated to assess the linearity of the data (see Appendix J). Visual examination of the partial regression plots did not indicate a curvature in the relationships between the dependent and independent variables for both direct and indirect measures models. The assumption of linearity was not violated.

Multicollinearity was assessed by evaluating the values of correlation coefficients of the variables, tolerance, and variance inflation factors (Tables 5.43, 5.44, and 5.45). Using direct measures, the correlations among the constructs ranged from 0.14 to 0.55. Using indirect measures, the correlations among the constructs ranged from 0.12 to 0.52.

Multicollinearity does not seem to be high or problematic in the data because none of the correlations between the variables were greater than 0.75.

Table 5.43: Correlation Matrix for the Direct Measures Variables

Direct Measure Variables	Intention	Attitude (direct)	Subjective norm (direct)	Perceived behavioral control (direct)	Past reporting behavior	Perceived moral obligation
Intention	1.00					
Attitude (direct)	0.42	1.00				
Subjective norm (direct)	0.55	0.46	1.00			
Perceived behavioral control (direct)	0.20	0.19	0.29	1.00		
Past reporting behavior	0.22	0.14	0.20	0.15	1.00	
Perceived moral obligation	0.51	0.37	0.62	0.20	0.18	1.00

Table 5.44: Correlation Matrix for the Indirect Measures Variables

Study Variables	Intention	Attitude (indirect)	Subjective norm (indirect)	Perceived behavioral control (indirect)	Past reporting behavior	Perceived moral obligation
Intention	1.00					
Attitude (indirect)	0.33	1.00				
Subjective norm (indirect)	0.43	0.41	1.00			
Perceived behavioral control (indirect)	0.47	0.42	0.52	1.00		
Past reporting behavior	0.22	0.20	0.12	0.19	1.00	
Perceived moral obligation	0.51	0.32	0.39	0.42	0.18	1.00

Table 5.45 shows tolerance and variance inflation factors (VIF). The VIF values ranged from 1.057 to 1.888. Tolerance values were high (range: 0.530 – 0.904) (see Table 5.45). Multicollinearity does not appear to be a problem because none of the VIF were greater than 10, and the tolerance values were high (close to 1) (Table 5.45).

Table 5.45: Tolerance and Variance Inflation Factors (VIF) of Independent Variables

Independent Variables	**Tolerance**	**Variance Inflation Factors**
Direct Measures		
Attitude	0.770	1.298
Subjective norm	0.530	1.888
Perceived behavioral control	0.904	1.057
Perceived moral obligation	0.602	1.662
Past reporting behavior	0.946	1.057
Indirect Measures		
Attitude	0.752	1.329
Subjective norm	0.662	1.510
Perceived behavioral control	0.639	1.565
Perceived moral obligation	0.759	1.318
Past reporting behavior	0.938	1.066

5.12 SUMMARY OF TESTS OF HYPOTHESES

Table 5.46 shows the summary of hypotheses test results. Eighteen of the 25 hypotheses were supported using direct measures and 15 hypotheses were supported using indirect measures. The decision reached (supported or not) was different using direct than indirect measures on 11 of the 25 hypotheses (44%) tested (Table 5.46).

Table 5.46: Summary of Hypotheses Test Results

Hypothesis	**Direct Measures**	**Indirect Measures**
H1: Favorable A is a positive and significant predictor of intention to report serious ADEs controlling for SN and PBC.	Supported	Supported
H2: SN supporting ADE reporting is a positive and significant predictor of intention to report serious ADEs controlling for A and PBC.	Supported	Supported
H3: Strong PBC is a positive and significant predictor of intention to report serious ADEs controlling for A and SN.	Not supported	Supported
H4: A + SN + PBC constructs explain a significant amount of variance in pharmacists' intention to report serious ADEs.	Supported	Supported
H5: PBC significantly increases the explanatory power of the regression model compared to only using A + SN to explain pharmacists' intention.	Not supported	Supported
H6: PRB significantly increases the explanatory power of the regression model compared to only using the A + SN + PBC to explain pharmacists' intention to report serious ADEs.	Supported	Supported
H7: PMO significantly increases the explanatory power of the regression model compared to only using the A + SN + PBC to explain pharmacists' intention to report serious ADEs.	Supported	Supported
$H_0$8: There is no significant difference in A to report serious ADEs by gender.	Supported	Supported
$H_0$9: There is no significant difference in SN regarding reporting serious ADEs by gender.	Supported	Not supported
$H_0$10: There is no significant difference in PBC over reporting serious ADEs by gender.	Supported	Supported
$H_0$11: There is no significant relationship between A to report serious ADEs and pharmacists' years of experience.	Supported	Not supported
$H_0$12: There is no significant relationship between SN to report serious ADEs and pharmacists' years of experience.	Supported	Not supported
$H_0$13: There is no significant relationship between PBC to report serious ADEs and pharmacists' years of experience.	Supported	Not supported

Table 5.46: Summary of Hypotheses Test Results Continued

Hypothesis	**Direct Measures**	**Indirect Measures**
$H_0$14. There is no significant difference in A toward ADE reporting by pharmacists' primary setting (community-independent, community-multiple/chain, community-government, hospital-non-government, hospital-government, and other).	Supported	Not supported
$H_0$15: There is no significant difference in SN regarding ADE reporting by pharmacists' primary setting (community-independent, community-multiple/chain, community-government, hospital-non-government, hospital-government, and other).	Supported	Supported
$H_0$16: There is no significant difference in PBC over ADE reporting by pharmacists' primary setting (community-independent, community-multiple/chain, community-government, hospital-non-government, hospital-government, and other).	Supported	Supported
$H_0$17. There is no significant relationship between the pharmacists' number of hours worked and A toward ADE reporting.	Supported	Not supported
$H_0$18: There is no significant relationship between the pharmacists' number of hours worked and SN regarding ADE reporting.	Not supported	Supported
$H_0$19: There is no significant relationship between the pharmacists' number of hours worked and PBC over ADE reporting.	Supported	Supported
$H_0$20: There is no significant difference in A toward reporting serious ADEs by the pharmacists' ethnicity.	Not supported	Supported
$H_0$21: There is no significant difference in SN regarding reporting serious ADEs by the pharmacists' ethnicity.	Supported	Supported
$H_0$22: There is no significant difference in PBC over reporting serious ADEs by the pharmacists' ethnicity.	Supported	Not supported
$H_0$23. There is no significant relationship between the pharmacists' knowledge of ADE reporting and A toward ADE reporting.	Not supported	Not supported
$H_0$24: There is no significant relationship between the pharmacists' knowledge of ADE reporting and SN regarding ADE reporting.	Not supported	Not supported
$H_0$25: There is no significant relationship between the pharmacists' knowledge of ADE reporting and PBC over ADE reporting.	Not supported	Not supported

CHAPTER SIX: DISCUSSION

This study investigated the predictive utility of the theory of planned behavior (TPB) in understanding Texas pharmacists' intentions to report serious adverse drug events (ADEs). The factors affecting Texas pharmacists' attitude (A), subjective norm (SN), and perceived behavioral control (PBC) toward ADE reporting were identified using the TPB model. In addition, the relative importance of past reporting behavior (PRB) and perceived moral obligation (PMO) in the prediction of Texas pharmacists' intention to report ADEs were assessed. The study also examined the roles of pharmacists' knowledge, demographic factors and practice characteristics in ADE reporting.

This chapter provides a discussion of the study results. The first section discusses the results of the hypothesis tests of the study, evaluates the study model, proposes possible explanations for the findings, and suggests institutional and organizational changes for improving ADE reporting. The second section discusses the implications and directions for future research. The final section addresses the main limitations of the study and conclusions.

6.1 FOCUS GROUP

Several important aspects were gleaned from the focus group participants. First, the focus group participants seemed to strongly agree that lack of time was a major constraint to reporting serious ADEs to the FDA. Participants felt that pharmacists did not have time to report ADEs. In addition, pharmacists often do not consider reporting ADEs. During the focus group, one pharmacist said, "It just does not occur to me that I should fill out a MedWatch form for the ADEs that I see." Also, it seemed apparent that participants had notable misconceptions on ADE reporting in general and MedWatch

specifically. For example, pharmacists were suggesting things that are already being implemented by the FDA and some asked questions that indicated their ignorance of MedWatch. Pharmacists' misconceptions were also reflected in the findings of the knowledge scores.

6.2 Response Rate

This study's response rate of 26.4 percent is comparable to one other mail survey involving pharmacists in Texas (27.0%) (Brown, Barner, & Shah, 2005). However, this study's response rate was low compared to other studies involving pharmacists in Texas that reported response rates ranging from 35.1 percent to 58.4 percent (Brown, 1998; Brown et al., 2007; Griggs & Brown, 2007; Mashburn et al., 2003; O'Donnell, Brown, & Dastani, 2006; Olson & Lawson, 1996), but comparable or higher to response rates in studies of healthcare professionals (HCPs): 21 percent (Herbert et al., 2006), 25 percent (Pradel, Obeidat, & Tsoukleris, 2007), and 19.7 percent (Belton & The European Pharmacovigilance Research Group, 1997).

6.3 Sample Characteristics

The study used a sample of Texas practicing pharmacists (n = 1,500). The sample was drawn from a Texas State Board of Pharmacy list (population/census) which contains information on all licensed pharmacists in Texas (N = 25,177). Although the sample and population of Texas pharmacists were similar on gender and ethnicity (Table 6.1), the African American and Mexican American groups seem to have been oversampled. However, overall the (study) sample was fairly representative of Texas pharmacists in terms of gender and ethnicity.

Table 6.1: Gender and Ethnicity of Texas Pharmacists, Study Sample and Respondents

Characteristic	**Census of Licensed Texas Pharmacists in 2008 (Frequency, %) N = 25,177)**	**Study Sample (Frequency, %) (n = 1,500)**	**Study Respondents Frequency, %) (n = 377)**
Gender			
Female	12,646 (50.2)	772 (51.5)	177 (47.1)
Male	12,531 (49.8)	728 (48.5)	199 (52.9)
Ethnicity			
Caucasian/non-Hispanic white	15448 (61.4)	881 (58.7)	262 (70.2)
Asian American/Pacific Islander	3912 (15.5)	220 (14.7)	37 (9.9)
African American/non-Hispanic black	3127 (12.4)	214 (14.3)	27 (7.2)
Mexican American/Hispanic	1879 (7.5)	141 (9.4)	33 (8.8)
Other	401 (1.6)	23 (1.5)	11 (2.9)
American Indian or Alaska Native	195 (0.8)	8 (0.5)	3 (0.8)
Not specified/Other	215 (0.9)	13 (0.9)	11 (2.9)

The mean age of respondents in this study of 51.46 (SD = 12.69) years shows that pharmacists who responded to this study were middle-aged, and had been practicing pharmacy for an average of 25 years. In other studies involving pharmacists, the respondents were younger: 45 (SD = 12.0) years (Pradel, Obeidat, & Tsoukleris, 2007), 48.6 (SD = 12.46) years (Mashburn et al., 2003), 49.45 (SD = 14.35) years (Griggs & Brown, 2007), 44.8 (SD = 12.5) years (Brown et al., 2007); and had fewer years of experience: 11.0 (SD = 9.9) years (Farris & Schopflocher, 1999), 18 (SD = 12.4) years (Coleman, 2003), and 24.3 (SD = 13.2) years (O'Donnell, Brown, & Dastani, 2006).

6.4 INTENTION TO REPORT SERIOUS ADES

The overall mean intention score was high (mean = 5.29, SD = 1.41; possible range: 1 – 7, neutral = 4), suggesting that pharmacists intended to report serious ADEs to the FDA. This finding is positive, encouraging and was expected given that reporting

serious ADEs promotes drug and patient safety, which is a key responsibility of pharmacists (Beard & Lee, 2006). ADE reporting fits in well with pharmacists' responsibility of ensuring the safe use of medicines, and has become standard practice for pharmacists in many countries (Griffin, 1986). Previous research studies using theoretical models found that pharmacists have moderate intentions to provide services that help patients and contribute towards the safe use of medicines such as the provision of MTMS, pharmaceutical care and medication counseling (Farris & Schopflocher, 1999; Herbert et al., 2006; Mason, 1983; Pradel, Obeidat, & Tsoukleris, 2007).

In the literature, behavioral intention has been found to be a valid proxy measure for behavior; there is good correspondence between measures of health professionals' intentions and their subsequent behavior (Eccles et al., 2006; Farris & Schopflocher, 1999; Godin & Kok, 1996; Godin, Naccache, Morel, & Ebacher, 2000; Millstein, 1996; O'Boyle, Henly, & Larson, 2001; Renfroe, O'Sullivan, & McGee, 1990; Sheeran, Conner, & Norman, 2001). Intention is the most important predictor of subsequent behavior (Godin & Kok, 1996). A recent systematic review reported that on average, intentions account for 28 percent (range: 0.15 – 0.40%) of the variance in subsequent behavior (Eccles et al., 2006). Thus, pharmacists' participation in ADE reporting can be increased by targeting their intentions and the predictors of intentions.

Intention was positively and significantly related with pharmacists' knowledge. Pharmacists who knew more about how to report serious ADEs intended to report more than those who knew less on how to report. As expected, intenders had significantly more favorable A, higher SN, and higher PBC (indirect measures only) than non-intenders. This suggests that pharmacists' salient beliefs and knowledge were key factors in determining their decision to report serious ADEs.

6.5 Evaluation of the Study Model

The hypothesis that the TPB model would predict a significant amount of variance in ADE reporting intentions was supported by the data. Using direct and indirect measures, the combination of A, SN and PBC explained 34.0 and 28.8 percent of the variance in intent to report serious ADEs to the FDA, respectively. Explaining 34 or 29 percent of the variance in pharmacists' reporting of serious ADEs may be extremely worthwhile from a practical point of view, given the small number of predictors. In the literature, explaining 10 percent or more of the variance in the dependent variable is considered worthwhile from a practical viewpoint particularly if a small number of predictors are used (Sutton, 1998).

The proportion of variance in intention explained in this study (direct measures - 34.0%) is comparable to those obtained by Conner and Sparks (33.7%) and Godin and Kok (40%) (Conner & Sparks, 2005; Godin et al., 2008). One study involving pharmacists reported that the TPB constructs explained 19 percent of the variance in intention (Walker et al., 2004). Elsewhere, the TPB constructs explained a higher proportion of variance in intention (belief-based measures - 37.1%; direct measures - 73.5%) (Mashburn et al., 2003). A systematic review of studies on HCPs' intentions and behaviors based on social cognitive theories found an overall frequency-weighted mean R^2 of 0.31 and 0.59 for prediction of behavior and intention, respectively (Godin et al., 2008).

The TPB appears to be an appropriate theoretical model and a useful framework for studying pharmacists' reporting of serious ADEs. This corroborates previous research studies involving HCPs (Godin et al., 2008; Millstein, 1996; Sheeran, Conner, & Norman, 2001). The TPB may be well suited to ADE reporting among pharmacists.

Theory of Planned Behavior Constructs

Direct Measures: As hypothesized, favorable A and SN supporting ADE reporting were positive and significant predictors of intention to report serious ADEs. The study results show that SN was the most important and significant predictor of intention. However, the hypothesis that PBC was a positive and significant predictor of intention to report serious ADEs controlling for A and SN was not supported by the data.

Indirect Measures: The hypotheses that favorable A, SN supporting ADE reporting and strong PBC were positive and significant predictors of intention after controlling for other variables in the model were supported. PBC significantly increased the explanatory power of the regression model compared to only using A and SN to explain pharmacists' intention. PBC was the strongest predictor of intention.

In general, the data were consistent with the predicted relationships among the TPB model components (A, SN, PBC, and BI). As expected, there were positive correlations between direct and indirect measures of the TPB predictors (Ajzen, 2002; Montano & Kasprzyk, 2002). Although direct and indirect measures[9] have different assumptions about the underlying cognitive structures (Francis et al., 2004), they are expected to be correlated because they are indicators of the same underlying construct (Ajzen, 2002). Based on Cohen's classification,[10] there was a small correlation[11] between PBC direct and PBC indirect measures, moderate correlation between direct and indirect

[9] "Briefly, indirect measures are based on responses to items about specific beliefs and scores are then combined by the researcher. The assumptions are that the method used for combining responses (weighting and then averaging the scores) reflects the methods that individuals use when forming, for example, an attitude, and that all relevant beliefs have been represented among the questionnaire items. Direct measurement effectively asks individuals themselves to combine the separate beliefs. It does not rely on the assumption that all relevant beliefs have been represented in the questionnaire but assumes that people can accurately combine and report a global attitude, subjective norm, and perceived level of control over the behavior in question" (Francis et al., 2008).

