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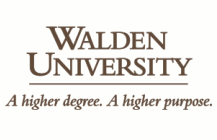

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Under-reporting of Adverse Drug Reactions to the Food & Drug Administration

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Walden University

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Walden University

College of Health Sciences

This is to certify that the doctoral dissertation by

James A. Lamb

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Walden University
2018

Abstract

Under-reporting of Adverse Drug Reactions to the Food & Drug Administration

by

James A. Lamb

MPH, West Chester University of Pennsylvania, 2009

BS, West Chester University of Pennsylvania, 2006

Dissertation Submitted in Partial Fulfillment

of the Requirements for the Degree of

Doctor of Philosophy

Public Health Epidemiology

Walden University

November 2018

Abstract

This study examined the potential significant differences in the distribution of adverse drug reactions (ADRs) by reporter (consumer versus physician) and patient outcome at case and event level. This study also contains exploratory questions to evaluate reporting of ADRs by consumers versus physician by system organ class (SOC) and reporter demographics within the United States Food & Drug Administration Adverse Event Reporting System (FAERS). The theoretical foundation applied in this quantitative study was the social amplification of risk framework. Data from the second quarter of 2016 were obtained from FAERS, and a total of 87,807 ADR reports corresponding to 143,399 ADRs were analyzed by utilizing the chi-square test, the odds ratio, and logistic regression. Cross-sectional design was employed to compare reporting of ADRs at the case and event level (case-based and event-based analyses, respectively) between reporters (consumer versus physician), specifically, for patient outcome, as well as SOC and reporter demographics. For both the case-based and event-based analyses, findings revealed that consumers reported more serious ADRs in comparison to physicians. Furthermore, findings confirmed a difference in ADR reporting between consumers and physicians depending on SOC groups. Additionally, consumers reported more nonserious ADRs in comparison to physicians. The results from this study may have implications for positive social change by augmenting pharmacovigilance systems at a national and international level to identify risks and risk factors spontaneously reported after drugs have been on the market.

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Dedication

I would like to dedicate this dissertation to the love of my life, Oksana. I could not have done this without you being so supportive. As my wife and my rock, I want you to know that this PhD is for us and our future together. Thank you for everything. I love you with all my heart and soul!

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Chapter 1: Introduction to the Study

Introduction

In this study, I examined the differences in reporting adverse drug reactions (ADRs) to the Food & Drug Administration (FDA) between consumers and physicians in the United States (US) at case and event level. ADRs are considered harmful effects arising from the use of medications (Abraham, & Ballinger, 2012). However, reporting differences may exist between consumers and physicians for different reporting categories resulting in a potential public health issue (Alatawi & Hansen, 2017). I addressed, in this study, those reporting differences between reporters (specifically, physicians and consumers) and the severity of ADRs based on patient outcome. Additionally, I evaluated the reporting of ADRs within different system organ classes (SOCs) and demographics.

The under-reporting of ADRs is a limitation of current Pharmacovigilance (PV) systems within the US, thereby leading to the inability of regulators to estimate total safety risk (Alatawi & Hansen, 2017). The findings from this study determined whether consumer reporting was an important factor in ADR reporting, and if these reports (also used interchangeably referred to as "cases") added value to the safety profile of a product. In addition, the results from this study have implications for positive social change in that may potentially be able to augment PV systems at a national and international level to identify risks and risk factors spontaneously reported after such drugs have been on the market (Pal, Duncombe, Falzon, & Olsson, 2013).

In this chapter, I first provide a background and the purpose of the study. Then, I identify the problem examined in the study, provide the theoretical framework of the study, describe the nature of the study and state the research questions and hypotheses. Last, I list the key definitions of terms used in the study, discuss the study assumptions, scope, delimitations, and limitations, and describe the significance of the study.

Background

PV is the science that serves as a crucial component in detecting, evaluating, and inhibiting ADRs or any other drug-related issues and/or effects (World Health Organization [WHO], 2017). The objective of PV is to facilitate the intake of medicines in a safe manner, evaluate and convey the risks and benefits of medicines on the market, and to disseminate information and educate consumers about drugs and other medicines (WHO, 2012). ADRs, which can be defined as harmful and involuntary responses resulting from doses used in humans, are deemed a limiting factor that arises from issues with patient compliance and medication adherence (Tadesse, Mekonnen, Tesfaye, & Tadesse, 2014). Researchers have discovered that nonadherence to medication stems from the following: patients (i.e., failure to comprehend essential health information regarding their own health); physicians (i.e., lack of communication with patients with regards to prescription of complex drug regimens); and, healthcare systems (i.e., office visit time limitations, limited access to care, and shortage of health information technology) (Brown & Bussell, 2011).

Additionally, ADRs have continued to persist as a concern and public health issue, especially within underdeveloped countries in which sufficient drug toxicity

monitoring and reporting systems are virtually nonexistent (Sen, 2016). Researchers have revealed findings suggesting that, on national and international scales, more than 5% of hospital admissions were related to ADRs (Sultana, Cutroneo, & Trifirò, 2013), thereby responsible for nearly 20% of deaths annually among hospitalized patients (FDA, 2016a). Due to the nature of ADRs, public health agencies are faced with substantial economic consequences namely, on average, the medical expenditures of a hospital admission associated with an ADR ranges from circa $10,000 to $13,000 per person (Pillans, 2008). The US spends more than 30 billion dollars per year in managing ADRs, and these expenditures may be further magnified as a result of increased hospitalization, prolongation of hospital stay, and further clinical investigations in more serious cases (Sultana et al. 2013). Hence, ADRs have deleterious effects on the clinical, social, and economic aspects of society (Inácio, Cavaco, & Airaksinen, 2016). Therefore, to counteract the negative impact of ADRs, it is of paramount importance for regulatory agencies, such as the US FDA, to work in tandem with healthcare systems and pharmaceutical industries to constantly detect any drug safety issues and ensure a product's label is current (Leroy, Dauxois, Théophile Haramburu, Tubert-Bitter, 2014).

To scrutinize and effectively manage the risks and adverse reactions related to drugs to which the public has access, regulatory agencies should enhance their postmarketing surveillance of drugs by implementing an efficient spontaneous reporting system (SRS) (Inácio et al., 2016). The objective of SRS during the postmarketing phase is the identification of new ADRs that may have otherwise gone undetected during clinical trials Phases I-III (WHO, 2012). The US FDA Adverse Event (AE) Reporting

System (FAERS), as a type of SRS, is a national postmarketing surveillance database that gathers data on ADRs, medication error reports, and product quality complaints leading to AEs submitted to the FDA by reporters, including consumers and physicians (FDA, 2017). The FDA employs the FAERS database (the major postmarketing surveillance database used by the FDA for collecting ADRs reported by reporters) to detect safety signals (a new, potential causal association or a new aspect of a previously known relationship between an ADR and a drug or intervention) relating to ADRs and further assess additional potential safety concerns once they are discovered (Hauben & Aronson, 2009). Hence, upon scrutinizing potential safety concerns from the FAERS system, the FDA can subsequently make informed regulatory decisions in an effort to ameliorate product safety and safeguard the health and well-being of the public, including, but not limited to, the following: updating the labeling information of a drug or product; limiting drug consumption or product usage; disseminating new safety information to the public; or, removing a product from the market (also known as product recall) (FDA, 2017).

Healthcare systems need a system of spontaneous reporting of ADRs by consumers and physicians (and other healthcare professionals) to determine new reactions, record the rate of ADR occurrence, and present this information to prescribers to inhibit subsequent ADRs (Alatawi & Hansen, 2017; Pillans, 2008). Spontaneous reporting of ADRs during postmarketing (Phase IV) and approval by the FDA is a crucial strategy of ADR detection, thereby allowing the identification of serious, unpredicted, and uncommon ADRs that may not have been observed during clinical trials Phases I-III (Alatawi & Hansen, 2017; Pillans, 2008). Although one of the advantages of SRS, such

as FAERS, is its ability to detect ADRs in an economic manner, the major disadvantage of SRS is under-reporting of ADRs, which impedes the successful detection of signals and proper identification of safety issues and concerns (Sakaeda, Tamon, Kadoyama, & Okuno, 2013). Hence, given the significance of the reporting of ADRs, the under-reporting of ADRs to the FDA by consumers and physicians is an impediment to ensuring the completeness of the safety profile of product.

Researchers have estimated that more than 1 million serious ADRs are reported in the US on an annual basis (Maciejewski et al, 2017). Of these, 5 to 10% are fatal, while others lead to patient suffering, hospitalization, and increased health system burden (Lazarou, Pomeranz, & Corey, 1998). Furthermore, ADRs are one of the leading causes of mortality within the US, thereby comprising more than 40,000 deaths on an annual basis (Hoyert & Xu, 2012). Researchers have also estimated that only 6% of all ADRs are reported in the US (Alatawi & Hansen, 2017). This rather high rate of under-reporting hinders signal detection, which can be defined as the process of identifying a new, potential causal association (or a new aspect of a previously known relationship) between an ADR and a drug or intervention (Hauben & Aronson, 2009). Consequently, the failure to establish an association between an ADR and a drug can lead to more individuals at risk of developing an AE that results in potential patient outcomes like (a) death, (b) life-threatening (LT) situations, (c) initial or prolonged existing inpatient hospitalization, (d) persistent or significant disability or incapacity, (e) a congenital anomaly or birth defect, (f) necessary intervention to inhibit permanent damage, or (g) other (important) medical outcome, event, or reaction (FDA, 2016b). Hence, the under-reporting of ADRs has a

negative effect on public health due to the inability for healthcare professionals (HCPs) (particularly physicians) to detect and approximate the magnitude of drug risks, verify actionable issues, and ascertain potential action from regulatory agencies (Sen, 2016; Inácio et al., 2016).