[10] Jacob Cohen classified correlations into three: large (> 0.5), moderate (0.3 – 0.5) and small (0.1 – 0.3). Correlations smaller than 0.1 are considered trivial and not substantial (Cohen, 1998).

[11] The small correlation between PBC direct and PBC indirect measures may have resulted from problems arising from measuring PBC direct measures as only two (2) items were used.

A measures, and large correlations between direct and indirect SN measures. In addition, our findings were consistent with Montano and Kasprzyk (2002) who reported that the TPB direct measures (taken together) were stronger predictors of intention than indirect measures.

Past Reporting Behavior

As expected, PRB significantly increased the explanatory power of the regression models (direct and indirect measures models) compared to only using A, SN, and PBC to explain pharmacists' intention to report serious ADEs ($p < 0.05$). The R^2 change associated with the addition of PRB for both the direct and indirect measures models were significant ($p < 0.05$). These findings confirm the results from previous studies that reported that past behavior significantly improved the prediction of intention over and above the TRA and TPB constructs (Albarracin et al., 2001; Bagozzi, 1981; Leone, Perugini, & Ercolani, 1999; Mashburn et al., 2003; Quine & Rubin, 1997; Schaalma, Kok, & Peters, 1993; Walker, Grimshaw, & Armstrong, 2001). Taken together, these findings indicate that past behavior is an important predictor and, thus, should be included in models of ADE reporting intentions among pharmacists.

Perceived Moral Obligation

As hypothesized, PMO significantly increased the explanatory power of the regression models (direct and indirect measures models) compared to only using A, SN and PBC to explain pharmacists' intention to report serious ADEs ($p < 0.05$). The R^2 change associated with the addition of PMO for both the direct and indirect measures models were significant ($p < 0.05$). This finding corroborates previous research that reported that PMO is an important predictor of HCPs' intention especially in moral situations (Fazekas, Senn, & Ledgerwood, 2001; Godin et al., 2008; Gorsuch & Ortberg, 1983; Randall & Gibson, 1991; Werner & Mendelsson, 2001). This study confirms the

importance of PMO with respect to reporting serious ADEs. This finding suggests that ADE reporting is a moral imperative for pharmacists.

In summary, the TPB is a useful model and appropriate framework for predicting pharmacists' reporting intentions and behavior. Intention to report serious ADEs was predictable from the TPB constructs. SN (direct measures) and PBC (indirect measures) were the strongest TPB predictors of intention. The study data are consistent with the predicted relationships among the TPB model components. PRB and PMO had a strong effect on intention beyond the TPB constructs.

6.6 Attitudes Toward Reporting Serious ADEs

As hypothesized, favorable A was a significant and positive predictor of intention to report serious ADEs after controlling for SN and PBC. Thus, an understanding of the factors affecting pharmacists' A can provide insight into how to increase ADE reporting by pharmacists. Implementation strategies aimed at increasing ADE reporting should address pharmacists' A toward ADE reporting. The overall mean A (direct measure) score was positive (mean = 0.92, SD = 0.98; possible range: -3 to +3, 0 = neutral), suggesting that respondents had a positive A toward reporting serious ADEs. Pharmacists believed that ADE reporting was valuable, good and beneficial. However, pharmacists did not exhibit very strong support for these outcomes, with most responses falling around zero. The mean A (indirect measures) score was high (mean = 24.45, SD = 6.73; possible range: 1-49, 16 = neutral) signifying that Texas pharmacists held a favorable A towards reporting serious ADEs to the FDA. The finding that pharmacists had a favorable A toward ADE reporting is consistent with previous studies (Bawazir, 2006; Irujo et al., 2007; van Grootheest, Mes, & de Jong-van den Berg, 2002). In other studies involving pharmacists' A toward patient safety and patient care, pharmacists have been reported to hold a favorable A towards correcting drug therapy problems, providing MTMS and

asthma counseling (Farris & Schopflocher, 1999; Herbert et al., 2006; Pradel, Obeidat, & Tsoukleris, 2007).

Primary Drivers of Attitude

The strongest positive beliefs driving A towards reporting serious ADEs to the FDA were to improve patient safety, and educate others about drug risks. In addition, the beliefs with the strongest negative influence were that reporting will increase the risk of malpractice, break trust with patients and compromise the relationship with physicians.

The beliefs that reporting serious ADEs to the FDA will improve patient safety and educate others about drug risks were the strongest beliefs (i.e., had highest mean product of behavioral belief and outcome evaluation scores). At the time of approval, little is known about the safety of a drug. Inevitably, more is learned as the drug is widely used on the market. Rare, serious, uncommon and unpredictable events that may surface after approval are identified through voluntary ADE reporting (Meadows, 2002). These events enhance and improve understanding of the drug's risk profile. Voluntary ADE reports are an important source of information concerning drug risks to the FDA, HCPs and patients (e.g., educates other HCPs and patients about drug risks). New drug risks identified through serious ADE reports are added to the drug's label and the information is communicated to doctors (Meadows, 2002). This information further contributes to patient safety through informing better and safer methods of using medicines and, in rare cases when evidence suggests that the drug is unsafe, the drug may be withdrawn from the market. It is encouraging that pharmacists' beliefs were in line with the primary advantages of ADE reporting—to improve patient safety and to educate others about drug risks. Similar findings have been reported elsewhere (Irujo et al., 2007; Vessal, Mardani, & Mollai, 2009). Physicians have been reported to believe that reporting ADEs informs their colleagues of the adverse experiences they have encountered (Inman, 1985).

Although Texas pharmacists believed that increased risk of malpractice was a bad outcome, they did not believe that reporting serious ADEs to the FDA increased the risk of malpractice. This finding is contrary to previous research findings that reported that ADE reporting or self-identification could result in repercussions, investigation and malpractice suits (Ashcroft et al., 2006; Bateman, Sanders, & Rawlins, 1992). In the literature, open reporting of ADEs is reported to be deterred by the threat of litigation, professional disciplinary action, investigation or reprisal (Institute of Medicine Report, 2004; Kaufman, Stoukides, & Campbell, 1994; Vincent et al., 2006). For example, in a classic study, Inman identified fear of possible involvement in litigation or investigation of prescribing costs by health departments as one of the seven main reasons why medical doctors did not report suspected ADRs (Inman, 1978). This study's finding is, however, consistent with other studies (Belton & The European Pharmacovigilance Research Group, 1997; Granas, Buajordet, Stenberg-Nilsen, Harg, & Horn, 2007; Hasford et al., 2002; Herdeiro et al., 2006; Lopez-Gonzalez, Herdeiro, & Figueiras, 2009; Sweis & Wong, 2000). The passage of the Patient Safety and Quality Improvement Act of 2005 (P.L. 109-41), which grants "peer review protection from report disclosure during legal proceedings, and protection of providers who report from professional retaliation" (Institute of Medicine of the National Academies, 2007b, p. 91), together with the confidentiality and anonymity of reporting accorded by MedWatch may explain our findings.

Pharmacists also believed that reporting serious ADEs to the FDA did not break trust with patients and did not compromise their relationship with physicians. Similarly, elsewhere ADR reporting was found to build rather than destroy patient trust (Bawazir, 2006). Furthermore, ADR reporting was reported to show that pharmacists took patients' complaints seriously (Bawazir, 2006) and that they took greater responsibility for patient care (Biriell & Edwards, 1997).

In addition, pharmacists believed that reporting serious ADEs to the FDA is personally beneficial/rewarding to the pharmacist, time consuming and disrupted the normal workflow. However, they did not exhibit very strong support for these advantages and disadvantages (outcomes) with most of the responses to these items falling around 4 (neither agree nor disagree) on a scale of 1 to 7. The beliefs that ADE reporting disrupted the normal workflow, though not strong, are consistent with previous findings (Sweis & Wong, 2000). Similar to previous findings, it may be that pharmacists consider reporting ADEs as an additional duty or not to be an integral part of their professional duties (Sweis & Wong, 2000). Pharmacists could submit more reports if they considered reporting to be an integral part of their duties, as is the case in the Netherlands (van Grootheest, Mes, & de Jong-van den Berg, 2002).

Attitude Differences Between Intenders and Non-Intenders

Results showed that those pharmacists who were intending to report serious ADEs to the FDA were more likely to believe that reporting serious ADEs educates others about drug risks, is personally beneficial/rewarding to the pharmacist, and improves patient safety ($p < 0.05$) than those who did not intend to report. As a result, interventions that increase pharmacists' awareness of the benefits of ADE reporting could be valuable. Pharmacists ought to be educated on the benefits of reporting serious ADEs (see Section 6.8).

Factors Associated with Attitude

Using direct measures, the study found that pharmacists practicing in the hospital-multiple chain group had a significantly more favorable A than those practicing in the community-independent group. This is consistent with previous studies that found that hospital pharmacists are more likely to report ADRs than community pharmacists (Herdeiro et al., 2006; Taras-Zasowski & Einarson, 1989). Practice setting was also

reported to be associated with reporting among medical practitioners (Belton & The European Pharmacovigilance Research Group, 1997; Eland et al., 1999; Figueiras et al., 1999; Herdeiro et al., 2005). Hospital pharmacists have a more favorable A than community pharmacists because they are more knowledgeable about clinical pharmacy and pharmacovigilance, have access to patient medical records and tend to see more patients with serious ADEs (Calvert, 1999; Pirmohamed et al., 2004; Rawlins, 1995; van Grootheest & de Jong-van den Berg, 2005). In addition, hospital pharmacists are more directly involved in patient care, and have access to state of the art computer systems which may not be available in the community setting (Dormann et al., 2000; Emerson et al., 2001). These factors increase their chances of detecting serious ADEs compared to community pharmacists.

Using indirect measures, A was negatively associated with the pharmacists' years of experience. Pharmacists with more years in pharmacy practice were likely to have a less favorable A than those who had fewer years of experience. This is in contrast with other studies in Europe that reported a positive association between tendency to report ADRs and years of experience (seniority) (Generali, Danish, & Rosenbaum, 1995; Irujo et al., 2007; Kelley & Tucci, 2001; McGettigan, Golden, Conroy, Arthur, & Feely, 1997; Sweis & Wong, 2000).

Pharmacists' A (indirect measures) was positively correlated with the number of hours worked. As observed by Sweis and Wong (2000), pharmacists who worked more hours tended to have a more favorable A than those who worked less hours. In addition, pharmacists who were younger had a more favorable A towards reporting ADEs than other pharmacists. Focus should be given to the needs of the more experienced pharmacists, those pharmacists practicing in community independent settings and those who work less hours when implementing activities aimed at positively increasing pharmacists' A.

6.7 SUBJECTIVE NORM REGARDING ADE REPORTING

The hypothesis that SN supporting ADE reporting is a positive and significant predictor of intention to report serious ADEs controlling for A and PBC was supported by the data. The direct SN measure was positive (mean = 1.88, SD = 1.0; range: -3 to +3, neutral = 0) and the mean 'normative beliefs' by 'motivation to comply' product (indirect measures) score was high (mean = 28.75, SD = 9.38; possible range: 1-49, neutral = 16), indicating that pharmacists felt social pressure to report serious ADEs to the FDA. Using direct measures, SN was the best TPB predictor of intention to report serious ADEs after controlling for A and PBC. SN has also been found to be the most important predictor of intention in pharmacy research (Herbert et al., 2006). As noted in the literature review, SN is stronger than A in the prediction of behaviors that affect others compared to behaviors that do not (Quine, Rutter, & Arnold, 1998). In other words, when an individual forms an intention about a behavior that carries implications for others, the perceived views of significant others are of greater importance (Quine, Rutter, & Arnold, 1998). Thus, SN may have played a greater role in the formulation of intentions to report serious ADEs because ADE reporting is seen to have implications for other people (e.g., doctors, patients, and workmates) too. For example, pharmacists may believe that reporting ADEs will affect the safe use of medicines by their patients.

Professional campaigns that use role models, peer educators and patient advocates to encourage reporting may be effective. The use of peer-led educational interventions (led by peer educators or role models) has been reported to be effective in improving participants' attitude and knowledge (Gibson, Shah, & Mamoon, 1998; Kirby, Obasi, & Laris, 2006; Li et al., 2010; Shah et al., 2001; Tobler, 1992); however, such programs have not been tested empirically for the promotion of ADE reporting. Pharmacists may be more likely to change if the message is presented by someone they can relate to or perceive as important to this reporting decision. Interventions that incorporate such important others to enhance or promote positive social norms may be effective in

changing ADE reporting. The finding that SN predicts intention is consistent with prior research supporting the TPB (Ajzen, 1991; Feng & Wu, 2005; Godin et al., 2008; Herbert et al., 2006; Randall & Gibson, 1991).

Primary Drivers of Subjective Norm

The most important salient referents were the FDA, patients, pharmacy associations, pharmacy managers/bosses and hospitals and hospital groups. Pharmacists believed that these salient referents were interested in whether or not they report serious ADEs to the FDA. The study results also show that pharmacists were likely to comply with what all nine groups included in the study wanted them to do concerning ADE reporting. These referents could be used to communicate with pharmacists the need to report serious ADEs to the FDA.

The FDA was the most salient referent. A close look at the results shows that 85.3 percent of the respondents believed that the FDA likely wanted them to report serious ADEs and 80.7 percent of the respondents were likely to do what the FDA would want them to do when it comes to reporting ADEs. This result is not surprising and is in agreement with opinion poll results that show that the FDA commands the respect of more than two-thirds of the American adult population (Harris Interactive, 2007). The FDA is responsible for protecting the public health by assuring the efficacy and safety of all drugs sold within the U.S. borders. Drug safety is an essential component of the FDA's mission. In line with its mission, the FDA expects all pharmacists to report serious ADEs that they encounter. Most pharmacists seem to accept the role of the FDA in drug safety. However, a few pharmacists had negative perceptions of the FDA's conduct of postmarketing surveillance (PMS) activities and seven made negative comments[12] at the end of the survey.

[12] Some of the comments made by the pharmacists at the end of the survey are as follows: "I think the FDA looks the other way on a large number of adverse drug events. Personally, I feel the FDA is just an

The patients also emerged as important referents for pharmacists' intent to report serious ADEs to the FDA. A majority of respondents were likely to comply with what their patients wanted them to when it comes to reporting serious ADEs. Direct to consumer advertising and the widespread availability of health information on the internet and other sources makes patients more knowledgeable and engaged in their treatment, and in reporting serious ADEs to the FDA. About 15 percent of the 422,889 ADE reports submitted to the FDA in 2004 were submitted directly by consumers. Studies have found that patients respect pharmacists and respond favorably to pharmacist services in the community setting (Ukens, 1998; Whitley, Jones, & Peal, 1996). Pharmacists, especially community pharmacists, mostly obtain information about serious ADEs directly from patients (Herbert et al., 2006).

In addition, the study results indicate that physicians also influenced pharmacists' intent to report serious ADEs. A majority of respondents (65.7%) were likely to comply with what physicians would want them to do when it comes to reporting serious ADEs. Physicians have varied reactions to pharmacists' reporting of serious ADEs to the FDA. A study in Utah found that physicians were less willing to having pharmacists help patients manage ADRs or suggest alterations in patients' drug regimens (Bradshaw & Doucette, 1998). The study also found a negative correlation between a physician's attitude toward community pharmacists acting as patient advocates on drug-related matters and age (Bradshaw & Doucette, 1998). The negative attitude of physicians towards pharmacists' drug therapy recommendations, and difficulty in making direct contact with physicians (Amsler et al., 2001; Hughes & McCann, 2003) may limit the interprofessional liaison between pharmacists and physicians (Herbert et al., 2006).

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extension of the drug companies." "The FDA is slow to respond and is reluctant to confront PMA members." "I am well aware that the FDA is greatly understaffed and unable to adequately perform its duties." "I am not convinced that the FDA bureaucracy is efficient enough to manage the information that is reported" and "Previous FDA response has been none."

Similar to Cosentino and colleagues (1997) and Irujo and colleagues (2007), drug manufacturers were found to have a weak but positive influence on pharmacists' reporting of serious ADEs to the FDA Irujo and colleagues (2007) reported that few pharmacists communicated the occurrence of ADRs to drug manufacturers. Pharmaceutical companies did not appear to have much influence on pharmacists' reporting of serious ADEs, perhaps because pharmacists find them not to be trustworthy about drug safety. This may be explained by the fact that drug companies do not always reveal all they know about their products' safety profiles to the FDA, HCPs and the public (Caplovitz & The New Jersey Public Intrest Research Group Law and Policy Center, 2006; Psaty, Furberg, & Ray, 2004; Topol, 2004) and have little economic incentive to search and publicize information about ADEs associated with their products (Stern, 2003). In addition, the sponsoring of false and misleading drug advertisements (making unsubstantiated claims and misrepresenting drug risks) by drug manufacturers may also play a role (Caplovitz & The New Jersey Public Intrest Research Group Law and Policy Center, 2006). However, drug manufacturing companies are required by law to forward to the FDA all the ADEs that are reported to them by HCPs or patients.

SN Differences Between Intenders and Non-Intenders

Pharmacists who intended to report (mean = 5.91, SD = 1.26) had significantly higher mean normative beliefs than those who did not intend to report (mean = 5.02, SD = 1.43, $p < 0.001$). Higher SN for ADE reporting predicted higher intention to report serious ADEs in the future. Pharmacists intending to report ADEs (mean = 5.15, SD = 1.47) were more likely to believe that physicians would like them to report serious ADEs than those not intending to report (mean = 4.22, SD = 1.72, $p < 0.001$). The differences in normative beliefs between intenders and non-intenders may be explained by differential access or lack of direct access to physicians (Amsler et al., 2001).

Factors Associated with Subjective Norm

SN (indirect measures) was negatively associated with years of experience and was associated with gender—female respondents had significantly higher SN than males. Other studies found a similar association between gender and ADE reporting (Kurz, Van Ermen, Roisin, & Belton, 1996; Lee, Chan, Raymond, & Critchley, 1994). Another study conducted in Spain however, found male physicians to be more likely to report ADEs than female physicians (Figueiras et al., 1999). Using direct measures, this study found that the number of hours worked per week was significantly and positively correlated with pharmacists' SN. The pharmacists who worked less hours were likely to have less SN than those who worked more hours. These factors (gender, years of experience, and hours worked) should be considered in designing interventions aimed at enhancing the SN.

6.8 Perceived Behavioral Control Over Reporting Serious ADEs

As hypothesized, after controlling for A and SN, the belief-based PBC measure was a significant and the strongest predictor of intent. This finding implies that pharmacists do not have complete volitional control over reporting serious ADEs to the FDA and that reporting depends on skills, resources, opportunities, information and availability of time. This finding is consistent with other pharmacy-related studies (Farris & Schopflocher, 1999; Herbert et al., 2006; Pradel, Obeidat, & Tsoukleris, 2007). The findings confirm the importance of PBC in explaining HCPs' behavior (Godin et al., 2008; Godin & Kok, 1996). A meta-analysis found that PBC significantly added to the prediction of intention in 65 of the 76 analyses reported in the studies (Godin & Kok, 1996). In the literature PBC is a stronger predictor of intention and behavior when

perceived control is low (Madden, Ellen, & Ajzen, 1992). Thus, interventions are needed to increase the self-efficacy and perceived control of pharmacists.

The results show that pharmacists perceived themselves as having some control over reporting and believed that it was mostly up to them whether or not they reported serious ADEs to the FDA. However, PBC (direct measure) was not a significant predictor of intent to report. This finding should be reviewed with caution given the problems associated with directly measuring the PBC construct reported in the literature (Conner & Sparks, 1996; Courneya, Conner, & Rhodes, 2006; Kraft, Rise, Sutton, & Roysamb, 2005) and the small number of items (n = 2) used to measure the construct. The problems associated with directly measuring the PBC may explain the non-significance of PBC among other studies involving pharmacists (Mashburn et al., 2003; Saengcharoen et al., 2008; Walker et al., 2004).

Primary Drivers of Perceived Behavioral Control

Some of the strongest beliefs driving PBC of reporting serious ADEs to the FDA were: being a drug expert, a clear knowledge of what constitutes a reportable ADE, improved awareness of ADE reporting, and awareness of drug risks by patients. A majority of respondents indicated that having a clear knowledge of what constitutes a reportable ADE (85.1%), being a drug expert (78.8%) and having improved awareness of ADE reporting (71.9%) would enhance their control over reporting. In addition, the results of the eight-item knowledge scale showed that many pharmacists (43.3%) were not clear on reportable ADEs and how to report ADEs. Furthermore, a majority of respondents (65.7%) considered themselves to have inadequate knowledge concerning ADE reporting, a finding corroborated by anecdotal comments made by (some) respondents on their questionnaires. Taken together, these findings suggest a substantial lack of knowledge of ADE reporting and they (the findings) corroborate previous research that suggest that medical professionals (Bateman, Sanders, & Rawlins, 1992;

Eland et al., 1999; Hasford et al., 2002; Martin et al., 1998) and pharmacists (Backstrom, Mjorndal, & Dahlqvist, 2002; Granas et al., 2007; Green et al., 2001; Sweis & Wong, 2000) have deficient ADE reporting knowledge. Knowledge of ADE reporting is a major driver of PBC, which in turn is associated with intent to report. This study's finding improves our understanding of how knowledge works in shaping intentions with respect to reporting serious ADEs. The positive association between knowledge and ADE reporting (who, what, how and where) and the number of ADE reports submitted by HCPs has been observed in the literature (Irujo et al., 2007; Lopez-Gonzalez, Herdeiro, & Figueiras, 2009).

Educational interventions have been found to be effective in increasing reporting and improving the quality of reports (Backstrom, Mjorndal, & Dahlqvist, 2002; Figueiras, Herdeiro, Polonia, & Gestal-Otero, 2006; Green et al., 2001; Hazell & Shakir, 2006). More training and educational programs (CEs, seminars, undergraduate and post graduate pharmacy training) should be offered to pharmacists in order to increase their knowledge concerning reporting. Several pharmacists recommended (anecdotal comments[13]) continuing education and training on ADE reporting. In line with the study findings, the training and education should cover the types of ADEs that should be reported, definition of serious ADEs, how to detect and report ADEs, the operations of MedWatch and the benefits/value of pharmacovigilance. All the relevant stakeholders (e.g., FDA, employers, and managers/bosses) should prioritize and support the provision of ADE reporting education and training to pharmacists.

A majority of pharmacists believed that increased patient counseling (65.0%) would make it easier to report serious ADEs to the FDA. Before pharmacists can report

[13] Some of the comments made by the pharmacists include: "I would like a refresher on ADE reporting", "There should be continuing education on ADE and reporting", "I would like to know more details on this subject", and "All employers should include ADE reporting in their training modules for employees—mandatory!"

serious ADEs, they need to first identify them. Through spending more time counseling patients (e.g., interviewing and advising patients, encouraging patients to ask questions, and reconciling medications), pharmacists increase their potential to identify serious ADEs (Kuyper, 1993; Nolan, 2000; Viktil & Blix, 2008). The role of patient counseling in aiding ADE reporting and improving patient outcomes is established in the literature (Nolan, 2000; Viktil & Blix, 2008). However, pharmacists are not adequately devoting time to counseling their patients (Farris & Schopflocher, 1999; Pradel, Obeidat, & Tsoukleris, 2007; Suh et al., 2001), which can be explained by various factors including lack of time, lack of private counseling space, and limited access to relevant patient-specific clinical data (Amsler et al., 2001).

Interestingly, a majority of respondents indicated that employer support for ADE reporting (78.2%) would make it easier to report serious ADEs. Similarly, Green and colleagues (2001) reported that encouragement from managers and departments would improve reporting. However, due to commercial pressures in pharmacy practice and the high prescription volumes, ADE reporting may not be prioritized by employers and managers. Employers and managers should be sensitized to the importance of pharmacovigilance and should be encouraged to support pharmacists in their quest to report serious ADEs.

The results of this study also indicate that a majority of pharmacists believed that having a complete patient medical history (54.3%) would make it easier to report serious ADEs to the FDA. Community pharmacists do not have access to complete patient medical histories and some considered this to be an impediment to ADE reporting. Without patient medical histories, pharmacists may find it difficult to establish an association between a drug and the adverse event. Having access to patients' medical history may enhance pharmacists' confidence in iatrogenic diagnosis and patient counseling (Kuyper, 1993) and thus foster reporting. This is particularly relevant given

that many pharmacists (35.1%) were not aware that they could report serious ADEs even if they did not have all the details (e.g., complete patient history and demographic data).

Offering financial compensation or some other form of incentive (e.g., lottery tickets, educational bulletin linked to educational credits and free advice) has been associated with an increased number and improved quality of ADE reports (Bäckström & Mjörndal, 2006; Bracchi et al., 2005; Feely, Moriarty, & O'Connor, 1990; Jankovic, 2003). Direct economic inducements may offset or compensate for the inconveniences involved in submitting ADE reports. However, most respondents in other studies did not think that economic inducements (e.g., fees or lottery tickets) were an incentive to report ADRs (Bäckström & Mjörndal, 2006; Bawazir, 2006; Green et al., 2001). Our findings show that most of the respondents (55.1%) indicated that having some type of reward or compensation neither made it easier nor more difficult to report serious ADEs. Only about a third of respondents indicated that having some type of reward or compensation (36.1%) would make it easier to report serious ADEs.

Most pharmacists believed that lack of time (80.7%) made it more difficult for them to report serious ADEs to the FDA. Lack of time is a deterrent to ADE reporting. This finding corroborates previous research that suggested that lack of time to fill a report or to look for ADEs limits ADE reporting (Bateman, Sanders, & Rawlins, 1992; Bawazir, 2006; Belton et al., 1995; Granas et al., 2007; Green et al., 2001; Herdeiro et al., 2006; Nita, Batty, & Plumridge, 2005; Sweis & Wong, 2000; Vallano et al., 2005; van Grootheest, Mes, & de Jong-van den Berg, 2002). The pharmacists' working conditions and other workplace issues may make it difficult for pharmacists to devote time to reporting. These include increased workload (Bateman, Sanders, & Rawlins, 1992; Belton et al., 1995), high turnover, shortage of pharmacists, too much time spent on insurance-related problems, hectic pace of practice, and increased prescription volumes (Amsler et al., 2001; Anonymous, 1999; Gidman, Hassell, Day, & Payne, 2007; Knapp, Quist, Walton, & Miller, 2005). Previous studies show that lack of time also affects

pharmacists' participation in other clinical activities (Coleman, 2003; Janke & Plamondon, 1997; Pradel, Obeidat, & Tsoukleris, 2007; Venkataraman, Madhavan, & Bone, 1997). There is an urgent need to address these organizational factors so that pharmacists can find more time to submit reports. One suggestion is to incorporate ADE reporting into the daily routines of pharmacists through linking the dispensing computer software to the online MedWatch reporting form. Such convergence will allow pharmacists to submit ADE reports as part of dispensing or through a touch of a button. Furthermore, the software can be designed to automatically populate patient and drug information on the MedWatch form. If implemented, this measure will reduce the time needed to submit a report and also make reporting more convenient than at present. Information gathered during focus groups shows that pharmacists think that such computerized support would be valuable. In addition, the time required to report can be reduced through further simplifying the MedWatch form and streamlining the reporting process, which have been reported to increase ADE reporting rates (Brewer & Colditz, 1999).

Factors Associated with Perceived Behavioral Control

Pharmacists who were in practice for a longer time were likely to have lower PBC over reporting than those who had fewer years of experience. In addition, using indirect measures, there was a significant difference in mean PBC ratings toward reporting serious ADEs by pharmacists' ethnicity with the African American/non Hispanic black group having higher perceived control than the Caucasian/non-Hispanic white group. Knowledge levels were positively correlated with PBC over reporting serious ADEs, indicating that pharmacists who had more knowledge of ADE reporting perceived themselves to have more control over reporting serious ADEs. Personal factors may be playing a role in shaping reporting decision-making and should be targeted in behavior

change strategies. The pharmacists with more years of practice experience, Caucasians, and those who are less knowledgeable of ADE reporting should be prioritized.

6.9 Past Reporting Behavior

As expected, the addition of past reporting behavior (PRB) construct to the TPB model significantly increased the power of the regression model in explaining intention to report serious ADEs to the FDA. The R^2 change for both the direct and indirect measures models were significant ($p < 0.05$). Pharmacists who had reported serious ADEs in the past had higher intentions to report serious ADEs than those who had never reported. The results of this study confirm the findings of previous studies that reported that the addition of past behavior significantly improved the prediction of intention over and above the TPB constructs (Albarracin et al., 2001; Bagozzi, 1981; Hart & Morris, 2008; Leone, Perugini, & Ercolani, 1999; Mashburn et al., 2003; Quine & Rubin, 1997; Walker, Grimshaw, & Armstrong, 2001). Taken together, these findings indicate that past behavior is an important predictor and, thus, should be included in models of ADE reporting intentions among pharmacists.

The study results show that seven percent of the respondents had reported ADEs in the previous 12 months and 32 percent had reported ADEs to the FDA in the past, although about 45 percent of pharmacists indicated that they had encountered reportable ADEs in their practice in the past. The proportion of pharmacists who had ever reported ADEs (32%) in this study is comparable to the proportion of reporters found in previous studies: 33.2 percent obtained among Dutch doctors (Belton & The European Pharmacovigilance Research Group, 1997) and 33.7 percent obtained among Swedish general practitioners and hospital pharmacists (Bäckström et al., 2000). Other studies found lower percentages of healthcare professionals (HCPs) who had ever reported ADRs: 25.6 percent (Green et al., 2001), 23.3 percent (Irujo et al., 2007), and 19.4

percent (Belton & The European Pharmacovigilance Research Group, 1997). However, other studies reported higher percentages of HCPs who had ever reported ADRs (Belton et al., 1995; Eland et al., 1999).

The study results show that a large proportion of respondents are not fully engaged in reporting ADEs to the FDA, despite them having favorable BI, A, SN and PBC toward reporting. Similar findings were reported in the non-pharmacy (Fried, DeVore, & Dailey, 2001; Meyer, Battles, Hart, & Tang, 2003), and pharmacy (Granas et al., 2007; Lee et al., 1994; Pradel, Obeidat, & Tsoukleris, 2007) literature. In these studies, a majority of pharmacists had a favorable A towards the behavior yet most of them were not performing the behavior. Lee (1994) reported that 93 percent of pharmacists agreed that ADR reporting was important, yet only 14.7 percent had done so in the previous year. These results may mean that pharmacists viewed intention and performance as being mutually exclusive (Meyer et al., 2003), or indicate existence of challenges that impede the translation of intentions into behavior. There are several factors that may moderate the intention-behavior link and consistency (Eccles et al., 2006; Sheeran, 2002; Sutton, 1998; Webb & Sheeran, 2006). Some of the factors include the presence of facilitating conditions, (perceived) control over the behavior, the extent to which the behavior is habitual, stability and context of performance, frequency of behavior performance, coping appraisals (e.g., perceptions of the efficacy and costs), strength of the respective intentions, time interval between intention and behavior, type of behavior measure (objective vs. self-report) and type of sample (Armitage, Sheeran, Conner, & Arden, 2004; Randall & Wolff, 1994; Sheeran & Orbell, 1998; Sheeran, Trafimow, & Armitage, 2003; Triandis, 1980; Wood & Quinn, 2005). Owing to the above factors, BI may prove to be a poor predictor of behavior.