Typically, physicians have been almost entirely responsible for spontaneous reports of ADRs (WHO, 2012). However, the rather high rate of under-reporting has made it challenging for health authorities to protect the health and well-being of the public (Inácio et al., 2016). Researchers have discovered that insufficient knowledge about PV and ADR reporting, as well as apathetic attitudes on the part of HCPs are among the factors associated with under-reporting (Sen, 2016; Pillans, 2008). Furthermore, published findings suggest that the following factors may contribute to under-reporting by HCPs: reactions after drug consumption that are either unknown or well-known; an uncertainty regarding a causal association; lack of awareness of reporting requirements; lack of comprehension of the objective of spontaneous reporting schemes and the aim of SRSs; challenges in accessing report forms; and, an inadequate amount of reporting time (Biagi et al., 2013; Pillans, 2008). Moreover, results from qualitative research studies have suggested that the knowledge and attitudes of HCPs with regards to ADR reporting may be impacting under-reporting based on the survey responses of HCPs, who rationalized their lack of reporting ADRs via the following beliefs: serious adverse reactions will be extensively recorded when the medicine or product reaches the market; only safe medications or products may be related to ADR reporting; or, one case reported by a single physician will not contribute to medical knowledge (Herdeiro,

Figueiras, Polónia, & Gestal-Otero, 2005). Hence, researchers have concluded that it is essential to improve these factors to positively influence the quality and quantity of postmarketing surveillance data (Inácio et al., 2016; Sen, 2016; Biagi et al., 2013; Pillans, 2008).

In an effort to ameliorate the rate of under-reporting, public health authorities and PV centers require complete, accurate, and quality spontaneous reports. However, given the challenge of under-reporting of ADRs by physicians, public health authorities and PV centers have been recently relying upon consumer reporting, which is the reporting of suspected side effects of a drug by a consumer and not the HCP (WHO, 2012).

Consumer reporting is a wider term that encompasses not only patients, but consumers as well (WHO, 2012). A patient may be defined as an individual who is receiving or is registered to receive medical treatment from physicians or other HCPs. The patient who was prescribed an analgesic from his/her physician, and the individual who purchases over-the-counter drugs at the pharmacy without a prescription are both consumers of a medicinal product (WHO, 2012). Hence, not all individuals who consume medicines are patients, but all patients are consumers.

Although ADR reporting to national databases has typically been performed by HCPs, researchers have resorted to direct consumer reporting of ADRs to combat the persistent and negative consequences of ADRs, as well as to bolster the SRS (Aagaard & Hansen, 2013). Furthermore, although consumer reporting is not universally recognized in PV, it has been integrated within the PV systems in a select few countries, such as the US, Canada, the United Kingdom (UK), Australia, New Zealand, Sweden, Denmark, and

the Netherlands, which accept this form of reporting (Pillans, 2008). Moreover, there is scant evidence of the significance of spontaneous reporting by consumers. Consumers are being motivated to report ADRs to a SRS, and such organizations as the FDA, the WHO, and the European Commission, recognize the significance of the consumer in spontaneous reporting (European Medicines Agency, 2010). Hence, consumer reporting is gradually becoming more of a part of the PV process, especially concerning the relay of risk information (Sen, 2016; Van Grootheest, & de Graaf, 2003).

Researchers have discovered that consumer reports are more comprehensive and specific than physicians' reports, thereby detailing certain symptoms in a lucid manner (Sen, 2016). Consumer reports typically contain a detailed, direct, and personal account of the effects of ADRs from drug consumption in comparison to reports from physicians. Furthermore, consumer reporting possesses several advantages, including, but not limited to, the following: an increase in ADRs reported, especially new and previously unreported ADRs; early signal detection of ADRs; and, a potential strategy to prevent medication errors (Sen, 2016). Consumer reports describe the prevention of medication errors by identifying and describing new reactions to medications, as well as detailing patients' reporting of their symptoms to their HCPs or to regulatory agencies (Britten, 2009). According to Robertson and Newby (2003), direct and spontaneous consumer reporting provides greater insight for PV by facilitating the comprehension of ADRs, thereby potentially serving as a missing link for the issue of under-reporting of ADRs by physicians. Hence, researchers have determined the significance of the role of the consumer in spontaneous ADRs.

In this study, I evaluated the FAERS database in an effort to compare the differences between consumers and physicians in reporting ADRs to the FDA in the US at case and event level. Based on the research and analyses that was conducted, it was determined whether consumer reporting needed to be bolstered within PV in the US. A SRS that includes both consumer and HCP reporters has an increased chance of identifying ADRs at an early stage (Health Action International, 2015; Mitchell, Henry, Hennrikus, & O'Connell, 1994). Positive social change in overall patient safety was a major outcome of this study. For example, the combination of consumer reports with reports from HCPs yielded an increase in signal detection, which stimulated a more successful way to detect ADRs. Furthermore, it was determined that an increase in physician reporting, in combination with consumer reporting, reduced the rate of under-reporting and this serves as a crucial factor in overall PV and drug safety (Health Action International, 2015). Hence, it was also determined that the combination of reports from both HCPs and consumers fostered the growth and progression of PV systems within the US and other countries as well.

Problem Statement

The problem I addressed in this study is the lack of reporting from different categories of reporters (consumer versus physician). The lack of reporting is a limitation of current PV systems within the US, thereby hindering regulators' ability to quantify risk of under-reporting of ADRs (Alatawi & Hansen, 2017). In this study, I addressed the aforementioned problem by examining the potential significant difference in the distribution of ADRs by reporter (consumer versus physician) and patient outcome at

case and event level. I also evaluated the reporting of ADRs by consumers versus physician by SOC and demographics.

Purpose of the Study

In this quantitative study, I examined the statistical significance in the distribution of ADRs within the FAERS database by reporter (consumer versus physician) and patient outcome, and I also evaluated reporter differences in SOC and demographics. The factors explored and compared included the differences in under-reporting of consumer versus physician, thereby elucidating whether consumer reporting plays a pivotal role in AE reporting. It was anticipated that the outcome would have some bearing on the frequency of physician and consumer reporting and on differences in reporting rates between them. The reporter (consumer versus physician) was the independent variable, thereby consisting of two levels: consumer and physician. Patient outcome, SOC, and reporter demographics were the dependent variables. The unit of analysis was the total number of ADR cases and reported ADRs. In the severity of patient outcome analysis, I grouped patient outcomes into a dichotomous variable by severity and tested this first. Since the results turned out to be significant, I then went on to test specific dyads (e.g. fatal vs non-fatal, LT vs non-LT, etc.) to further characterize the relationship. Within the exploratory research questions, I also evaluated the total number of ADR cases and reported ADRs of reporters (consumer and physician; independent variable) versus patient outcome (dependent variable) and SOC (dependent variable), and I also evaluated the total number of cases and reported ADRs of reporters (consumer and physician) versus reporter demographics.

Research Questions and Hypothesis

Primary Research Questions

Research Question 1A: Is there a statistically significant difference in the distribution of ADRs by reporter (consumer versus physician) and patient outcome?

$H_0$1A: There is no statistically significant difference in the distribution of ADRs by reporter (consumer versus physician) and patient outcome.

H_a1A: There is a statistically significant difference in the distribution of ADRs by reporter (consumer versus physician) and patient outcome.

Research Question 1B: Is there a statistically significant difference in the distribution of ADRs by reporter when comparing by severity of outcome?

$H_0$1B: There is no statistically significant difference in the distribution of ADRs by reporter when comparing by severity of outcome.

H_a1B: There is a statistically significant difference in the distribution of ADRs by reporter when comparing by severity of outcome.

Exploratory Research Questions

Research Question 2: Is there a statistically significant difference in the distribution of ADRs by reporter (consumer versus physician) and SOC?

$H_0$2: There is no statistically significant difference in the distribution of ADRs by reporter (consumer versus physician) and SOC.

H_a2: There is a statistically significant difference in the distribution of ADRs by reporter (consumer versus physician) and SOC.

Research Question 3: Is there a statistically significant difference in the distribution of ADRs by reporter (consumer and physician) and demographics?

$H_0$3: There is no statistically significant difference in the distribution of ADRs by reporter (consumer versus physician) and demographics.

H_a3: There is a statistically significant difference in the distribution of ADRs by reporter (consumer versus physician) and demographics.

Theoretical Foundation

The theoretical foundation most applicable to this study is known as social amplification of risk framework (SARF), which stems from the perception of risk framework. Risk comprises the likelihood and repercussions of the occurrence of an event (Adams, 1995). The theory holds that risk interrelates with the psychological, social, institutional, and cultural perceptions of individuals in a manner that may magnify or diminish individuals' responses to the risk or risk event (Kasperson & Ratick, 1988). These changes in the perception of risk elicit behavioral responses from individuals that alter the social and economic aspects of society, thereby increasing or decreasing the actual physical risk (Kasperson & Ratick, 1988). The perception of risk as it applies to the present issue involves the premise that different groups (HCPs and non-HCPs, researchers and the public, or HCPs and consumers) hold different views on the possible risks associated with ADR reporting as described earlier. The results from Bongard et al. (2002), which will be given in greater detail in Chapter 2, bolstered the claim that risk perception of ADRs varies between consumers and healthcare professionals, which was crucial for this study and addressed the issue of under-reporting of ADRs by consumers

versus HCPS. Therefore, with respect to ADR reporting, consumers frequently have contrasting views in their perception of risk versus HCPs (Sen, 2016; Aronson, 2006).