Studies of healthcare professionals on reporting show that low reporting may be due to several factors including lack of motivation, cues to action and not prioritizing ADE reporting (Giraldo-Matamoros, Alvarez-Díaz, & Ramos-Aceitero, 2007; Irujo et al.,

2007; WHO Collaborating Centre for International Drug Monitoring and The Uppsala Monitoring Centre, 2002). It has been established that cues to action are necessary to trigger action or behavioral change (Gasparotto, 2007; Rosenstock, 1974). "Cues to action are external events that prompt a desire to make a health change… A cue to action is something that helps move someone from wanting to make a health change to actually making a change" (Boskey, 2009, p. no page number). Cues to action can be anything (e.g., a person or event) that can trigger action or behavior change. Without appropriate cues to action, busy pharmacists tend to forget to report ADEs (Irujo et al., 2007; Kingston, Evans, Smith, & Berry, 2004). Thus, they may need to be periodically prompted to report ADEs (Figueiras et al., 2006). Appropriate cues to action not only trigger action/reporting but may also rekindle the pharmacists' motivation to report ADEs (Simon, 2002). Reporting cues that can be implemented include: a) promotion of the professional and public health benefits of ADE reporting; b) sending out drug safety bulletins to all pharmacists by the FDA; c) publishing more journal articles on ADE reporting; d) television advertisements and programs; e) provision of specific and detailed feedback to all who report serious ADEs; and f) provision of education and training. Cues to action are effective in increasing reporting rates among HCPs. For example, in New Zealand, "The use of especially designed prescription pads which prompted doctors to report on new drugs separately increased the reporting rate 14-fold" (Edwards, 1999, p. 140).

6.10 PERCEIVED MORAL OBLIGATION

The addition of the PMO construct to the TPB constructs (direct and indirect measures) significantly improved the prediction of intention; the change in R-squared was significant. This finding corroborates previous research that found that PMO is an important predictor of intention especially in moral situations (Fazekas, Senn, &

Ledgerwood, 2001; Gorsuch & Ortberg, 1983; Randall & Gibson, 1991; Werner & Mendelsson, 2001). A systematic review of studies based on social cognitive theories among HCPs' intentions and behavior found moral norm to be a consistently significant cognitive factor explaining intention (Godin et al., 2008). Moral norm (equivalent of PMO) was significant ($p < 0.05$) in 10 of the 14 studies assessed (Godin et al., 2008). This study was the first to examine the direct path from moral norm to intention to report serious ADEs by pharmacists.

The results show that a large number of pharmacists believed that they had a moral obligation to report serious ADEs that they encounter to the FDA. This finding may suggest that ADE reporting is a moral issue or a professional responsibility for pharmacists. Pharmacists in other countries also feel that they have a professional obligation to report ADRs (Green et al., 2001; Herdeiro et al., 2006; Vessal, Mardani, & Mollai, 2009) and ADE reporting is their professional duty (Figueiras et al., 1999). Physicians also believe that reporting ADEs is their professional duty and the WHO consider ADE reporting as a part of HCPs' duties (Figueiras et al., 1999; World Health Organization, 2002a).

6.11 Institutional and Organizational Changes

The continued occurrence of serious ADE underreporting may suggest an existence of inadequacies and shortcomings in the current institutional and organizational arrangements for addressing postmarketing surveillance (PMS) activities. As noted in Chapter Two, the licensing and labeling of all medicines and their PMS are conducted[14] by the FDA's Center for Drug Evaluation and Research (CDER). The FDA seems to pay more attention to evaluating new drugs than to PMS, as fewer resources (e.g., staff and

[14] There is a potential conflict between these roles as data from PMS activities often result in labeling changes or reversal of previous approval decisions or provide evidence to prove the initial approval decision was incorrect (Fontanarosa, Rennie, & DeAngelis, 2004; Wood, Stein, & Woosley, 1998).

funds) are channeled toward PMS activities. PMS activities at the FDA are also hampered by limited capacity, high attrition, lack of analytical sophistication, low staff morale, the existence of multiple competing priorities and limited regulatory authority over enforcement (Griffin, Stein, & Ray, 2004; Institute of Medicine of the National Academies, 2007a; Schmit, 2007; United States General Accounting Office, 2003; Wood, Stein, & Woosley, 1998). As a result, the FDA takes a long time to recognize and address safety signals, and to inform the public about safety problems. Little is being done to stimulate pharmacists and other HCPs to report ADEs (Institute of Medicine of the National Academies, 2007a). Furthermore, PMS is not comprehensive or systematic and is sub-optimal (Institute of Medicine of the National Academies, 2007a, p. 108; Moore, Psaty, & Furberg, 1998; Strom, 2006; Wood, Stein, & Woosley, 1998), thereby further exacerbating underreporting of serious ADEs.

Several long-term solutions have been suggested to enhance PMS or to increase ADE reporting including reforming and restructuring the FDA, and increasing resources to the FDA. Suggestions for restructuring and reforming the FDA that are relevant to PMS include decentralizing the FDAs PMS activities and establishing an independent drug safety board, respectively. These are briefly discussed below.

One suggestion for decentralizing the FDA's PMS activities includes establishing MedWatch regional reporting centers, similar to the New York Patient Occurrence and Tracking System (NYPORTS) (Motl, Timpe, & Eichner, 2004). The proposed regional centers can collect and evaluate serious ADEs, provide feedback to reporters, encourage HCPs to report, forward reported ADEs to MedWatch and provide targeted outreach support to HCPs including pharmacists. The proposed regional reporting centers can be integrated into the existing drug information centers (DICs) and poison control centers that most HCPs are already familiar and comfortable with (Motl, Timpe, & Eichner, 2004). The establishment of regional centers in the Netherlands, United Kingdom, France, and Spain helped bring the centers closer to reporters and resulted in more and

better quality ADE reports (Clarkson, Ingleby, Choonara, Bryan, & Arlett, 2001; Motl, Timpe, & Eichner, 2004).

The current institutional setup can be improved through the establishment of a drug safety board, that is independent of both the FDA and drug manufacturers, to oversee drug PMS activities (Griffin, Stein, & Ray, 2004; Moore, Psaty, & Furberg, 1998; Okie, 2005; Psaty & Furberg, 2005; Wood, Stein, & Woosley, 1998). The board may oversee the management of drug safety-related issues and make recommendations to improve drug safety to the FDA and the medical community. The establishment of such an agency would minimize conflicts of interests (separate post-marketing from new drug approval functions), separate powers, and ensure objectivity in the investigation of ADEs (Fontanarosa, Rennie, & DeAngelis, 2004; Psaty & Furberg, 2005; Wood, Stein, & Woosley, 1998). In 2005, the FDA established a Drug Safety Oversight Board to:

> Improve public knowledge of emerging important drug safety concerns; strengthen internal drug safety management; foster practical policy development to improve consistency and timely resolution of important drug safety concerns; and provide a standing venue for resolution of CDER organizational disputes (Cummins, 2006, p. 1).

The board consists of FDA staff (n = 10) and medical officers from other U.S. Department of Health and Human Services agencies (n = 2). This board falls short of the independent external oversight of drug safety that many have recommended (Wood, Stein, & Woosley, 1998). The effectiveness of the current board is compromised by the lack of resources, authority, and most importantly independence from the FDA (Harris, 2005).

The implementation of the above changes needs to be complemented with the provision of increased resources (e.g., staff and information technology) to the FDA to carry out drug safety work. The following recommendations have been forwarded for increasing FDA resources for PMS:

- Increase appropriations from Congress: Many have called for Congress to increase the resources appropriated to the FDA for carrying out PMS activities (Institute of Medicine of the National Academies, 2007a). Public funding is considered the best way to support the FDA's PMS activities (Institute of Medicine of the National Academies, 2007a).
- Reduce restrictions on the Prescription Drug User Fees Act (PDUFA) funds: Currently, only a small portion (5%) of the user fees (fees paid by pharmaceutical companies to the FDA) collected can be used for PMS activities. The FDA can raise more funds for PMS activities, if the current restrictions on the use of fees raised under PDUFA are relaxed (Zelenay, 2005).
- Introduce a tax: A small tax on prescriptions has been suggested as a way to raise funds for PMS activities. For example, "a tax of ten cents on every prescription would generate more than $100 million for the FDA budget" (Institute of Medicine of the National Academies, 2007a, p. 198). Others have suggested a tax on direct-to-consumer advertisements for new drugs (Institute of Medicine of the National Academies, 2007a).

6.12 IMPLICATIONS AND DIRECTIONS FOR FUTURE RESEARCH

There is an urgent need to increase ADE reporting rates by pharmacists. Although all pharmacists are responsible for ensuring the safe use of medicines, of which ADE reporting is an integral part, low ADE reporting rates among pharmacists persists. The failure to report serious ADEs that pharmacists encounter is a missed opportunity for preventing unnecessary and avoidable patient harm from drug use. Although most of our sample encountered reportable ADEs, only seven (7) percent reported submitting ADE reports to the FDA in the previous 12 months. There is an urgent need to boost ADE reporting rates among pharmacists.

All three TPB constructs (A, SN and PBC) were associated with an increased likelihood of intent to report serious ADEs. Pharmacists' overall evaluation of reporting serious ADEs, their perceived expectation of important others with respect to their reporting of serious ADEs and their beliefs about the degree of control they had over reporting serious ADEs are important and positive influences on intention. Interventions may need to focus on increasing pharmacists' A, SN and PBC. The application of the TPB holds promise for Texas pharmacists by identifying potentially modifiable factors for increasing intention and actual reporting of serious ADEs to the FDA. More serious ADE reports (safety signals) will facilitate the identification of unsafe products, facilitate the education and training of HCPs on the safe use of medicines and inform better and safer ways to use the available medicines. In the long term, improved reporting will minimize the potential for patient exposure to avoidable drug risks.

An understanding of the factors affecting pharmacists' A provides insight into strategies to increase ADE reporting by pharmacists. The most salient beliefs of the pharmacists were: (reporting) improves patient safety, educates others about drug risks, reduces the risk of malpractice, and builds trust with patients. Strategies to increase ADE reporting should address these beliefs to enhance pharmacists' A. The pharmacists' positive A can be enhanced through various ways including providing incentives for reporting, providing verbal expression of support for ADE reporting by the FDA and managers/bosses, among others, and educating pharmacists on the value/benefits of ADE reporting to the profession.

SN plays an important role in the formulation of intentions to report serious ADEs. This may imply that ADE reporting is influenced by others more than by the pharmacists' individual choices and that the opinions of others are of great importance in pharmacists' decision making. Interventions that enhance pharmacists' positive social norms may be effective in changing ADE reporting behavior. The most salient referents driving SN were the FDA, patients, pharmacy associations, pharmacy managers/bosses

and hospitals/hospital groups. Using the FDA, patients, pharmacy associations and pharmacy managers/bosses to communicate with pharmacists the need to report serious ADEs may be effective and worthwhile.

Because PBC (indirect measures) emerged as the strongest predictor of intention to report serious ADEs, interventions would be most beneficial if they targeted pharmacists' perceived barriers towards ADE reporting. The most important barriers perceived by the pharmacists include not being a drug expert, lack of knowledge of what constitutes a reportable ADE, limited awareness of ADE reporting, limited awareness of drug risks by patients and limited patient counseling. Interventions may need to focus on increasing the self-efficacy and perceived control of pharmacists through education (e.g., CEs) on ADE reporting and ADEs and through professional campaigns that use role models or peer educators to encourage ADE reporting. In addition, pharmacy managers and the FDA need to ensure that pharmacists have sufficient resources and psychological support for reporting and to make reporting as convenient as possible.

The findings of this study show that PRB and PMO enhanced the prediction of intentions to report serious ADEs to the FDA over and above the TPB constructs (A, SN and PBC). Similarly, other studies found that the inclusion of PRB and PMO increased the proportion of explained variance in intention (Albarracin et al., 2001; Bagozzi, 1981; Fazekas, Senn, & Ledgerwood, 2001; Gorsuch & Ortberg, 1983; Hart & Morris, 2008; Leone, Perugini, & Ercolani, 1999; Mashburn et al., 2003; Nwokeji, 2007; Quine & Rubin, 1997; Randall & Gibson, 1991; Walker, Grimshaw, & Armstrong, 2001; Werner & Mendelsson, 2001). Taken together, these findings indicate that PRB and PMO are important predictors and, thus, should be included in models of ADE reporting intentions among pharmacists. Interventions to increase ADE reporting should enhance pharmacists' perception of their moral norms concerning ADE reporting. This can be done through portraying ADE reporting as promoting the wellbeing of others, and avoiding harm and distress to others (beneficence and nonmaleficience). In addition, to

enhance the PRB, interventions should give pharmacists an opportunity to practice reporting serious ADEs.

There are several issues that need further investigation. First, the study population consists of Texas practicing pharmacists, and therefore, the results cannot be extrapolated to non-practicing pharmacists or to pharmacists in other states. More empirical research should be conducted to confirm the study findings using a different population.

Second, more experimental designs (use of a control group) that can offer an insight on causality of predictors should be conducted. This could be set up through having intervention and control groups. Using longitudinal data would provide conclusive evidence of the causal relationships among the constructs.

Third, this study focused on pharmacists' intention to report serious ADEs to the FDA. More research should be conducted to investigate the link between intention to report serious ADEs and actual behavior and also between PBC and behavior. Typically, A, SN, PBC and intention should be measured and then behavior measured after a time interval (Montano & Kasprzyk, 2002). The intention-behavior relationship is an important component of the TPB. The resulting information could provide further opportunities for influencing behavior.

Fourth, the frequency and consistency of ADE reporting by pharmacists was not investigated in this study and is largely unknown. The TPB is primarily a model of intention formation and does not effectively distinguish regular and consistent reporters from one-time reporters nor is it effective in predicting the maintenance of behavior over time (Sheeran, Conner, & Norman, 2001). Future studies should be conducted to predict the frequency (never reported, reported once, and reported multiple times) and consistency of ADE reporting by pharmacists. Processes of change based on the transtheoretical model (Prochaska, DiClemente, & Norcross, 1992) may provide valuable insights on the differences between consistent reporters and non-consistent reporters. Understanding these processes and differences could further enhance the prediction of

pharmacists' intention to report serious ADEs to the FDA and actual subsequent behavior.

Finally, future research should pay more attention to the reporting context. The use of vignettes or hypothetical serious ADEs could help contextualize the performance of ADE reporting. Vignettes and hypothetical ADEs have been successfully used to predict physician prescribing and reporting behavior (Eland et al., 1999; Harrell & Bennett, 1974) and pharmacists' reporting behavior (Green et al., 2001). Vignettes and hypothetical cases may be effective in predicting pharmacists' reporting of serious ADEs.

6.13 LIMITATIONS

Findings of this study should be interpreted in light of its limitations as discussed below. First, this study used a cross-sectional study design and the findings provide a snapshot picture only. The study does not unequivocally demonstrate the causal nature of the structural relationships and these relationships may change over time.

Second, the study used self-reports from pharmacists which are prone to inaccurate responses. The study could not verify the pharmacists' responses since the responses were anonymous. The pharmacists' responses could have been influenced by response bias, poor recall or social desirability factors associated with an expected behavior. It has been reported that physicians overestimate their adherence to guidelines in their self-reports by as much as 20 percent (Adams, Soumerai, Lomas, & Ross-Degnan, 1999). Some pharmacists may have provided socially desirable responses to questions especially pertaining to A, SN, PBC and intentions. This leads to difficulties in interpreting the findings, especially if people differentially overestimate their performance. However, responses in this study were anonymous and a majority of those who responded admitted that they had never reported ADEs. Although, this is no guarantee of accuracy of the data, it seems there was no incentive to be deceptive.

Third, despite using a second mailing to improve the survey response rate, only 26.4 percent of the selected sample returned complete survey responses. Since the study was anonymous, non-responders and responders could not be compared. Selection bias may be a problem; it is possible that the study mainly attracted pharmacists with high intentions and favorable attitudes toward ADE reporting. This low response rate may limit the generalizability of the results from this study.

Fourth, the length of the survey may have discouraged some potential responders. The survey, designed following TPB guidelines, was 6 pages long and consisted of 94 items. Some respondents may have found the survey instrument used in this study to be too long. In addition, some items in the questionnaire had similar wording. Some respondents may have considered some similarly worded questions to be the same, thus leading them to doubt their own responses (Young, Lierman, Powell-Cope, Kasprzyk, & Benoliel, 1991), or to pay less attention to these questions, resulting in response set bias (Meyer et al., 2003).

Fifth, PBC (direct measure) and PRB were each measured using only two (2) items. A measure with more than two (2) items is likely to have higher internal consistency. However, at the time of this study, the author was unaware of other measures that had undergone methodological testing for construct validity.

Sixth, the correlations among variables and constructs in this study may have been artificially inflated owing to shared method and shared sources (e.g., self-report measures). It was not feasible to collect data through other methods and from other sources given the anonymity of the ADE reporting process.

Seventh, the items used to measure intentions were not precise on the time frame of the intentions. This was due to the difficulty in predicting the timing of pharmacists' next encounter with serious ADEs. It was assumed that the time pertained to the next time pharmacists will encounter serious ADEs. Similar challenges have been encountered in coming up with operational definitions of intention in studies of physician samples,

given the complexity of clinical-related behaviors (Godin et al., 2008). The fact that the intention measure did not specify the time frame could have inflated the intention scores and may reduce the accuracy of intention in predicting future behavior. However, it seems unlikely this consideration seriously threatens the validity of the present analyses, because the study did not investigate the intention-behavior relationship.

6.14 CONCLUSION

The study findings indicated that a majority of pharmacists held favorable behavioral, normative and control beliefs concerning reporting of serious ADEs. Pharmacists intended to report serious ADEs that they encounter to the FDA. The study data supported the TPB model: A, SN and PBC predicted pharmacists' intentions to report serious ADEs, explaining 34.0 percent (direct measures) and 28.8 percent (indirect measures) of the variance in intention. In general, the data were consistent with the predicted relationships among the TPB model components (A, SN, PBC, and BI). Although the PBC (direct measure) was not a significant predictor of intent to report, but as hypothesized, after controlling for A and SN, the belief-based PBC measure was a positive and the strongest predictor of intent. The TPB appears to be an appropriate theoretical model and a useful framework for studying pharmacists' reporting of serious ADEs.

PRB and PMO increased the explanatory power of the regression model compared to only using the A + SN + PBC to explain pharmacists' intention to report serious ADEs. PRB and PMO had a strong effect on intention beyond the TPB constructs. The fit of the model on pharmacist ADE reporting intentions may be improved through the addition of PRB and PMO constructs to the TPB.

The pharmacists' A, SN, and PBC toward reporting serious ADEs were mostly unrelated to practice characteristics and demographic factors. Pharmacists' knowledge of ADE reporting was the only characteristic that was significantly related with all the TPB constructs using both direct and indirect measures. Pharmacists' A, SN, PBC may be modified through increasing their knowledge concerning reporting. Modifying pharmacists' beliefs through educational interventions and breaking down the barriers to reporting are likely to be successful in increasing pharmacists' reporting of serious ADEs to the FDA. More training and educational programs (CEs, seminars, undergraduate and

post graduate pharmacy training) related to ADE reporting should be offered to pharmacists. All the relevant stakeholders (e.g., FDA, employers, and managers/bosses) should prioritize and support the provision of ADE reporting education and training to pharmacists.

This study is the first to use a theoretical model to examine pharmacists' intention to report serious ADEs. Based on the TPB, this study identified the predictors of Texas pharmacists' intention to report serious ADEs to the FDA through MedWatch. The study findings offer a theoretically-based understanding of individual factors that influence pharmacists' intention to report serious ADEs. Public health officials, drug safety experts and pharmacy educators can gain insight from these findings in developing strategies to increase ADE reporting by pharmacists. Pharmacy educators need to further examine the results of this study and use them to direct teaching strategies. Solving the problem of underreporting requires multifaceted solutions.

Appendix A: MedWatch Reporting Form

U.S. Department of Health and Human Services

MEDWATCH

The FDA Safety Information and Adverse Event Reporting Program

For VOLUNTARY reporting of adverse events, product problems and product use errors

Page 1 of ____

Form Approved: OMB No. 0910-0291, Expires: 12/31/2011
See OMB statement on reverse.

FDA USE ONLY
Triage unit sequence #

PLEASE TYPE OR USE BLACK INK

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event or Date of Birth:	3. Sex	4. Weight
In confidence		☐ Female ☐ Male	____ lb or ____ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☐ **Adverse Event** ☐ **Product Problem** *(e.g., defects/malfunctions)*
☐ **Product Use Error** ☐ **Problem with Different Manufacturer of Same Medicine**

2. **Outcomes Attributed to Adverse Event** *(Check all that apply)*
☐ Death: _____ *(mm/dd/yyyy)*
☐ Disability or Permanent Damage
☐ Life-threatening
☐ Congenital Anomaly/Birth Defect
☐ Hospitalization - initial or prolonged
☐ Other Serious (Important Medical Events)
☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)

3. Date of Event *(mm/dd/yyyy)*	4. Date of this Report *(mm/dd/yyyy)*

5. **Describe Event, Problem or Product Use Error**

6. **Relevant Tests/Laboratory Data, Including Dates**

7. **Other Relevant History, Including Preexisting Medical Conditions** *(e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)*

C. PRODUCT AVAILABILITY

Product Available for Evaluation? *(Do not send product to FDA)*

☐ Yes ☐ No ☐ Returned to Manufacturer on: _____ *(mm/dd/yyyy)*

D. SUSPECT PRODUCT(S)

1. **Name, Strength, Manufacturer** *(from product label)*

#1 Name:
Strength:
Manufacturer:

#2 Name:
Strength:
Manufacturer:

2. Dose or Amount	Frequency	Route
#1		
#2		

3. **Dates of Use** *(If unknown, give duration) from/to (or best estimate)*
#1
#2

4. **Diagnosis or Reason for Use** *(Indication)*
#1
#2

6. Lot #	7. Expiration Date
#1	#1
#2	#2

5. **Event Abated After Use Stopped or Dose Reduced?**
#1 ☐ Yes ☐ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

8. **Event Reappeared After Reintroduction?**
#1 ☐ Yes ☐ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

9. **NDC # or Unique ID**

E. SUSPECT MEDICAL DEVICE

1. **Brand Name**

2. **Common Device Name**

3. **Manufacturer Name, City and State**

4. Model #	Lot #	5. Operator of Device
		☐ Health Professional
Catalog #	**Expiration Date** *(mm/dd/yyyy)*	☐ Lay User/Patient
		☐ Other:
Serial #	**Other #**	

6. If Implanted, Give Date *(mm/dd/yyyy)*	7. If Explanted, Give Date *(mm/dd/yyyy)*

8. **Is this a Single-use Device that was Reprocessed and Reused on a Patient?**
☐ Yes ☐ No

9. **If Yes to Item No. 8, Enter Name and Address of Reprocessor**

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates *(exclude treatment of event)*

G. REPORTER *(See confidentiality section on back)*

1. **Name and Address**
Name:
Address:
City: State: ZIP:

Phone #	E-mail

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☐ No		☐ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. **If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box:** ☐

FORM FDA 3500 (1/09) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

ADVICE ABOUT VOLUNTARY REPORTING

Detailed instructions available at: http://www.fda.gov/medwatch/report/consumer/instruct.htm

Report adverse events, product problems or product use errors with:

- Medications *(drugs or biologics)*
- Medical devices *(including in-vitro diagnostics)*
- Combination products *(medication & medical devices)*
- Human cells, tissues, and cellular and tissue-based products
- Special nutritional products *(dietary supplements, medical foods, infant formulas)*
- Cosmetics

Report product problems - quality, performance or safety concerns such as:

- Suspected counterfeit product
- Suspected contamination
- Questionable stability
- Defective components
- Poor packaging or labeling
- Therapeutic failures (product didn't work)

-Fold Here-

Report SERIOUS adverse events. An event is serious when the patient outcome is:

- Death
- Life-threatening
- Hospitalization - initial or prolonged
- Disability or permanent damage
- Congenital anomaly/birth defect
- Required intervention to prevent permanent impairment or damage (devices)
- Other serious (important medical events)

Report even if:

- You're not certain the product caused the event
- You don't have all the details

How to report:

- Just fill in the sections that apply to your report
- Use section D for all products except medical devices
- Attach additional pages if needed
- Use a separate form for each patient
- Report either to FDA or the manufacturer *(or both)*

Other methods of reporting:

- 1-800-FDA-0178 - To FAX report
- 1-800-FDA-1088 - To report by phone
- www.fda.gov/medwatch/report.htm - To report online

If your report involves a serious adverse event with a device and it occurred in a facility outside a doctor's office, that facility may be legally required to report to FDA and/or the manufacturer. Please notify the person in that facility who would handle such reporting.

-Fold Here-

If your report involves a serious adverse event with a vaccine, call 1-800-822-7967 to report.

Confidentiality: The patient's identity is held in strict confidence by FDA and protected to the fullest extent of the law. FDA will not disclose the reporter's identity in response to a request from the public, pursuant to the Freedom of Information Act. The reporter's identity, including the identity of a self-reporter, may be shared with the manufacturer unless requested otherwise.

The public reporting burden for this collection of information has been estimated to average 36 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer (HFA-710)
5600 Fishers Lane
Rockville, MD 20857

Please DO NOT RETURN this form to this address.

OMB statement:
"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number."

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

FORM FDA 3500 (1/09) (Back) **Please Use Address Provided Below -- Fold in Thirds, Tape and Mail**

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

Official Business
Penalty for Private Use $300

NO POSTAGE NECESSARY IF MAILED IN THE UNITED STATES OR APO/FPO

BUSINESS REPLY MAIL
FIRST CLASS MAIL PERMIT NO. 946 ROCKVILLE MD

POSTAGE WILL BE PAID BY FOOD AND DRUG ADMINISTRATION

MEDWATCH
The FDA Safety Information and Adverse Event Reporting Program
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20852-9787

U.S. Department of Health and Human Services

MEDWATCH

The FDA Safety Information and Adverse Event Reporting Program

(CONTINUATION PAGE)

For VOLUNTARY reporting of adverse events and product problems

B.5. **Describe Event or Problem** *(continued)*

B.6. **Relevant Tests/Laboratory Data, Including Dates** *(continued)*

B.7. **Other Relevant History, Including Preexisting Medical Conditions** *(e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)* *(continued)*

F. Concomitant Medical Products and Therapy Dates *(Exclude treatment of event)* *(continued)*

Appendix B: Survey Instrument

SURVEY INSTRUMENT

We are interested in factors that influence your willingness to report serious adverse drug events (ADEs) to the U.S. Food and Drug Administration (FDA) through the MedWatch program. Please answer the following questions to the best of your knowledge of ADE reporting.

First, we would like to determine your beliefs about pharmacists reporting serious ADEs to the FDA. Please circle the number that corresponds to your choice using the scales listed below.

1. How likely do you think the following outcomes will be if you report serious ADEs to the FDA?	**Extremely unlikely**			**Neither likely nor unlikely**			**Extremely likely**
a. educates others about drug risks	1	2	3	4	5	6	7
b. personally beneficial/rewarding to the pharmacist	1	2	3	4	5	6	7
c. improves patient safety	1	2	3	4	5	6	7
d. increases risk of malpractice	1	2	3	4	5	6	7
e. compromises relationship with physicians	1	2	3	4	5	6	7
f. breaks trust with patients	1	2	3	4	5	6	7
g. disrupts the normal workflow	1	2	3	4	5	6	7
h. time consuming to report	1	2	3	4	5	6	7

Even though you may not agree with the outcomes listed, how good or bad do you feel each of the following outcomes would be if you reported serious ADEs to the FDA?

2. How good or bad do you feel each of the following outcomes would be if you reported serious ADEs to the FDA?	**Extremely bad**			**Neither bad nor good**			**Extremely good**
a. educates others about drug risks	1	2	3	4	5	6	7
b. personally beneficial/rewarding to the pharmacist	1	2	3	4	5	6	7
c. improves patient safety	1	2	3	4	5	6	7
d. increases risk of malpractice	1	2	3	4	5	6	7
e. compromises relationship with physicians	1	2	3	4	5	6	7
f. breaks trust with patients	1	2	3	4	5	6	7
g. disrupts the normal workflow	1	2	3	4	5	6	7
h. time consuming to report	1	2	3	4	5	6	7

Next, please circle the number that corresponds to your level of intention with the following statements.

3. I intend to report serious ADEs that I will encounter to the FDA.

extremely unlikely	1	2	3	4	5	6	7	extremely likely

4. I will try to report serious ADEs that I will encounter to the FDA.

strongly disagree	1	2	3	4	5	6	7	strongly agree

5. I plan to report serious ADEs that I will encounter to the FDA.

strongly disagree	1	2	3	4	5	6	7	strongly agree

Next, we would like to know how you feel about reporting ADEs. Please complete the following statement based on each of the following adjectives.

6. I feel that reporting serious ADEs to the FDA each time I encounter them is:

Worthless	-3	-2	-1	0	1	2	3	Valuable
Unpleasant	-3	-2	-1	0	1	2	3	Pleasant
Bad	-3	-2	-1	0	1	2	3	Good
Unenjoyable	-3	-2	-1	0	1	2	3	Enjoyable
Harmful	-3	-2	-1	0	1	2	3	Beneficial

Next, we are interested in what groups or individuals would influence your willingness to report serious ADEs to the FDA. Please circle the number that corresponds to your choice using the scales listed below.

7. How likely is it that each of the following groups or individuals would think that you should report serious ADEs to the FDA?	**Very unlikely**			**Neither likely nor unlikely**			**Very likely**
a. Physicians	1	2	3	4	5	6	7
b. Patients	1	2	3	4	5	6	7
c. Drug manufacturers	1	2	3	4	5	6	7
d. Food and Drug Administration	1	2	3	4	5	6	7
e. Pharmacy associations	1	2	3	4	5	6	7
f. Family/spouse/significant others	1	2	3	4	5	6	7
g. Pharmacy managers/bosses	1	2	3	4	5	6	7
h. Hospitals or hospital groups	1	2	3	4	5	6	7
i. Other pharmacists (colleagues/peers)	1	2	3	4	5	6	7

8. Generally speaking, how likely are you to do what the following <u>individuals or groups</u> would want you to do when it comes to ADE reporting?	**Very unlikely**			**Neither likely nor unlikely**			**Very likely**
a. Physicians	1	2	3	4	5	6	7
b. Patients	1	2	3	4	5	6	7
c. Drug manufacturers	1	2	3	4	5	6	7
d. Food and Drug Administration	1	2	3	4	5	6	7
e. Pharmacy associations	1	2	3	4	5	6	7
f. Family/spouse/significant others	1	2	3	4	5	6	7
g. Pharmacy managers/bosses	1	2	3	4	5	6	7
h. Hospitals or hospital groups	1	2	3	4	5	6	7
i. Other pharmacists (colleagues/peers)	1	2	3	4	5	6	7

9. Most people who are important to me think that

I should not	-3	-2	-1	0	1	2	3	I should

report serious ADEs that I encounter to the FDA.

10. The people in my life whose opinions I value would

Disapprove	-3	-2	-1	0	1	2	3	Approve

my reporting of serious ADEs that I encounter to the FDA.

11. The pharmacists whose opinions I value

Do not report	-3	-2	-1	0	1	2	3	Report

serious ADEs to the FDA.

12. I believe I have a moral obligation to report serious ADEs that I will encounter to the FDA.

strongly disagree	1	2	3	4	5	6	7	strongly agree

Next, we are interested in the extent to which the following factors would make it easy or difficult for you to report serious ADEs to the FDA. Please circle the number that corresponds to your choice using the scales below.

13. How easy or difficult will the following factors make it for you to report serious ADEs that you encounter to the FDA?	**Extremely difficult**			**Neither easy nor difficult**			**Extremely easy**
a. a complete patient medical history	1	2	3	4	5	6	7
b. lack of time	1	2	3	4	5	6	7
c. improved awareness of ADE reporting	1	2	3	4	5	6	7
d. a streamlined MedWatch form and reporting process	1	2	3	4	5	6	7
e. employer support of ADE reporting	1	2	3	4	5	6	7
f. some type of reward or compensation	1	2	3	4	5	6	7
g. ADE reporting as a part of the normal workflow	1	2	3	4	5	6	7
h. increased patient counseling (spending more time with patients)	1	2	3	4	5	6	7
i. awareness of drug risks by patients	1	2	3	4	5	6	7
j. being a drug expert	1	2	3	4	5	6	7
k. clear knowledge of what constitutes a reportable ADE (e.g., definition)	1	2	3	4	5	6	7

14. How much control do you feel you have over the following <u>factors</u> when it comes to reporting serious ADEs to the FDA?	**No control**			**Neither complete control nor no control**			**Complete control**
a. a complete patient medical history	1	2	3	4	5	6	7
b. lack of time	1	2	3	4	5	6	7
c. awareness of ADE reporting	1	2	3	4	5	6	7
d. a streamlined MedWatch form and reporting process	1	2	3	4	5	6	7
e. employer support of ADE reporting	1	2	3	4	5	6	7
f. some type of reward or compensation	1	2	3	4	5	6	7
g. ADE reporting as a part of the normal workflow	1	2	3	4	5	6	7
h. increased patient counseling (spending more time with patients)	1	2	3	4	5	6	7
i. awareness of drug risks by patients	1	2	3	4	5	6	7
j. being a drug expert	1	2	3	4	5	6	7
k. clear knowledge of what constitutes a reportable ADE (e.g., definition)	1	2	3	4	5	6	7

Next, we would like you to answer the following two statements in a general sense. Please circle the number that corresponds to your choice using the scales listed below.