Nature of the Study

This study was quantitative in nature, and secondary analysis of these data were performed by utilizing the chi-square test and the odds ratio (*OR*). This study was cross-sectional and descriptive. The non-experimental research design (known as the cross-sectional design) was employed to compare reporting of ADRs at case and event level between reporters (consumer versus physician), specifically, for patient outcome, as well as SOC and demographics. The independent variable was the reporter (consumer versus physician), whereas patient outcome, SOC and reporter demographics were the dependent variables. The unit of analysis was the total number of ADR cases and reported ADRs. The analysis focused on describing statistical relationships between the variables that were chosen for examination. This particular design enabled data collection without manipulating the independent variables (Field, 2013). Hence, the cross-sectional design enabled the examination of associations or relationships among variables by using statistical data analysis techniques (Frankfort-Nachmias, 2014).

In this study, I analyzed secondary data (see Aagaard, Nielsen, & Hansen, 2009), specifically, ADRs that were submitted by consumers and physicians to the FDA, from the FAERS database, which contained quarterly data files that were extracted for analysis (FDA, 2016b). The data containing the spontaneous ADR reports from the FAERS database were accessed and downloaded from the quarterly data file data selection time period containing a quarter's worth (3 months) of data: 01 April 2016 through 30 June

2016. Each quarterly data file within FAERS had variations in data due to the number of ADRs reported in the interval (3 months). Each data file was not representative of all four quarters for the year. In this study, my justification for selecting three-month's worth of data was to provide a more specific perspective of AE reports received by the FDA and to be in alignment with the FDA website (Institute for Safe Medication Practices, 2015). In addition, without access to some licensed software tools, such as Empirica Signal®, more than 3 months would have been very cumbersome. Once the ADR data was collected, spontaneous reports from consumers and physicians were subsequently assessed for ADRs.

Definitions

According to WHO (2012), the following is a brief listing of key terms and phrases that were considered ambiguous, controversial, or operational terms used throughout this study:

Adherence: The degree to which an individual's behavior (consumption of medication, adherence to a diet and exercise regimen, and/or implementation of changes in lifestyle) is in conformity with the recommendations from a healthcare provider.

Adverse drug reaction: Harmful and involuntary responses resulting from doses used in humans for preventive treatment, diagnosis, or for diseases and therapy.

Adverse event: An unwanted outcome related to the consumption of any substance or combination of substances used for treating or preventing diseases in humans.

Anatomical Therapeutic Chemical Classification System: is used for the classification of active ingredients of drugs according to the organ or system on which they act and their therapeutic, pharmacological and chemical properties.

"*Direct*" *Case/Report*: cases/reports voluntarily submitted to the FDA by non-manufacturers.

Expedited Case/Report: case/report expedited to the FDA within 15 days.

FAERS: The US FAERS database is a national postmarketing surveillance database that gathers data on ADRs, medication error reports, and product quality complaints leading to AEs submitted to the FDA by reporters, including consumers and physicians.

Periodic Case/Report: Non-Expedited cases/reports from manufacturers to the FDA.

Pharmacovigilance: PV is the science that serves as a crucial component in detecting, evaluating, and inhibiting ADRs or any other drug-related issues and/or effects.

Serious adverse event or *serious suspected adverse reaction*: An AE or suspected adverse reaction that is deemed “serious” if, from the perspective of the investigator or sponsor, it may result in any of the following patient outcomes: death; LT; persistent or significant disability or incapacity; a congenital anomaly or birth defect; initial or prolonged existing inpatient hospitalization; or, a medically significant outcome, event, or reaction.

Side effect: any undesirable effect or problem resulting from medicinal product that occurs in addition to a desired therapeutic effect.

Signal: A new, potential causal association or a new aspect of a previously known relationship between an ADR and a drug or intervention.

Spontaneous reporting: A voluntary submission of ADR reports by different types of reporters, including, HCPs, consumers, pharmacists, and lawyers, as well as pharmaceutical companies to national regulatory authority agencies.

Spontaneous Reporting System: A SRS is a system that is employed during the postmarketing phase to identify new ADRs that may have otherwise gone undetected during clinical trials.

Under-reporting: Under-reporting of ADRs is the reporting of less than the actual amount of ADRs that are being reported.

Assumptions

It was assumed that the collection and synthesis of data from FAERS over the specified timeframe was adequate to conduct this study. Furthermore, it was also assumed that the FAERS database was sufficient to provide the appropriate amount of data. Moreover, in terms of quality, it was further assumed that the types of reports received from consumers were similar in content and presumed accuracy to those of physician reports (Blenkinsopp, Wilkie, Wang, & Routledge, 2007). Additionally, it was assumed that consumer reports yielded information on patient outcome, drug therapy and demographics in comparison to physician reports.

Scope and Delimitations

This quantitative study covered the potential significant difference in the distribution of ADRs by reporter (consumer versus physician) and patient outcome, as

well as SOC, and reporter demographics within the FDA FAERS database at case and event level. There were not any studies in which the FAERS database was employed to compare under-reporting of ADRs between consumers and physicians specifically with the aforementioned methods used in this study (Sakaeda et al., 2013). This particular focus was chosen due to the fact that there is a gap in the literature of the under-reporting of ADRs by consumers versus physicians in the FAERS safety database.

This quantitative study did not cover the under-reporting of ADRs to the FDA by consumers and physicians since the data are limited to only ADRs that were actually reported. Moreover, since this study employed secondary data analysis, recruitment of the participants was not made, especially those in vulnerable populations, including, but not limited to the following: minors (age 17 and under); adult students of the researcher; subordinates of the researcher; patients of the researcher; nursing home residents; prisoners; mentally impaired or disabled individuals; emotionally impaired or disabled individuals; physically impaired or disabled individuals; individuals residing within the US who may not be fluent in English; undocumented immigrants; victims/witnesses of violent crime or other trauma (e.g. natural disasters); active duty military personnel; and, any other individuals who may not be able to protect their own rights or interest (Walden University, n.d.).

Limitations

Some anticipated limitations of the FAERS data, as well as the secondary data analysis in this study, must be acknowledged. For example, not all reports for every AE or medication error that occurred with a product were submitted to the FDA. Moreover,

duplicate reports existed in which the same report was submitted by a consumer and by another reporter (the physician). Hence, neither incidence rates nor an estimation of drug risk could be calculated from the FAERS data (FDA, 2017).

Given that quantitative methods were employed, consumer perception of ADRs were not assessed, since the latter requires qualitative methods. Since the correlational cross-sectional research design was utilized, the secondary data led to under-reporting and recall bias, which yielded misclassification or information bias (Gualano, Gili, Scaioli, Bert, & Siliquini, 2015). Furthermore, the use of this particular design provided a rather limited amount of information of the sample (Gualano et al., 2015). The correlational cross-sectional research design presented challenges regarding the determination of causal relationships between the distribution of ADRs by reporter (consumer versus physician) and patient outcome, as well as SOC and reporter demographics. The correlational cross-sectional design contained several limitations that were significant to examine, including internal validity, which is only germane to such a design as experimental that attempts to establish a causal relationship (Frankfort-Nachmias, 2014). Since researchers do not alter the independent variables, they must render logical or theoretical inferences in terms of the direction of the causation by taking into account that correlation between variables does not imply causation (Field, 2013). Hence, it is challenging for researchers to make causal inferences.

To overcome several methodological limitations of correlational cross-sectional designs, researchers frequently employ statistical analyses, including cross-tabulation, for the purpose of organizing, describing, and summarizing their observations, as well

approximating some of the processes inherent within experimental designs (Frankfort-Nachmias, 2014). When the data are categorized, researchers are able to make contrasts between the categorical groups (Frankfort-Nachmias, 2014).

Significance of the Study

To date, there have not been any studies within the US in which the FDA FAERS database was used to compare under-reporting of ADRs by reporter (consumers and physicians) and patient outcome, as well as SOC and reporter demographics at case and/or event level (see Sakaeda et al., 2013). Therefore, I examined in this study the statistical significance in the distribution of case and event level ADRs within the FAERS database by reporter (consumer versus physician) and patient outcome, as well as SOC and reporter demographics. This research fills a gap in the literature by focusing on whether consumers may report ADRs to the FDA more frequently than physicians may, and whether these differences may be tied in some way to the severity of the ADRs, especially within SOC (Blenkinsopp et al., 2007). This, in turn, enables greater comprehension of consumer and physician perceptions, as well as determine if there was a need for a better safety reporting system in the US (Blenkinsopp et al., 2007). Consumer reports could enhance the overall drug safety system by providing additional information not reported by HCPs or other professional reporters (Health Action International, 2015). A SRS that can divulge the proportion of reports that arise from both consumers and physicians has a greater likelihood of early signal detection of ADRs that were not observed and reported in premarketing clinical trials (Health Action International, 2015; Mitchell et al., 1994).

By integrating consumer reports within HCP reports, signal detection may considerably increase, thereby yielding a more comprehensive ADR detection strategy. Based on the results from this study, my findings identified areas where reporting by one kind of reporter or the other is less meaningful, and these findings identified situations where efforts to increase education and awareness might be especially helpful to the public health community. The findings from this study will lead to recommendations for future research, including ameliorating existing PV systems to employ methods that detect and measure medicine safety, recognize certain risk factors and high-risk groups, classify ADRs linked to certain drugs or medications and in certain groups or communities, and pinpoint issues stemming from medication errors and medications with low or suboptimal quality (Pal et al., 2013). Hence, the results from this study have implications for positive social change surely enhance PV systems at the national and global scales to detect risks and risk factors in a rapid fashion after medications or drugs have been marketed to potentially inhibit ADRs, thus ultimately enabling patients to receive optimal treatment and quality of care at a fraction of the cost to the healthcare system (Pal et al., 2013).

Summary

In essence, given the relatively high rate of under-reporting by physicians, an urgent need exists to revolutionize the surveillance system for pharmaceutical drugs during the postmarketing phase, as evidenced by the amount of ADRs that were experienced by consumers (Lazarou et al., 1998). The inclusion of consumer reports to an SRS influences the validity of safety surveillance systems, thereby potentially yielding

considerable amelioration of the existing PV surveillance system (Jarernsiripornkul, Krska, Capps, Richards, & Lee, A. 2002). As a crucial component in PV, consumers may contribute to new and serious ADRs that can be identified in an expeditious manner via consumer reporting in comparison to physician reporting (Jarernsiripornkul et al., 2002). Furthermore, consumers may also report unforeseen or unanticipated benefits. This new additional information may lead to the enhancement of safety signals, as well as influence the awareness and implications of ADRs (Hammond, Rich, & Gibbs, 2007). Although consumer reports should never be deemed as a substitute for HCP reports, consumer reports may nonetheless serve as a counterpart to HCP reports. Hence, by obtaining reports on ADRs directly from consumers, the issue of under-reporting may ultimately be diminished.

In Chapter 2, I provide a literature review of consumer versus physician reporting, identify the existing gap in the literature, and discuss the theoretical framework most applicable to this study. In Chapter 3, I provide a review of the research methods that were employed for performing the secondary data analysis of the data in the FAERS database. In Chapter 4, I provide the results of the study. Lastly, in Chapter 5, I provide a discussion of the results, study limitations, recommendations for future research, and the implications for social change.

Chapter 2: Literature Review

Introduction

ADRs are a grave issue to the health and well-being of the public, particularly in less developed nations in which adequate drug toxicity monitoring and reporting systems are often lacking (Sen, 2016). Researchers have shown that, on a national and global level, greater than 5% of hospital admissions resulted from ADRs (Sultana et al., 2013), thereby responsible for close to 20% of deaths per year among patients who are hospitalized (FDA, 2016a). Consequently, a considerable economic burden is placed on the health of the public, as evidenced by public health costs of a hospital admission ranging from roughly $10,000 to $13,000 per hospitalized patient (Pillans, 2008). The US spends more than 30 billion dollars per year in managing ADRs, and these expenditures may be further magnified as a result of increased hospitalization, prolongation of hospital stay, and further clinical investigations in more serious cases (Sultana et al., 2013). Therefore, ADRs have a negative influence on the clinical, social, and economic aspects of society (Inácio et al., 2016). Therefore, to counteract the negative impact of ADRs, it is of paramount importance for regulatory agencies to work with marketing authorization holders to ensure a product's safety profile is current (Leroy et al., 2014).

The problem that I addressed in this study was the differences in the proportion of case and event level ADR reporting, from different reporting categories with a focus on patient outcome, as well as SOC, and reporter demographics within the US. The potential statistical significance in the distribution of case and event level ADRs within the FAERS database by reporter (consumer versus physician) and patient outcome, as well as SOC,

and reporter demographics, was examined. I anticipated that the findings of this study could provide information regarding variability in the proportions of ADR reporting between consumers and physicians and that the outcome might be further balanced in ADR reporting.

In the previous chapter, ADRs were discussed as a common problem within society. First, I addressed the under-reporting of ADRs by consumers and physicians as a recurring issue that continues to plague the well-being of the public. Second, I discussed the necessity of integrating consumer reporting alongside physician reporting as necessary to transform the surveillance system. In this chapter, I provide a history of ADR reporting in the US and the relevant SRS (FAERS), a history of ADR reporting in international countries and a literature review of consumer versus physician reporting. In doing so, I identified an existing gap in the literature, and discuss the theoretical framework most applicable to this study. The following literature review shows evidence that consumers may report some ADRs more frequently than physicians, and these differences may be tied in some way to the severity of the ADRs (Blenkinsopp et al., 2007).

Literature Search Strategy

The databases of MEDLINE and Google Scholar were reviewed. ADRs, under-reporting of ADRs by consumers versus HCPs, and related terms as keywords were searched. The following key search terms were employed: *ADRs*; *direct consumer reporting*; *direct patient reporting*; *under-reporting of ADRs; under-reporting of ADRs by consumers, patients, physicians, HCPs;* PV; *drug safety*; *spontaneous*, *healthcare*

professional, *patient*, and *physician*. The date range of reviewed published literature falls within the years of 2004 to 2017, inclusive.

History of ADR Reporting in the US and Overview of FAERS SRS

Circa the end of the 19th century and beginning of the 20th century, the mandate for the safety and efficacy of medicines and drugs was not implemented and enforced, thereby precluding the FDA from maintaining and exercising any official control or power to render legal decisions and judgments (Cobert, 2011). Consequently, unsafe or hazardous products infiltrated the US market, claiming hundreds of fatalities.

The number of mass poisonings is exemplified by the release of an elixir of sulfanilamide in 1937 by a company within the US (Cobert, 2011). Given that the mandate for drug safety testing was nonexistent during that time, the company failed to conduct any safety and efficacy testing of this product. The following year, the Federal Food, Drug and Cosmetic Act was enacted, thus prompting the safety testing of drugs and products to the FDA via a New Drug Application to protect the public's health (Cobert, 2011).

In the early 1960s, more than 20 years after the Federal Food, Drug and Cosmetic Act, the thalidomide disaster occurred during which thousands of infants all over the world were born with malformed limbs after the thalidomide drug was internationally marketed as a sleeping pill safe for pregnant women (Science Museum, n.d.). While this drug was never released on the market within the US, due to the opposition of the FDA's drug examiner Dr. Frances Kelsey, thalidomide was nonetheless used in clinical trials in the US. During the late 1950s, GlaxoSmithKline had conducted clinical trials with

thalidomide involving more than 800 study participants, including pregnant women (Bren, 2001). Consequently, 17 babies were born in the US with severely deformed arms and legs as a result of thalidomide (Bren, 2001). Due to this worldwide recognition of the lack of safety when using thalidomide, in 1962 the Kefauver-Harris Amendment was legislated, marking the advent of a new age of drug regulation. Hence, pharmaceutical companies were obligated to prove to the FDA the safety and efficacy of a new drug prior to its inception on the market (Cobert, 2011).

For the purpose of collecting information about the safety and efficacy of new drugs, in 1969, a SRS of suspected ADRs, now known as FAERS, was launched. This system was created as a repository of drug surveillance data for more than 6,000 marketed drugs, thereby enabling the FDA to render regulatory decisions regarding the safety and efficacy of these drugs. Since 1993, the FDA has been accepting direct consumer ADR reports electronically, by phone, or mail (FDA, 2015). Between the late 1990s to the mid-2000s, the number of ADRs reported to the FDA increased from approximately 100,000 per quarter to 300,000 per quarter in 2015 (Mezher, 2017). Presently, FAERS contains more than 8 million reported ADRs, thereby showing its exponential growth rate (Mezher, 2017). In 2016, the FDA has received more than 1.6 million ADR reports directly from consumers, physicians, manufacturers, and other reporter types (FDA, n.d.).

Despite the strengths inherent within the FAERS database, the limitations are also worthy to describe. The correct assessment of FAERS data are complicated by the fact that multiple drug compositions bear different names and various drug substances, as

exemplified by the active ingredient fluoxetine found in the drug Prozac for which researchers (Maciejewski et al., 2017) discovered nearly 400 “synonyms” (Mezher, 2017). The ability for researchers to make correlations between drugs and their adverse effects and render causal associations can be obfuscated by numerous drug synonyms associated with each drug in FAERS. On average, researchers determined 16 synonyms per one active ingredient within the FAERS database (Mezher, 2017), thereby impeding the ability to cluster ADRs to determine whether ADR reporting patterns differed across anatomical therapeutic classes (ATC) (Maciejewski et al., 2017). To correct this shortcoming, researchers suggested to consolidate drugs by their active component, which may enable easier detection of drug-ADR signals versus combining drugs based solely on synonym grouping (Mezher, 2017).

The researchers discovered an additional limitation within the FAERS database, namely, reporters misinterpreting adverse reactions as an indication of a drug (Mezher, 2017). The researchers stated that nearly 5% of all reports describe a drug’s indication as an AE. According to the researchers, some reports classified diabetes as a side effect for the drug rosiglitazone used to treat type 2 diabetes. To ameliorate the FAERS system, the researchers encouraged proper reporter education for the purpose of minimizing the number of reports in which misinterpretations between indication and side effect occur (Mezher, 2017).

Despite the limitations of the FAERS SRS, submitted ADR reports assist in the detection of serious AE (SAE)s that are subsequently included in the labeling information

of a drug. However, additional regulations, such as removing the product from the market, can be imposed in extreme circumstances.