15. It is mostly up to me whether or not I report serious ADEs to the FDA.

strongly disagree	-3	-2	-1	0	1	2	3	strongly agree

16. How much control do you believe you have over reporting serious ADEs that you encounter to the FDA?

no control	-3	-2	-1	0	1	2	3	complete control

Next, we would like to know about your <u>past behavior</u> regarding the reporting of ADEs. Please check the appropriate response or circle the number where appropriate.

17. Have you <u>ever</u> reported an ADE to the FDA through MedWatch?

_____(1) Yes
_____(2) No

18. Have you reported any ADEs to the FDA through MedWatch in the <u>previous 12 months</u>?

_____(1) Yes
_____(2) No

19. Have you encountered any reportable ADEs in your practice in the past?
_____(1) Yes
_____(2) No
_____(3) Don't know

Now, we would like to know a little about you and your practice setting so that we can better understand your responses. Please check the appropriate response or write in your responses where appropriate.

20. Which of the following best describes your ethnic/racial background?
_____(1) African American/non-Hispanic black
_____(2) American Indian or Alaska Native
_____(3) Asian American/Pacific Islander
_____(4) Caucasian/non-Hispanic white
_____(5) Mexican American/Hispanic
_____(6) Other (please specify)_____

21. Please indicate your type of practice setting at your primary place of employment.
_____(1) Community-Independent
_____(2) Community-Multiple/Chain (3 or more pharmacies under common ownership)
_____(3) Hospital-Independent
_____(4) Hospital-Multiple/Chain (3 or more pharmacies under common ownership)
_____(5) Other (please specify)_____

22. What is your current job title at your primary place of employment?
_____(1) Pharmacy Owner/Partner
_____(2) Pharmacy Manager/Supervisor
_____(3) Clinical Pharmacist
_____(4) Staff Pharmacist
_____(5) Relief Pharmacist
_____(6) Other (please specify)_____

23. What is your gender?
_____ (1) Male
_____ (2) Female

24. In what year where you born? 19_____

25. Which of the following best describes the area/setting of your primary place of employment?
_____(1) Urban
_____(2) Suburban
_____(3) Rural

26. How many years have you been practicing pharmacy? _____years

27. On average, how many hours per week do you work at your primary place of employment?
_____hours/week

28. On average, how many hours per week do you dispense medication and/or interact with patients at your primary place of employment? _____hours/week

29. On average, how many prescriptions/medication orders do you dispense per day? _____prescriptions/medication orders

30. Based on your knowledge, please circle the number that corresponds with your answer.	**True**	**False**
a. All ADEs, irrespective of severity, should be reported to the FDA.	1	0
b. Pharmacists should report serious ADEs even if they are uncertain that the product caused the event.	1	0
c. Pharmacists should report serious ADEs even if they do not have all the details (e.g., complete patient history and demographic data).	1	0
d. All serious ADEs are known before a drug is marketed.	1	0
e. The FDA does not disclose the ADE reporter's identity in response to a request from the public.	1	0
f. Pharmacists can report ADEs to the FDA anonymously.	1	0
g. Adverse experiences with cosmetics and special nutritional products (e.g., dietary supplements, infant formulas) may be reported to the FDA.	1	0
h. One case reported by a pharmacist does not contribute much to knowledge on drug risks.	1	0
i. I have adequate knowledge on ADE reporting (e.g., what to report and how to report)	1	0

31. Please write in any other comments you have about reporting ADEs to the FDA.

_____
_____
_____
_____

If you would like an aggregate summary of the results, please e-mail Paul Gavaza at pgavaza@mail.utexas.edu.

THANK YOU FOR YOUR PARTICIPATION!

Appendix C: Letter to Focus Group Participants

Focus Group Invite

Dear Pharmacist Colleague,

You have been selected to participate in a focus group conducted as part of research study entitled: A qualitative analysis of the attitudes and beliefs of Texas pharmacists toward reporting serious adverse drug events (ADEs). As you may be aware, the Food and Drug Administration allows you as a pharmacist to report ADEs that you come across through MedWatch. To date, no research has focused on how Texas pharmacists' beliefs and attitudes toward ADE reporting relate to their intent to report ADEs. This focus group is part of a dissertation research project being conducted in the Division of Pharmacy Administration at the University of Texas at Austin. Up to 12 pharmacists will participate in this focus group. This focus group will determine the advantages and disadvantages of reporting ADEs by pharmacists, the factors that would make it easier or difficult for pharmacists to report ADEs as well as the individuals or groups who would approve or would not approve pharmacists reporting ADEs.

Because you are one of a small group of people selected for this study, we hope that you will participate so that our results will be a good representation of Texas pharmacists. Your decision to participate or not will not affect your present or future relationship with the University of Texas at Austin. Your participation in this study is voluntary. The focus group is expected to last approximately 1 – 1 $^{1}/_{2}$ hours. The focus will be conducted at [venue, address] at [time] on the [date]. Risks to participants are considered minimal. Sessions will be audio-taped;

- tapes will be coded so that no personally identifying information is visible on them;
- tapes will be kept in a secure place (e.g., a locked file cabinet in the investigator's office);
- tapes will be heard or viewed only for research purposes by the investigator and his or her associates; and
- tapes will be destroyed after they are transcribed or coded.

If you have any questions, please do not hesitate to contact us by phone at (512) 961-1692 and (512) 471-2374 or e-mail pgavaza@mail.utexas.edu and cmbrown@mail.utexas.edu. If you have questions about your rights as a research participant, complaints, concerns, or questions about the research please contact Jody Jensen, Ph.D., Chair, The University of Texas at Austin Institutional Review Board for the Protection of Human Subjects at (512) 232-2685 or the Office of Research Support at (512) 471-8871 or email: orsc@uts.cc.utexas.edu. Thank you in advance for your time and cooperation in participating in this important study.

If you agree to participate, please let us know via e-mail or phone.

Sincerely,

Paul Gavaza, M.S.
Ph.D. Candidate
Pharmacy Administration Division

Carolyn M. Brown, R.Ph., Ph.D.
Professor and Dissertation Advisor
Pharmacy Administration Division

Appendix D: Focus Group Informed Consent

IRB Approved on: (ORSC Use Only) **Expires on:**

Protocol Title:
A qualitative analysis of the attitudes and beliefs of Texas pharmacists toward reporting serious adverse drug events (ADEs)

Conducted by:
Paul Gavaza, MS., (pgavaza@mail.utexas.edu), The University of Texas at Austin, College of Pharmacy; 512-961-1692 and Carolyn Brown, Ph.D., (cmbrown@mail.utexas.edu), The University of Texas at Austin, College of Pharmacy; 512-471-2374.

You are being asked to participate in a research study. This form provides you with information about the study. The person in charge of this research will also describe this study to you and answer all of your questions. Please read the information below and ask any questions you might have before deciding whether or not to take part. Your participation is entirely voluntary. You can refuse to participate without penalty or loss of benefits to which you are otherwise entitled. You can stop your participation at any time and your refusal will not impact current or future relationships with UT Austin or participating sites. To do so simply tell the researcher you wish to stop participation. The researcher will provide you with a copy of this consent for your records.

Purpose of the research study:
This purpose of the study is to identify the advantages and disadvantages of reporting ADEs by pharmacists as well as the individuals or groups who would approve or would not approve pharmacists reporting ADEs. The study will also discuss the factors that would make it easier or difficult for pharmacists to report ADEs.

What you will be asked to do in the study:
This meeting could have up to 11 other pharmacists. If you agree to participate in this study, we will ask you to do the following things:

- Participate in a focus group discussion; and
- Respect and protect the confidentiality of the other participants in this focus group.

Time required:
1 - $1^{1}/_{2}$ hours

Risks:
Loss of confidentiality

- The researchers will protect the confidentiality of all participants in this focus group by using pseudonyms when transcribing. The tapes will be kept locked in the principal investigator's office. After they have been transcribed, the tapes will be destroyed.
- This study may involve risks that are currently unforeseeable. If you wish to discuss the information above or any other risks you may experience, you may ask questions now or call the Principal Investigator listed on the front page of this form.

Benefits of being in the study are to identify advantages, disadvantages, factors that would make it easier or difficult to report ADEs and the individuals and groups who would approve of pharmacists reporting ADEs.

Compensation:

- There is $25.00 compensation for participation.

Confidentiality and Privacy Protections:

- Sessions will be audio-taped;
  - tapes will be coded so that no personally identifying information is visible on them;
  - tapes will be kept in a secure place (e.g., a locked file cabinet in the investigator's office);
  - tapes will be heard or viewed only for research purposes by the investigator and his or her associates; and
  - tapes will be destroyed after they are transcribed or coded.

The records of this study will be stored securely and kept confidential. Authorized persons from The University of Texas at Austin, members of the Institutional Review Board, and (study sponsors, if any) have the legal right to review your research records and will protect the confidentiality of those records to the extent permitted by law. All publications will exclude any information that will make it possible to identify you as a subject. Throughout the study, the researchers will notify you of new information that may become available and that might affect your decision to remain in the study.

Contact and questions:

If you have any questions about the study please ask now. If you have questions later, want additional information, or wish to withdraw your participation call the researchers conducting the study. Their names, phone numbers, and e-mail addresses are at the top of this page. If you have questions about your rights as a research participant, complaints, concerns, or questions about the research please contact Jody Jensen, Ph.D., Chair, The University of Texas at Austin Institutional Review Board for the Protection of Human Subjects at (512) 232-2685 or the Office of Research Support and Compliance at (512) 471-8871 or email: orsc@uts.cc.utexas.edu.

You will be given a copy of this information to keep for your records.

Agreement:

I have read the above information and have sufficient information to make a decision about participating in this study. I consent to participate in the study.

Signature:_____ Date: _____

_____ Date: _____
Signature of Person Obtaining Consent

Signature of Investigator:_____ Date: _____

Appendix E: Focus Group Guide

Introduction

My name is Paul Gavaza and I will be the moderator for this focus group session. The purpose of this focus group session is to identify the advantages, disadvantages of reporting ADEs, the factors that make it easier or difficult to report ADEs and the individuals or groups who would or would not approve pharmacists reporting ADEs. The information obtained from this focus group session will be used to develop a survey instrument that will be administered to a larger group of Texas pharmacists.

This session will be audio (tape) recorded. However, no names will be used for any portion of the larger study. Information obtained from this focus session will not be associated with any specific focus group participant. The audio recording of the focus group session ensures that all the important information is captured and available for inclusion in the survey instrument. The audio tapes will be stored in a locked file cabinet and will be used only by research personnel. This session is expected to last one to one and a half hours and you have the right to stop participating at any time.

Group Rules

As the moderator, I will ask the questions and keep everyone on track. I will keep track of time, and therefore, I may need to interrupt the discussion and move forward if I see we are getting short on time. It is important that everyone feels comfortable and easy going during the discussion. There are no right and wrong answers. Everyone's input is vital. I encourage you to speak openly about the issues discussed in this session.

General Question

1. Briefly tell me what you think about when you think of the reporting of ADEs to the FDA (through the MedWatch program).

Key Questions

1. What do you think are some of the advantages associated with pharmacists reporting ADEs to the FDA?

2. What do you think are some of the disadvantages associated with pharmacists reporting ADEs to the FDA?

3. Are there any other advantages and disadvantages associated with pharmacists reporting ADEs to the FDA?

4. Are there any individuals or groups who would approve pharmacists reporting ADEs to the FDA?

5. Are there any individuals or groups who would not approve pharmacists reporting ADEs to the FDA?

6. Are there any other individuals or groups who would or would not approve pharmacists reporting ADEs to the FDA?

7. What do you think would make it easier to report ADEs to the FDA?

8. What do you think would make it difficult to report ADEs to the FDA?

9. Is there anything else we should have discussed that we did not discuss?

Appendix F: Mail Survey Cover Letters

Survey Cover Letter

Dear Pharmacist Colleague,

You have been selected to participate in a state-wide research study entitled: Using the theory of planned behavior to predict Texas pharmacists' intention to report adverse drug events (ADEs). As you may be aware, the Food and Drug Administration allows you as a pharmacist to report ADEs that you come across through MedWatch. To date, no research has focused on how Texas pharmacists' beliefs and attitudes toward ADE reporting relate to their intent to report ADEs. This questionnaire is part of a dissertation research project being conducted in the Division of Pharmacy Administration at The University of Texas at Austin. This study questionnaire measures your attitudes and beliefs about ADE reporting. Your responses to the study questionnaire will be a great help to us in improving our understanding of what factors help explain ADE reporting.

Because you are one of a small group of people randomly selected for this study, we hope that you will participate so that our results will be a good representation of the entire population of Texas pharmacists. Your decision to participate or not will not affect your present or future relationship with The University of Texas at Austin. Although participation is voluntary, we feel that it is important that you make yourself heard on an issue that may affect your practice.

The survey takes approximately 10 minutes to complete. All your responses will be kept confidential and the records of this study will be stored securely. Reponses will only be reported in aggregated form and results can in no way be linked to you. Completing the mail survey will serve as your consent to participate in the study. After completing the survey, please fold it with the business reply on the outside, secure it with tape, and mail it back to us by May 28, 2009. No postage is necessary.

If you have any questions, please do not hesitate to contact us by phone at (512) 961-1692 and (512) 471-2374 or e-mail pgavaza@mail.utexas.edu and cmbrown@mail.utexas.edu. If you have questions about your rights as a research participant, complaints, concerns, or questions about the research please contact Jody Jensen, Ph.D., Chair, The University of Texas at Austin Institutional Review Board for the Protection of Human Subjects at (512) 232-2685 or the Office of Research Support at (512) 471-8871 or email: orsc@uts.cc.utexas.edu. Thank you in advance for your time and cooperation in participating in this important study.

Sincerely,

Paul Gavaza, M.S.
Ph.D. Candidate
Pharmacy Administration Division

Carolyn M. Brown, R.Ph., Ph.D.
Professor and Dissertation Advisor
Pharmacy Administration Division

Follow up Cover Letter

Dear Pharmacist Colleague,

About three weeks ago, you were contacted regarding a questionnaire asking about your perceptions and attitudes toward ADE reporting. If you have already completed the questionnaire, please accept our sincere thanks. If you have not yet completed the questionnaire, we kindly ask for your assistance by completing it as soon as possible.

Again, this questionnaire is part of a dissertation research project being conducted in the Division of Pharmacy Administration at The University of Texas at Austin. This study questionnaire measures your attitudes and beliefs about ADE reporting. Your responses to the study questionnaire will be a great help to us in improving our understanding of what factors help explain ADE reporting. Because you are one of a small group of people randomly selected for this study, we hope that you will participate so that our results will be a good representation of the entire population of Texas pharmacists. Your decision to participate or not will not affect your present or future relationship with The University of Texas at Austin. Although participation is voluntary, we feel that it is important that you make yourself heard on an issue that may affect your practice.

The survey takes approximately 10 minutes to complete. All your responses will be kept confidential and the records of this study will be stored securely. Reponses will only be reported in aggregated form and results can in no way be linked to you. Completing the mail survey will serve as your consent to participate in the study. After completing the survey, please fold it with the business reply on the outside, secure it with tape, and mail it back to us by July 6, 2009. No postage is necessary.

If you have any questions, please do not hesitate to contact us by phone at (512) 758-1845 and (512) 471-2374 or e-mail pgavaza@mail.utexas.edu and cmbrown@mail.utexas.edu. If you have questions about your rights as a research participant, complaints, concerns, or questions about the research please contact Jody Jensen, Ph.D., Chair, The University of Texas at Austin Institutional Review Board for the Protection of Human Subjects at (512) 232-2685 or the Office of Research Support at (512) 471-8871 or email: orsc@uts.cc.utexas.edu. Thank you in advance for your time and cooperation in participating in this important study.