European Union Countries in Which Direct ADR Reporting Is Accepted

ADRs are considered a serious issue to the health of the public not only on the terrain of the US, but on the international arena as well. Researchers have conjectured that ADRs are responsible for circa 5% of all hospitalizations in the European Union (EU) countries (Van-Lierop & Bunyan, 2008). Furthermore, ADRs are the fifth leading cause of mortality in a hospital setting, thereby comprising almost 200,000 mortalities on an annual basis (Van-Lierop & Bunyan, 2008). Researchers have stated that between 1% to 10% of serious ADRs are reported in EU countries, thereby defining under-reporting to be prevalent not only in the US, but internationally as well (Prescrire International, 2015).

The history of ADR reporting in the EU is newer in comparison to that of the US. Denmark and the Netherlands were among the pioneering nations that began to accept ADR reporting by patients and consumers circa 2003. Italy, the UK, and Sweden followed their lead in 2004, 2005, and 2008, respectively (Herxheimer, Crombag, & Alves, 2010). Although many other countries have been currently accepting direct consumer ADR reporting, including, but not limited to, Bulgaria, France, Portugal, Romania, and Norway, this literature review will only discuss Denmark, the Netherlands, and Sweden, which are the most experienced countries in consumer reporting (Health Action International, 2015).

Since 2003, Denmark has been accepting consumer reporting directly to the Danish Health and Medicines Authority (Danish Medicines Agency [DHMA],

Sundhedsstyrelsen). Given that under-reporting is a considerable issue in Denmark, the DHMA has implemented and launched several information campaigns for the purpose of promoting spontaneous ADR reporting. In 2007, pharmacies and healthcare providers were issued brochures containing information on how to better consumer reporting electronically. Analogously, in 2010, the DHMA organized programs for health institutions' phone counseling services in an effort to provide additional information on ADRs and direct consumer ADR reporting (Blenkinsopp et al., 2007). In 2013, the DHMA initiated an awareness-raising campaign entitled "Not everybody reacts the same" in which pharmacies and health centers partnered with patient organizations in an effort to further stimulate consumer reporting (Blenkinsopp et al., 2007). Thanks to the efforts of DHMA initiatives and awareness-raising campaigns, the surveillance system used in Denmark has markedly improved, as evidenced by an increase in the number of ADR reports submitted to the DHMA. In 2013, the DHMA received 6,681 reports of suspected ADRs, which indicated an increase of 35% versus those in 2012 (Blenkinsopp et al., 2007). Additionally, in 2014, the DHMA directed its attention to increasing ADR reporting not only among consumers, but also among family members and physicians within the mental health sector.

Similar to Denmark, the Netherlands established its direct consumer reporting to regulatory authorities in April 2003 via the Lareb Center, which is a specialized national center and an independent source of SRS in the Netherlands (WHO, 2002). Lareb accepts ADR reports directly submitted by patients, consumers, HCPs, and other reporter types and subsequently examines reports to determine the impact of patient reports on PV.

Since 2013, Lareb has been appointed by the WHO Collaborating Center for PV in Education and Patient Reporting to aid WHO providing training workshops to Member Countries on the process of managing consumer reports (WHO, 2002). Analogous to the DHMA in Denmark, Lareb in the Netherlands has also been actively involved in launching awareness campaigns designed to provide education to consumers regarding submitting ADR reports electronically. Consequently, direct consumer reporting in the Netherlands has been enhanced, as evidenced by the number of total ADR reports submitted. In 2013 and 2014, Lareb collected more than 17,000 reports, and circa one-fourth of them were submitted by patients/consumers. Moreover, according to the 2014 data from Lareb, 95% of direct ADR reports were submitted electronically (Health Action International, 2015).

In 2008, Sweden has implemented direct patient reporting to the Swedish Medical Product Agency (Medical Products Agency [MPA], Läkemedelsverket), which, similar to Denmark and the Netherlands, has launched campaigns and information sessions designed to raise awareness on consumer reporting and educate consumers on directly submitting ADR reports electronically. As a result, direct consumer reporting in Sweden (in addition to improvements in online reporting mechanisms) has been heightened, as exemplified by the increase in the total number of ADR reports submitted to the MPA. In 2013, more than 6,000 ADR reports were submitted to the MPA, and circa 18% and 83% of those reports were directly submitted by consumers and HCPs, respectively. Furthermore, in 2014, nearly 7,000 ADR reports were received by the MPA, and nearly a

quarter of those reports were submitted electronically by consumers (Health Action International, 2015).

Medical Dictionary for Regulatory Activities Overview

In an effort to further safeguard the health and well-being of patients and consumers on a global scale, a set of standardized, harmonized, and universal medical terminology was needed to enable the electronic dissemination of medical information and suspected ADRs among regulatory officials and agencies, pharmaceutical companies, clinical research organizations, biotechnology firms, HCPs, academics, and other researchers on an international level (International Council for Harmonisation [ICH], 2013). Circa March 1999, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) created an international, clinically validated medical dictionary, known as The Medical Dictionary for Regulatory Activities (MedDRA), which contains a standardized set of terms pertaining to medical conditions, medical products and devices, and medicines that can be transmitted to regulatory agencies and pharmaceutical companies (ICH, 2013).

MedDRA can be employed for signal monitoring and detection, data input, coding, and retrieval, and assessment of products. Furthermore, MedDRA is crucial during the pre- and postmarketing phase of products, including, but not limited to, pharmaceuticals, biologics, vaccines, and drug-device combination products (ICH, 2013). MedDRA also contains standardized terminology for the classification and characterization of AEs, as well as the following medical information: symptoms, signs, diseases, syndromes and diagnoses; problems with a system, organ, or etiology (i.e.,

Infections); errors and failures in medical devices and products; medication errors; medical, social, and family history information; application, implant, and injection sites; medical and surgical procedures; approved uses for medications and medical devices; and, types of investigations (i.e., liver function analyses, metabolism tests) (ICH, 2013).

One of the chief advantages of MedDRA is its ability to group and analyze AEs according to its own hierarchical structure (ICH, 2013). MedDRA is organized into five levels ranging from very specific to very general (ICH, 2013). The most specific level is known as the "Lowest Level Terms" (LLTs), which contain greater than 70,000 terms that describe medical information. These LLTs depict the manner in which an observation or case can be reported (ICH, 2013). The next level, known as "Preferred Terms" (PTs), contains more than 20,000 terms, which are single medical concepts that characterize a symptom, sign, disease diagnosis, therapeutic indication, investigation, surgical or medical procedure, and medical social or family history characteristic (ICH, 2013). Each LLT is linked to only one PT, while each PT has at least one LLT (itself) in addition to synonyms (different terms for the same concept) and lexical variants (i.e., abbreviations, different word forms for the same expression). Related PTs are combined into more than 1,700 "High Level Terms" (HLTs) on the basis of anatomy, pathology, physiology, etiology, or function (ICH, 2013). Subsequently, HLTs are linked to 330 "High Level Group Terms", which are finally grouped into 26 "SOCs", which form the most general level of the MedDRA hierarchy. SOCs are groupings by etiology (e.g. Infections and infestations), manifestation site (e.g. Gastrointestinal disorders) or purpose (e.g. Surgical and medical procedures). In addition, there is a SOC relating to

products and one to contain social circumstances. SOCs are comprised of more specific subgroups that combine single medical concepts and equal terms used for codifying clinical information associated with AEs and ADRs (ICH, 2013).

Given the significance of MedDRA in the coding of AEs and ADRs based on its five-level hierarchical structure, especially SOC, MedDRA will be employed for coding ADRs reported by consumers and physicians in this study. Hence, SOCs will be identified via this method and compared according to reporter.

Theoretical Foundation

The theoretical foundation that is the most applicable to this study is known as SARF, which stems from the perception of risk framework. Risk comprises the likelihood and repercussions of the occurrence of an event (Adams, 1995). Researchers have theorized that individuals tend to differ between their attitude toward a likelihood or repercussion (Drottz-Sjöberg, 1991). A majority of definitions of risk include a probability estimate for the occurrence of a negative event (Brun, 1994). Adams (1995) explained risk (as per the definitions contained within medical and drug safety literature) as the likelihood that an AE occurring in the future is multiplied by its magnitude (Adams, 1995).

The theory holds that risk interrelates with the psychological, social, institutional, and cultural perceptions of individuals in a manner that may magnify or diminish individuals' responses to the risk or risk event (Kasperson & Ratick, 1988). These changes in the perception of risk elicit behavioral responses from individuals that alter the social and economic aspects of society, thereby increasing or decreasing the actual

physical risk (Kasperson & Ratick, 1988). Researchers have identified variations between HCPs and consumers in terms of reporting ADRs (Aagaard et al., 2009). SARF may be employed to elucidate the differences between HCPs and consumers' reporting of ADRs. The perception of risk as it applies to the present issue involves the premise that different groups (HCPs and non-HCPs, researchers and the public, or HCPs and consumers) hold different views on the possible risks associated with some action or environment. Researchers have discovered that several factors contribute to the perception of risk, including factors related to the individual, the presentation of the risk, and the attributes of the risk (Association of Reproductive Health Professionals, 2006). Hence, with respect to ADR reporting and drug therapy, consumers frequently have contrasting views in their perception of risk versus HCPs (Aronson, 2006). Therefore, the SARF framework is appropriate for this study with regards to identifying under-reporting of ADRs since it is assumed that the consumer's perception of risk differs from that of the physician.