Sincerely

Paul Gavaza, M.S.
Ph.D. Candidate
Pharmacy Administration Division

Carolyn M. Brown, R.Ph., Ph.D.
Professor and Dissertation Advisor
Pharmacy Administration Division

Appendix G: Histograms of Residuals From Regression Analysis

Figure G.1: Histogram of Standardized Residual from Regression of TPB Direct Measures Constructs

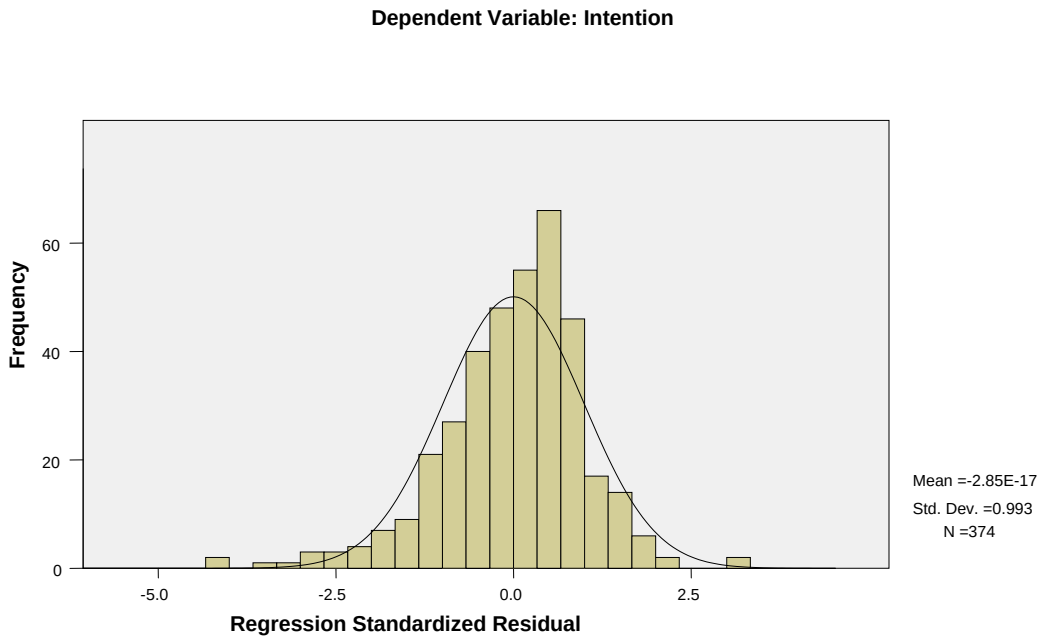
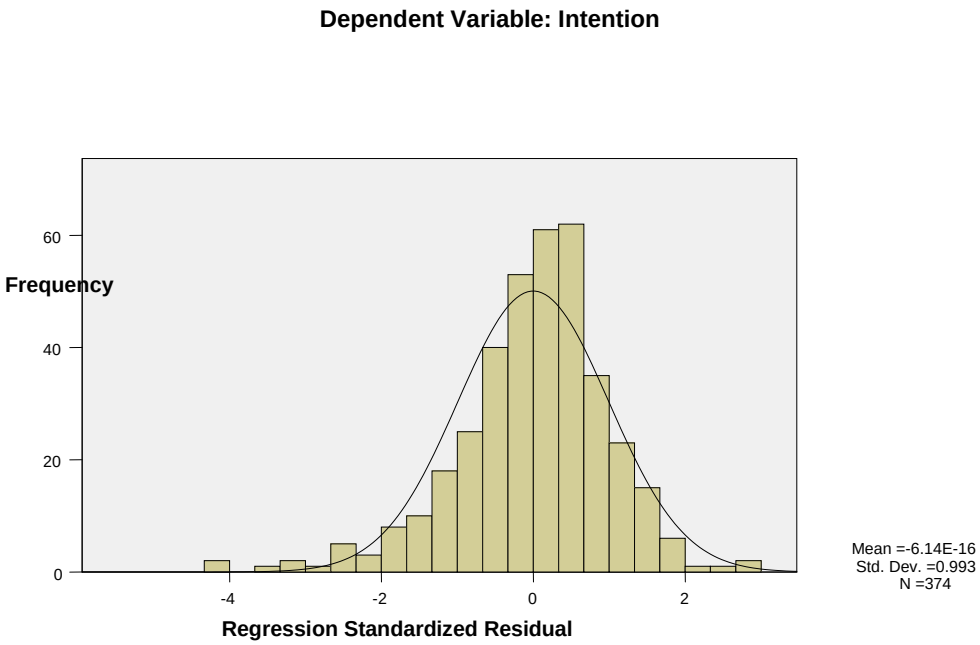


Figure G.2: Histogram of Standardized Residual from Regression of TPB Indirect Measures Constructs



Appendix H: Normal Probability Plots

Figure H.1: Normal P-P Plot of Regression Standardized Residuals—Direct Measures

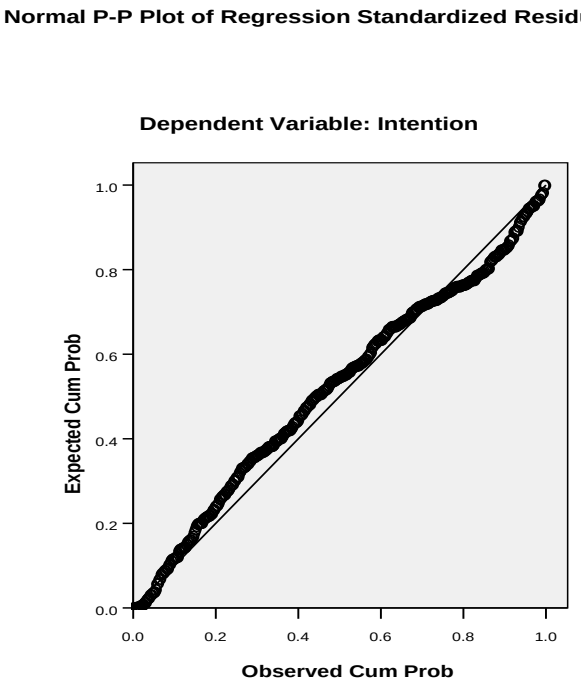
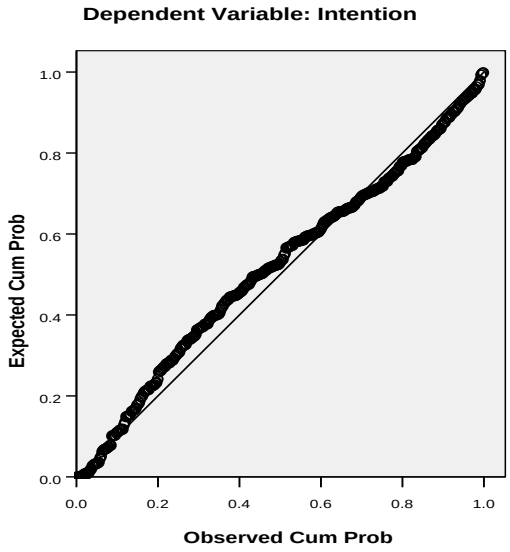


Figure H.2: Normal P-P Plot of Regression Standardized Residuals—Indirect Measures



Appendix I: Scatter Plots of Residuals

Figure I.1: Scatter Plots of Residuals for the TPB Direct Measures

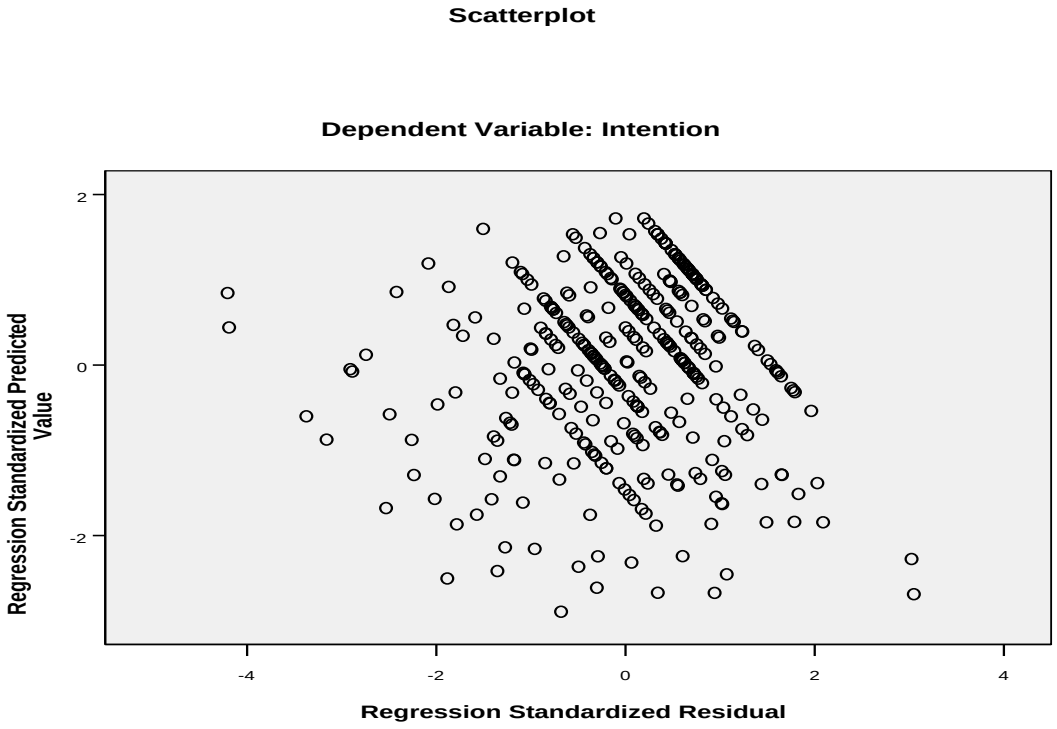
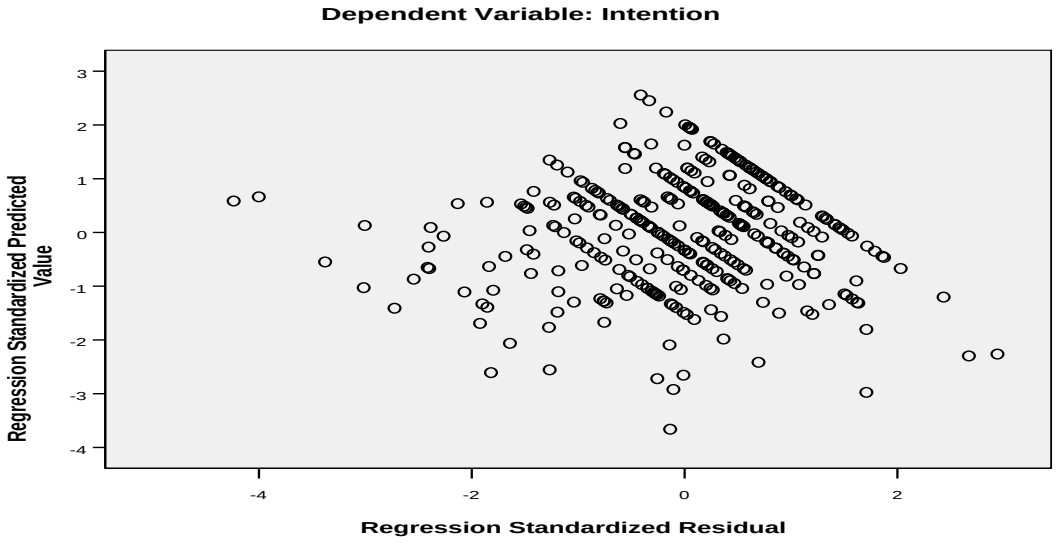


Figure I.2: Scatter Plots of Residuals for the TPB Indirect Measures



Appendix J: Partial Regression Plots

PARTIAL REGRESSION PLOTS FOR DIRECT TPB MEASURES

Figure J.1: Partial Regression Plot for Intention and Direct Measure Attitude

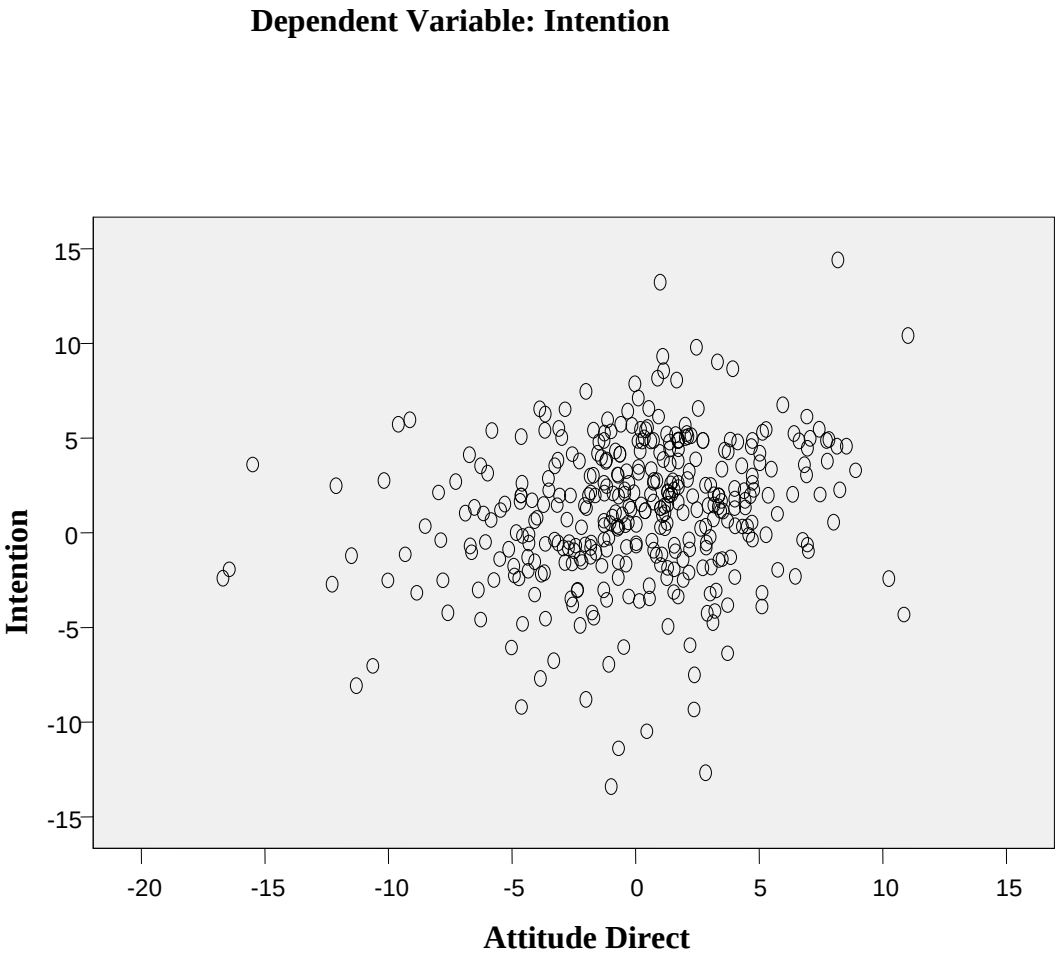


Figure J.2: Partial Regression Plot for Intention and Direct Measure Subjective Norm

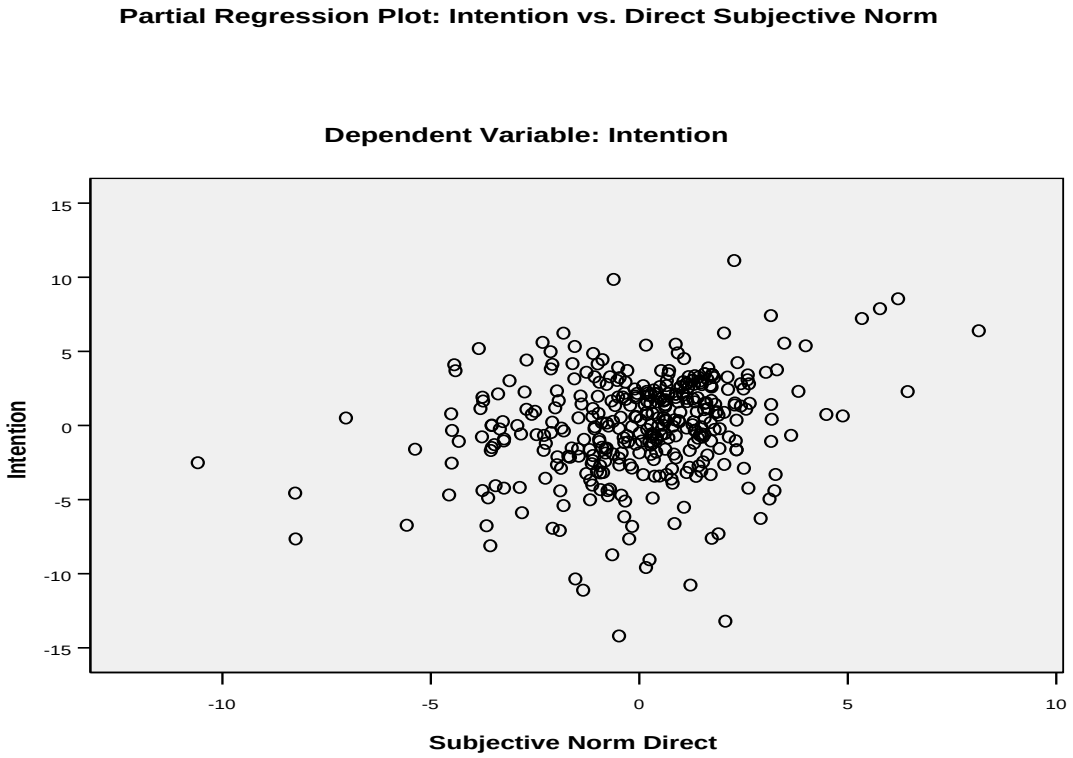


Figure J.3: Partial Regression Plot for Intention and Direct Measure PBC

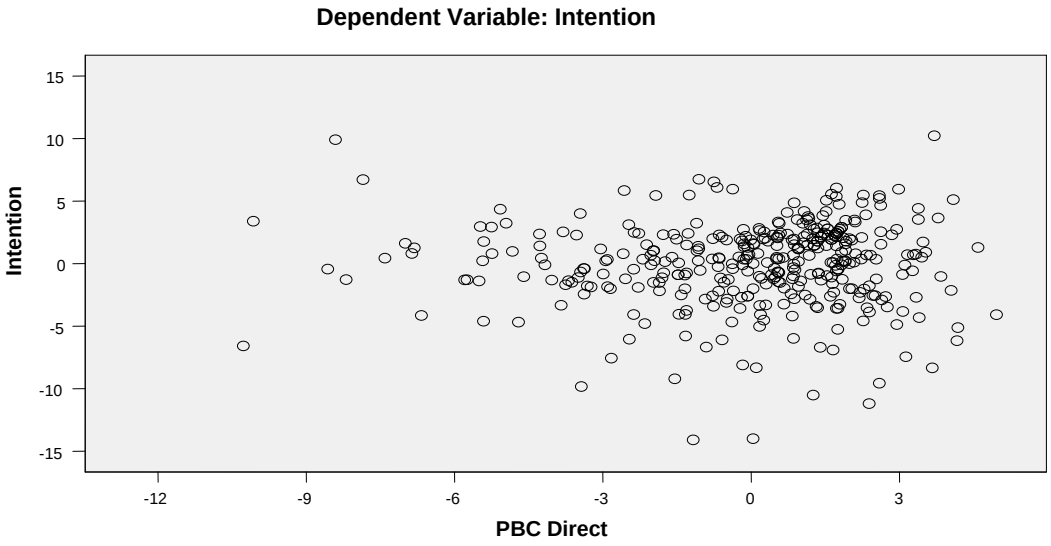
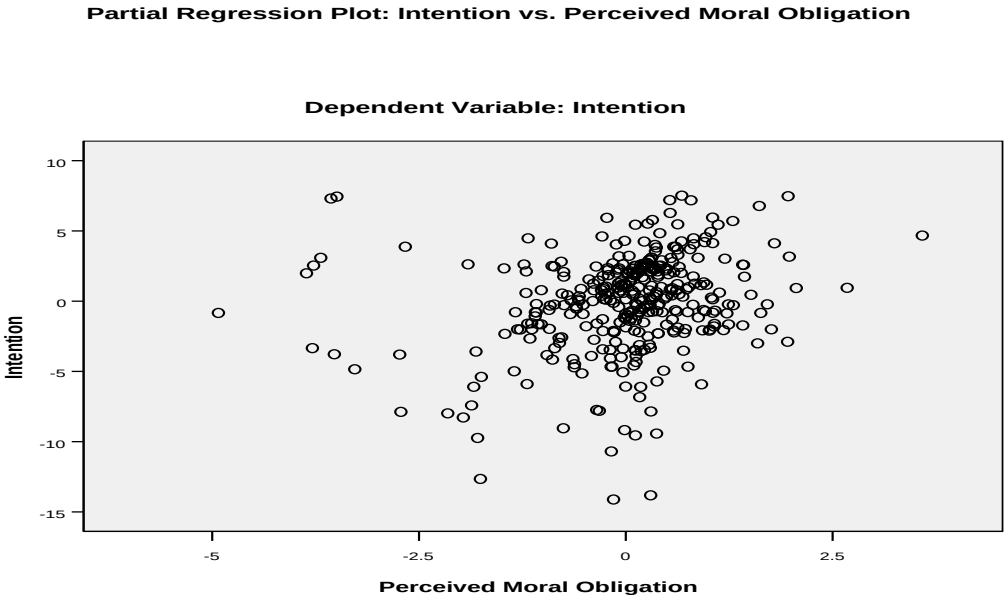


Figure J.4: Partial Regression Plot for Intention and PMO



PARTIAL REGRESSION PLOTS FOR INDIRECT TPB MEASURES

Figure J.5: Partial Regression Plot for Intention and Indirect Measure Attitude

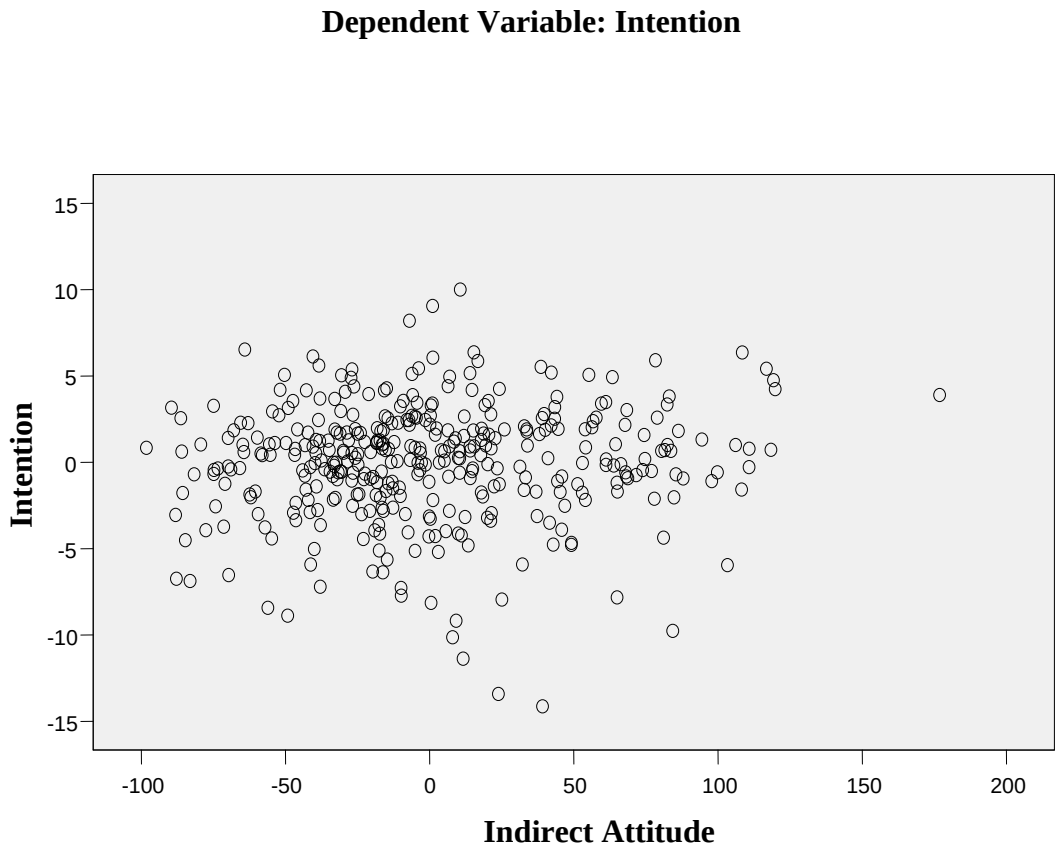


Figure J.6: Partial Regression Plot for Intention and Indirect Measure Subjective Norm

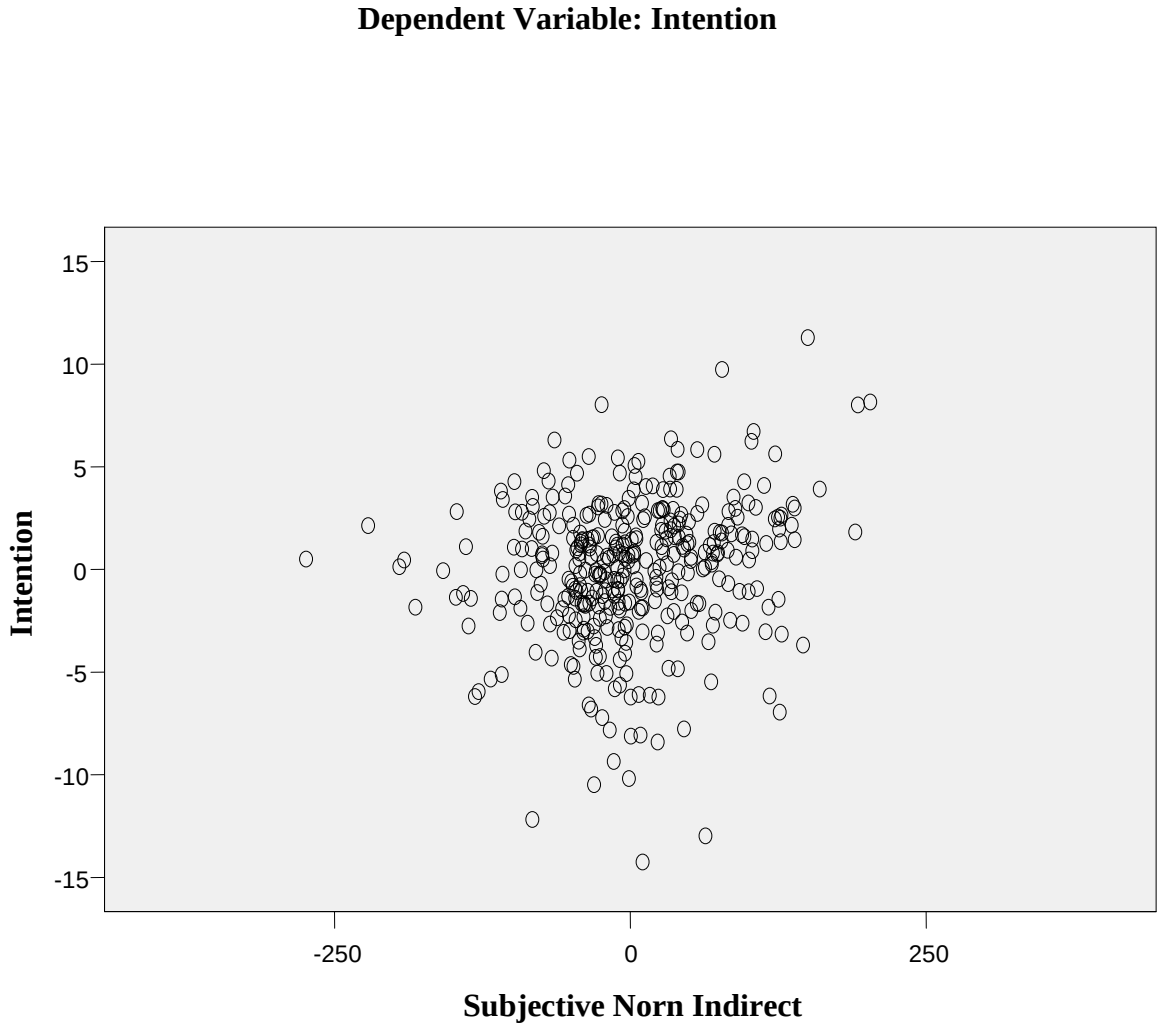


Figure J.7: Partial Regression Plot for Intention and Indirect Measure PBC

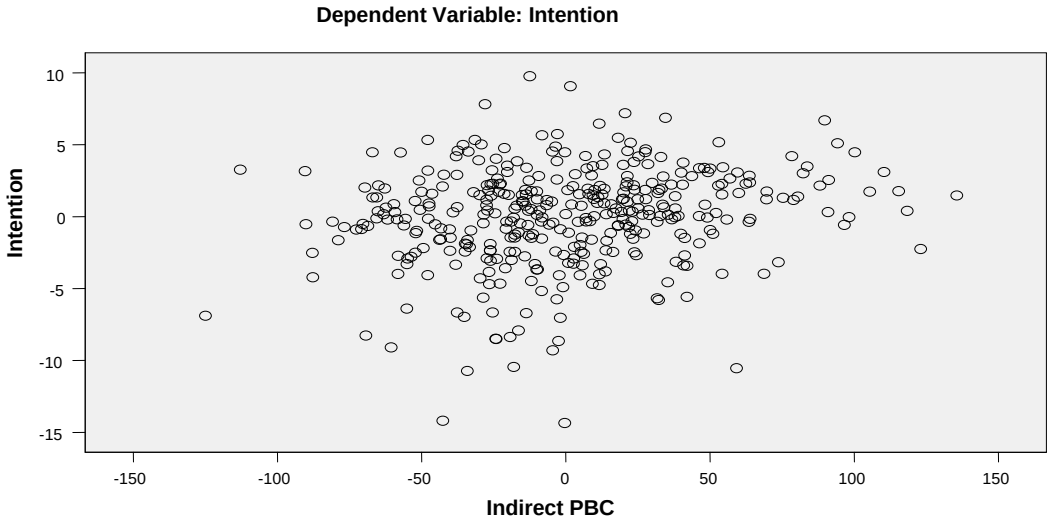
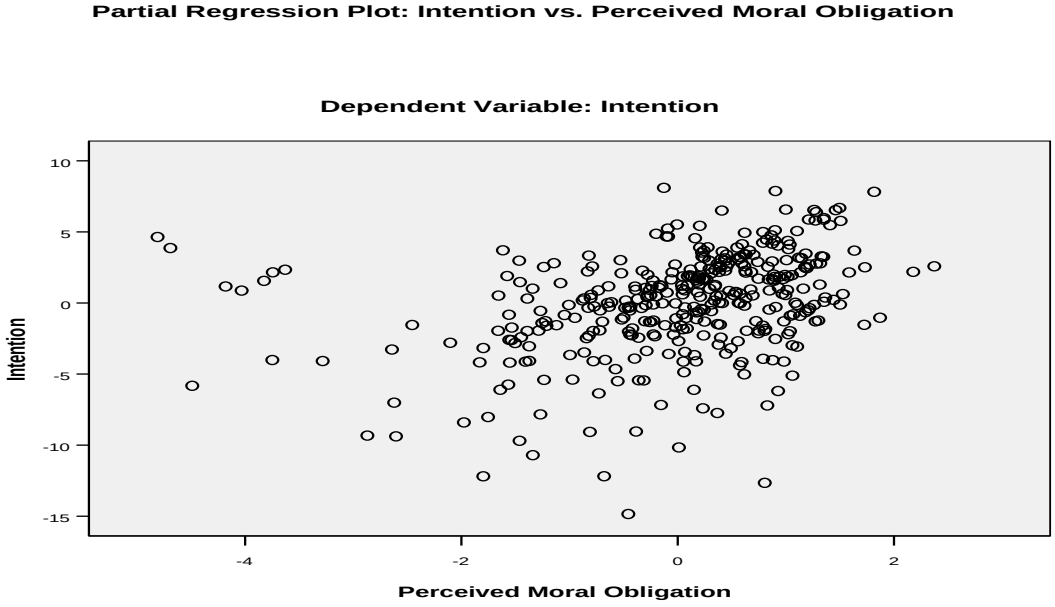


Figure J.8: Partial Regression Plot for Intention and Indirect Measure PMO



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Vita

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