The studies conducted by Bongard et al. (2002) and Durrie, Hurault, Damase-Michel, & Montastruc (2009) employ a similar theoretical foundation in relation to this study. The results from these studies have revealed how consumer's perception of risk differs from that of the physician, thereby justifying the use of the SARF framework. To determine whether perceived risk differs between HCPs and non-HCPs (consumers), researchers Bongard et al. (2002) conducted a study on 400 HCPs (consisting of general practitioners, pharmacists, and PV professionals) and 153 non-HCPs. To comprehend the risk perception of ADRs within the medical arena in comparison to the public, the researchers requested study participants to evaluate their risk perception of ADRs related

to 13 different drug classes via visual analogue scales, which were utilized to define a score of perceived risk of ADRs related to each drug class (ranking from 0 to 10). Based on the results from the study conducted by Bongard et al. (2002), the authors claimed that the risk perception of ADRs varied between both groups. HCPs gave the highest and second highest ranking to anticoagulants and nonsteroidal anti-inflammatory drugs (NSAIDs), respectively, thereby claiming that these drugs were most hazardous to the health and safety of patients and consumers. Contrarily, consumers gave a lower ranking to anticoagulants and NSAIDs, thereby claiming that these drugs posed a lesser threat. Moreover, non-HCPs gave the lowest ranking to aspirin, thereby stating that this drug posed the least threat. However, the ADRs related to the aforementioned drugs are significant, especially gastrointestinal (GI)-related ones. This perception of the safety of aspirin by the consumer may partially be attributed to the dearth of information presented on the risk of aspirin and the excess of information presented to the consumer through advertisements, Internet, and commercials (Durrie et al., 2009). Hence, the authors concluded that the public was incognizant of such ADRs and, therefore, underrated the risk associated with NSAIDs (Bongard et al., 2002). Additional findings from the study by Bongard et al. (2002) revealed that consumers gave the highest rank to sleeping pills, followed by tranquillizers and antidepressant drugs. Additionally, consumers highly ranked psychotropic drugs, thereby asserting that these drugs posed the greatest risk. Bongard et al. (2002) acknowledged that mass media's linking of psychotropic drugs with frequent suicide attempts may have influenced the public's perception of high-risk regarding these drugs. Since consumers and HCPs perceived the dangers of one drug

class over another drug class differently, the authors concluded that HCPs and non-HCPs possess differing risk perceptions of ADRs. Hence, the results from the study conducted by Bongard et al. (2002) bolster the claim that risk perception of ADRs varies between consumers and HCPs, which is crucial for this study and which may explain why HCPs report ADRs less frequently in comparison to non-HCPs.

Durrie et al. (2009) conducted a study that assessed the perceived risk of ADRs among 92 medical students (63 females and 29 males) and examined whether the perceived risk of ADRs differs before and after taking pharmacology courses and found this to be the case. The authors requested the medical student study participants to assess their risk perception of ADRs related to 13 different drug classes prior and subsequent to the pharmacology courses via a visual analogue scale, which was employed to define a score of perceived risk of ADRs related to each drug class (ranking from 0 to 10). The following drug classes were assessed: antibiotics; anticoagulants; antidepressants; aspirin; contraceptive pill; corticosteroids; drugs for arterial hypertension; drugs for diabetes (other than insulin); hypnotics; hypocholesterolaemic drugs; NSAIDs; postmenopausal hormone replacement therapy; and, tranquilizers. The findings from the study conducted by Durrie et al. (2009) revealed that the perceived risk of ADRs by medical students was different after taking pharmacology courses. Based on the results from the authors' study, the authors claimed that, prior to the pharmacology courses, medical students ranked hypnotics as the most hazardous drug (followed by antidepressants and anticoagulants) and contraceptive pills as the least hazardous. After pharmacology courses, antidepressants were ranked as the most dangerous drugs by medical students, followed

by anticoagulants and hypnotics. The authors claimed that, aside from several classes of drugs (antidiabetics, antihypertensive drugs, tranquillizers, corticosteroids, and hypnotics), upon completion of the pharmacology courses, there was a statistically significant increase in perceived risk for other classes of drugs. The highest increases were observed for contraceptive pills, NSAIDs, and aspirin, while the lowest increases were observed for hypocholesterolaemic and antidepressant drugs. The authors concluded that after completion of the pharmacology courses, medical students became more cognizant of potentially serious ADRs that are associated with drugs deemed relatively safe by non-HCPs, such as NSAIDs and aspirin. Hence, the findings from the study conducted by Durrie et al. (2009) are critical to this study and may explain the need for efficacious training and preparation, as well as adequate information for HCPs on ADRs, which may explain the under-reporting of ADRs by HCPs.

Literature Review of Consumer Versus Healthcare Professional ADR Reporting

In a published review that compared patient and physician reporting of suspected ADRs, the authors of Health Action International (2015) claimed that although HCPs are an essential element of evidence regarding the safety and efficacy of medicine and pharmaceutical drugs, they do not report ADRs as frequently as they should (Health Action International, 2015). To the author's opinion, one of the greatest challenges to reporting ADRs by physicians is the shortage of time. The same authors argue that physicians see many patients during their clinical visits per day and are often preoccupied with completing medical records and forms, as well as attending to other clinical priorities within the office or hospital setting. Consequently, HCPs only report the ADRs

they deem the most serious, as well as ADRs they may ascertain as associated with the usage of medicines or drugs. Moreover, although patients consider certain ADRs to be highly important with regards to affecting their quality-of-life, HCPs tend to not view such ADRs in the same aspect. The same authors of stated that patients' reports of their personal reactions to the drugs and the drugs' impact on their quality-of-life are typically more detailed than physicians' reports of their patients' ADRs. Hence, the same authors argued that if patients can collaborate with their physicians and discuss the ADRs experienced by patients, both parties may contribute to delivering effective reports of prospective safety issues of the drugs. Therefore, the authors of Health Action International (2015) contended that it is essential to combine the reports from HCPs and patients, as such a procedure may foster the growth and progression of systems of PV within Europe.

Parrella et al. (2014) performed computer assisted telephone interviews of 191 South Australian parents who reported an AE following immunization (AEFI) of their children. The authors compared parents reporting their children's AEFI to either HCPs or surveillance authorities with those who did not report their children's AEFI based on the following factors: awareness of surveillance, vaccine safety opinions, and demographics. Based on the findings from their study, Parrella et al. (2014) claimed that reporting an AEFI to an HCP or a surveillance authority was not statistically significantly related to an awareness of a surveillance system. Furthermore, the authors stated that there was a statistically significant relationship between AEFI reporters and the perception that a serious reaction was more likely to occur at their children's last immunization. Based on

their findings, the authors claimed that while reporting an AEFI was not statistically significantly related to an awareness of surveillance or socio-demographic factors, the findings revealed some differences in safety opinions. Parrella et al. (2014) concluded that additional research is needed to determine if these differences have existed or have occurred at a date earlier than the incidence of an AEFI or whether these differences are a result of the AEFI. The authors emphasized the significance of consumer reporting for postmarketing vaccine safety surveillance.

The aim of the descriptive-cross-sectional study performed by Vural, Ciftci, and Vural (2014) was to examine the knowledge, attitudes, and behaviors of 112 nurses employed in a public hospital regarding PV, ADRs, and AE reporting via a questionnaire. Based on the findings of their study, the authors claimed that nearly 74% of the nurses were cognizant of the definition of "severe adverse effect" of drug therapy. Almost 35% of nurses were aware that ADRs are reported to a contact individual working in the Turkish PV Center (TÜFAM). The same authors stated that while circa 70% of nurses had knowledge of the importance of ADR reporting, only 8% of the nurses actually reported ADRs to the TÜFAM. Based on these results, the authors stated that ADR event reporting was low among nurses. The authors concluded that the findings from their study revealed a deficit in knowledge regarding PV and ADR reporting. Vural et al. (2014) stressed the need for additional research to ameliorate the rate of reporting and to enhance the knowledge and understanding of PV not only among nurses, but also other healthcare practitioners.

Alatawi et al. (2017) compared reporting rates in FAERS to expected rates of known adverse drug events (ADEs). The authors chose three groups of drugs, including statins, biologics, and narrow therapeutics index drugs (NTI) to determine the difference in sensitivity to reporting. The results from the authors' research revealed that most drug-ADE pairs were statistically significantly under-reported by both consumers and physicians. The authors contended that the reporting differences between consumers and providers potentially stem from their perceptions of the seriousness of an ADE, which subsequently necessitates whether an event report needs to be made and submitted to the FDA. The authors claimed that circa 20% to 33% of the minimum number of expected serious AEs were reported with biologics and NTI drugs. The authors stated that under-reporting by both consumers and physicians significantly differs by the types of drug and perceived severity of ADRs, and an understanding of this difference in under-reporting is necessary when interpreting safety signals. The authors concluded that their study explains the rate of under-reporting of ADEs in spontaneous reporting data within the FAERS database.

The objectives of the study conducted by Di Maio et al. (2015) were to: compare reporting by patients and HCPs of six toxicities (anorexia, nausea, vomiting, constipation, diarrhea, and hair loss) occurring during anticancer treatment based on data prospectively collected in three randomized trials; determine the agreement between patients' and physicians' reports; and, calculate the rate of possible under-reporting of AEs by physicians. The authors calculated toxicity rates for each toxicity, as well as computed the agreement between patients and physicians (via inter-rater reliability scores) and the

under-reporting rate by HCPs. The results of their study revealed that the agreement between patients and physicians was rather low for all toxicities. Moreover, toxicity rates reported by HCPs were lower in comparison to those reported by patients. For patients who reported any severity of toxicity level (based on their responses of either "not at all," "a little," "quite a bit," or "very much" on a quality-of-life questionnaire), under-reporting by physicians ranged from 40.7% to 74.4%. For patients who reported "very much" toxicity, under-reporting by physicians ranged from 13.0% to 50.0%. The authors concluded that subjective toxicities were highly under-reported by physicians, even when prospectively gathered within randomized trials. Based on the findings from their study, the authors accentuated the need for patient reporting and encouraged the inclusion of patient-reported outcomes into toxicity reporting within clinical trials.

Medawar and Herxheimer (2004) conducted research in the UK comparing the reports from patients and primary care physicians regarding suspected reactions to an antidepressant drug called paroxetine. The doctors' reports were submitted via the Yellow Card (YC) scheme – an information-collecting UK system for suspected ADRs to medicines and drugs (Yellowcard, 2017). Based on the results from the research of Medawar and Herxheimer (2004), in comparison to reports from the YC, reports from patients were more comprehensive and specific, thereby detailing suicidality and withdrawal symptoms, including, but not limited to, weight gain, suicidal behavior, and/or loss of libido, in a lucid manner. Hence, the authors argued that reports from patients conveyed important information regarding ADRs that medical professionals were unable to deliver. Thus, the same authors concluded that an increase in physician

reporting, in conjunction with patient reporting, especially patients who directly report to physicians, would decrease the rate of under-reporting and ultimately play a potent role in PV and drug safety.

The objective of the study conducted by Farquhar et al. (2015) was to determine the proportion of maternal and perinatal death and illness cases due to SAEs by comparing the case reports from the Perinatal and Maternal Mortality Review Committee (PMMRC) to those from the Health Quality and Safety Commission (HQSC) in New Zealand. Based on the results from the study, the authors stated that less than 9% of maternal and perinatal SAEs were identified by the HQSC SAE reporting system. Farquhar et al. (2015) claimed that the proportion of maternal and perinatal AE reporting to the HQSC is low in comparison to that of PMMRC reporting of AEs. The authors concluded that these SAEs were not undergoing sufficient scrutiny at the local level and, consequently, the reporting of SAEs to the HQSC may not be a valid method to detect or ameliorate the quality of maternity services offered in New Zealand.

Moore and Bennett (2012) employed incidence studies that have been previously published to compute reporting rates for hemorrhage, emergency hospitalization, and venous thromboembolism (VTE) associated with four drugs: warfarin, clopidogrel, ticlopidine, and thalidomide. The AEs were reported by healthcare providers to the FDA's FAERS system. The authors discovered the following annual reporting rates with an associated AE: 1.15% for more than 33,000 emergency hospitalizations linked to warfarin for patients aged 65 years or older; 0.98% for greater than 13,000 hospitalizations attributed to clopidogrel and ticlopidine; and, 1.02% for more than

67,000 hemorrhage cases associated with warfarin. Moreover, the results from their research revealed a 9-year reporting rate of 2.33% for 48,000 VTE AEs linked to thalidomide. Based on these findings, Moore and Bennett (2012) stated that the incidence of these hematologic AEs is considerably high and reporting rates are rather low (near the lower boundary of the 1 to 15% range evident for other events). The same authors concluded that given the low reporting rates of AEs, the FDA FAERS system should be examined.

Goldsmith, Aikin, Encinosa, & Nardinelli (2012) studied AE reports for 123 drugs that originated directly from patients prior and subsequent to the 2007 US federal mandate of the print direct-to-consumer advertisement, which provides consumers with information to directly contact the FDA (via phone or agency's website) in order to report any AEs experienced following the consumption of medicines. The authors assessed the impact of this mandate via statistical model simulations and discovered that, if monthly expenditures on print direct-to-consumer advertising increased from 0 to $7.7 million per drug, patient-reported AEs would increase by three times (versus patient-reported AEs prior to the mandate). However, based on their findings, the authors claimed that the absolute increase per month was less than 0.24 reports per drug, thereby suggesting that the influence of the increase on the health of the public was rather small and that the AE reporting rate was still considerably low. The same authors concluded that additional measures, including a greater awareness of FDA FAERs, in addition to an increase in consumer education, is encouraged to stimulate patient reporting of AEs.

Blenkinsopp et al. (2007), examined literature on international experience from six countries, as well as seven studies that surveyed patients in hospital or primary care. According to the authors, published research has divulged findings suggesting that patients are inclined to detect and report more ADRs in comparison to HCPs. However, some patients neither discuss their ADRs with their HCPs nor do they report to healthcare authorities and regulatory agencies. The same authors admitted that although the root cause of patients failing to disclose all their ADRs to their physicians has not been elucidated, the results from their research can nonetheless provide some evidence of under-reporting of ADRs by patients due to patients' viewpoint that there was insufficient communication with their primary care physicians. Hence, Blenkinsopp et al. (2007) concluded that it is essential for patients concerns to be expressed and reported to health authorities.

Van Hunsel, Passler, & Grootheest (2009) compared ADR reports from patients and medical professionals regarding the advantages and jeopardies of statins. Based on the findings from the authors' research, a majority of the patients claimed that they did not receive proper knowledge about the drug, as well as adequate guidance from their physicians regarding the side effects from the drug. Consequently, patients, rather than HCPs, reported more frequently musculoskeletal and connective tissue disorders relating to statins. The same authors believed that HCPs refrained from reporting these ADRs to PV agencies due to them being specified in the Summary of Product Characteristics of statins. The results from the authors' research suggested that patient reports may yield insight into ADRs, especially those that have not been previously known. Hence,

Van Hunsel et al. (2009) concluded that patients' apprehensions regarding ADRs should be acknowledged in reports to national PV agencies.

The study by Golomb, McGraw, Evans, & Dimsdale (2007) examined patients' viewpoint of the patient-physician relationship, as well as physicians' acknowledgment of their patients' reporting of suspected ADRs resulting from statins, a class of drugs that lower the cholesterol level in the body. The findings from the study showed that 87% of patients instigated the conversation with their physicians regarding their condition after being treated with statins. Physicians were more inclined to refute than confirm the potential association between ADRs and statins by disregarding their patients' symptoms and possibility of those symptoms' relationship to statin use. Hence, Golomb et al. (2007) argued that physicians' failure to properly communicate with their patients might be the cause of under-reporting of ADRs by primary care physicians. Therefore, the same authors suggested an all-encompassing active postmarketing surveillance undertaking to target patients to report ADRs may contribute to an amelioration of ADR reporting systems.

The studies conducted by Aagaard et al. (2009) and de Langen, van Hunsel, Passier, de Jong-van den Berg, & Van Grootheest (2008) employ a similar type of data collection and/or data analysis methods in relation to this study. Aagaard et al. (2009) conducted a retrospective study by employing the Danish ADR database to compare ADR reports between consumers and other sources, including physicians, pharmacists, lawyers, pharmaceutical companies and other HCPs. Aagaard et al. (2009) examined 6,319 ADR reports containing 15,531 ADRs from 2004 to 2006 and analyzed the data

from these reports with regards to the reporter category, severity of the ADRs, the category of ADRs by SOC, and the suspected medicines on level 1 of the ATC classification system. The same authors computed chi-square and *OR*s to determine the relationship between the type of reporter and reported ADRs (classified by ATC or SOC). The confidence interval (95%) was calculated for all the *OR*s. Based on the results from the study of Aagaard et al. (2009), consumers reported 11% of the ADRs. Consumers' reporting of serious ADRs was analogous to that of physicians (approximately 45%), though lower than that of pharmacists and other HCPs. Consumers provided a different perspective of the ADRs, especially for the disorders of the nervous system. Furthermore, the same authors discovered that consumer reports provided greater detail on the prospective diagnosis made by the consumers themselves, which is a finding that HCPs do not typically anticipate from non-HCPs. In comparison to other sources, consumers were more likely to report ADRs from the following SOCs: nervous system disorders (*OR* = 1.27); psychiatric disorders (*OR* = 1.70); and, reproductive system and breast disorders (*OR* = 1.27). Moreover, compared with other sources, consumers were less likely to report ADRs from the SOCs blood and lymphatic system disorders (*OR* = 0.22) and hepatobiliary system disorders (*OR* = 0.14). Aagaard et al. (2009) stated that, in comparison to other sources, consumers were more likely to report ADRs from the following ATC groups: N (nervous system) (*OR* = 2.72); P (antiparasitic products) (*OR* = 2.41); and, S (sensory organs) (*OR* = 4.79). Additionally, compared with other sources, consumers were less likely to report ADRs from the following ATC groups: B (blood and blood-forming organs) (*OR* = 0.04); J (anti-infective for systemic use) (*OR* = 0.44); L

(antioneoplastic and immunomodulating agents) (*OR* = 0.19); and, V (various) (*OR* = 0.03). In the SOC 'nervous system disorders', consumers reported seven categories of ADRs, two of which were dysgraphia and parosmia, that were not reported by the other sources. Aagaard et al. (2009) claimed that, in comparison to other sources, consumers reported different categories of ADRs for different types of SOCs and ATC groups. Hence, the authors concluded that consumers should be active participants within systematic drug surveillance systems, including clinical settings, and their reports should be treated with as much importance as those from other sources. The study conducted by Aagaard et al. (2009) revealed significant findings suggesting that, in comparison to other sources, consumers reported different categories of ADRs for different types of drugs. Similar to this study's quantitative methodology (Chapter 3), the chi-square and the *OR* in the study by Aagaard et al. (2009) were computed to determine the relationship between the type of reporter and seriousness, as well as type of reporter and type of reported ADRs (classified by ATC or SOC). Although this study will not be focusing on ATC, the authors' statistical framework will nonetheless be beneficial to use in an effort to compare and contrast the results from this study.

de Langen et al. (2008) performed a study that compared ADR reports between consumers and HCPs from the Netherlands PV Center Lareb within a three-year time period from April 2004 to April 2007. Consequently, my study will focus on the US and the FDA FAERS database and focus solely on physician versus consumer, unlike Langen et al. (2008). This is important to be studied, as the lack of AE reporting is a limitation of current PV systems within the US, thereby hindering regulators' ability to quantify risk of

under-reporting of ADRs. My study will ultimately see if the FDA FAERS database is lacking in reporting of ADRs by consumers and/or physicians, thereby determining if FAERS needs improvement in this area. The authors examined 2,522 ADR reports comprising 5,401 ADRs that were submitted by consumers, and 10,635 reports comprising 16,722 ADRs that were submitted by HCPs. The authors analyzed the data from these reports with regards to the age and gender of the reporters, the attributes of the most frequently reported drugs, and the attributes of the most frequently reported ADRs, their seriousness, and their outcome. de Langen et al. (2008) computed chi-square to determine the relationship between the type of reporter (patient versus HCP), the number of reports submitted by type of reporter, patient characteristics, and information regarding the reported drugs and ADRs. Furthermore, the authors employed the *t*-test to determine statistically significant differences in the male to female ratio among reports from patients and HCPs.

de Langen et al. (2008) discovered statistically significant differences between patient reports and reports from HCPs with regards to the seriousness and outcome of reported ADRs in the Netherlands. In comparison to HCPs, patients reported a significantly higher number of LT ADRs (5.2% vs 2.7%) and disability (2.3% vs 0.4%). Moreover, patients reported significantly fewer ADRs leading to death (0.6% vs 1.5%) and hospitalization or prolongation of hospitalization (9.8% vs 12.0%). The authors also determined statistically significant differences in the outcome of the reported ADRs between patients and HCPs (87% vs 68%). Patients reported non-recovery (35.4%) from the ADR significantly more often than HCPs (16.7%). Contrarily, the same authors

claimed that no statistically significant differences were determined between patient reports and reports from HCPs with regards to the following attributes: patient characteristics (age and gender); most frequently reported ADRs from the five most involved organ systems (nervous system disorders, psychiatric disorders, gastrointestinal disorders, musculoskeletal disorders and general disorders/administration site conditions); and, most frequently reported drugs from the five most reported drug categories (HMG Co-A reductase inhibitors ("statins"), selective serotonin reuptake inhibitors, B-adrenoceptor antagonists ("B-blockers"), anticoagulants, and proton pump inhibitors). In addition to the aforementioned findings, de Langen et al. (2008) also discovered that patient reports offered an entirely different perspective in comparison to those of HCPs, especially in terms of recovery (full versus non-recovery).

The authors accentuated that although patient reporting should not substitute HCP reporting, (as HCPs are a reliable source for ADR reporting), patient reporting may nonetheless serve as a crucial component in healthcare, thereby placing patient safety and greater access to efficacious drugs at the forefront of PV. The authors encouraged the recognition and acknowledgment of patient reports, which they claimed will increase the number of reported ADRs received within a certain timeframe, thereby ultimately augmenting the statistical power for signal detection in an effort to yield signal detection of new ADRs. Hence, the same authors concluded that patient reporting in SRSs is advantageous, thereby fostering a valid PV.

The study conducted by de Langen et al. (2008) revealed significant findings suggesting that patients reported ADRs differently from HCPs with respect to the

seriousness and outcome of reported ADRs. Similar to the quantitative methodology in this study, the chi-square in the study by de Langen et al. (2008) was calculated to determine the relationship between the type of reporter (patient versus HCP) and seriousness and outcome of reported ADRs, patient characteristics, and attributes of the most frequently reported ADRs.

Summary and Conclusions

The findings from the literature review suggested that consumer reporting is imperative to successful PV. Researchers have argued that consumer reporting would increase the number of spontaneous reports submitted, which would subsequently enhance SRSs (Aagaard et al., 2009; de Langen et al., 2008; Blenkinsopp et al., 2007; van Hunsel et al., 2009). Within their reports, consumers may provide an in-depth account of their symptoms while consuming medication, thereby unveiling potential and new ADRs that may otherwise have been unknown and undetected (WHO, 2012). Based on the results from the literature review, the quality of reports from consumers is akin to or even higher than that of reports from HCPs, especially in terms of identifying potential new ADRs that had not previously been reported by HCPs (Blenkinsopp et al., 2007). The findings from the study conducted by Aagaard et al. (2009) and de Langen et al. (2008) revealed that, in comparison to physician reports, consumers reported different categories of ADRs for different types of medicines, thereby providing a unique perspective of their experiences with ADRs (Aagaard et al., 2009). By combining the reports from consumers with those of HCPs, the SRSs may be filled with a plethora of new information regarding ADRs, thereby accelerating signal detection (Health Action

International, 2015). Hence, the reports from consumers can deliver an understanding and awareness of ADRs in greater detail (Herxheimer et al., 2010).

The results from the literature review revealed that a majority of ADRs are under-reported since ADRs comprise more than 5% of all hospital admissions, and 10% of all hospitalized patients. Findings have also shown that the overall reporting rate of ADRs is circa 1%, although the rate considerably fluctuates due to the severity and type of reaction, as well as the characteristics of the drug. Furthermore, reporting rates of suspected ADRs by medical professionals is substantially low (Medawar & Herxheimer, 2004). Published research has shown that patients are inclined to detect and report more ADRs in comparison to HCPs. However, findings have also suggested that spontaneous reports from patients comprise a small proportion of total official reports, thereby emphasizing the importance of encouraging patient reporting of suspected ADRs and incorporating such reports into official systems (Blenkinsopp et al., 2007). While a scarcity of research has been published to assess the spontaneous reporting of suspected ADRs by patients, considerable and noteworthy experience from several countries in which patient reporting has progressed has divulged evidence that patients have detected potential new ADRs (Blenkinsopp et al., 2007; Medawar & Herxheimer, 2004). The select few countries that have released the reported experience of patients confirmed that such a patient reporting system will enable greater comprehension of consumer perceptions, which will ultimately lead to ameliorations in patient reporting. Thus, the advent of patient reporting should be taken into consideration by other countries (Blenkinsopp et al., 2007).

To date, there are no studies that compared and contrasted consumer reports with those of HCPs based on patient outcome in the US. Therefore, I will examine in my study the statistical significance in the distribution of case and event level ADRs within the FAERS database by non-HCPs (consumers) and HCPs (physicians) and patient outcome in an effort to fill the gap in the literature. In Chapter 3, I provide the research methods that will be employed for performing the secondary data analysis of the data contained in the FAERS database. In Chapter 4, I provide the results of the study. Lastly, in Chapter 5, I provide a discussion of the results, study limitations, recommendations for future research, and the implications for social change.

Chapter 3: Research Method

Introduction

In the previous chapter, I provided a literature review of consumer versus physician under-reporting, identified the existing gap in the literature, and discussed the theoretical framework that is the most applicable to this study. Specifically, in this study, I assessed whether a statistically significant difference existed in the distribution of case and event level ADRs by reporter (consumer versus physician) and patient outcome, as well as SOC and reporter demographics. The differences in under-reporting of physicians versus consumers were explored and compared to determine whether consumer reporting is imperative in AE reporting. It was anticipated that the outcome would impact frequency of physician and consumer reporting, as well as the differences in reporting rates between them. The independent variable was the reporter (consumer versus physician), whereas patient outcome, SOC, and reporter demographics were the dependent variables. The unit of analysis was the total number of ADR cases and reported ADRs. This chapter provides a description of the statistical methodology that was employed to compare consumer and physician reporting of ADRs. The essential elements of this study, including the research design, setting and sample, materials, data collection and analysis, threats to validity, and measures taken for protection of participants' rights, are discussed in this chapter.

Research Design and Rationale

In this study, I followed the design employed by Aagaard et al. (2009) in their analysis of the Danish ADR database known as The Danish Medicines Agency (Aagaard

et al., 2009). My study was cross-sectional and descriptive, and the non-experimental research design (known as the cross-sectional design) was employed to compare case and event level ADRs between reporters (consumer and physician), specifically, for the total number of case and event level ADRs reported and patient outcome, as well as SOC and reporter demographics. The independent variable was the reporter (consumer and physician), whereas patient outcome, SOC, and reporter demographics were the dependent variables. The unit of analysis was the total number of ADR cases and reported ADRs. The analysis focused on describing statistical relationships between the variables that have been chosen for examination. This particular design enabled data collection without manipulating the independent variables (see Field, 2013). Hence, the cross-sectional design enabled the examination of associations or relationships among the aforementioned variables by using statistical data analysis techniques (see Frankfort-Nachmias, 2014).

In this study, I employed quantitative methods, which are frequently used to analyze spontaneous data (see Aagaard et al., 2009). Chi-square test and *OR*s, as the most appropriate statistical methods, were conducted to investigate the relationship between reporter and reported ADRs. The test for association or dependence between the reporter and the total number of reported ADRs, as well as patient outcome, SOC, and reporter demographics, were conducted using the chi-square test and/or logistic regression (unless specified otherwise).

The chi-square test, as the most appropriate analytical strategy to employ in this study, was used to test for association between two categorical variables (see Gerstman,

2008). The statistical significance in association between reporter and total number of case and event level reported ADRs, as well as patient outcome, SOC, and reporter demographics, were shown with a *p*-value of less than 0.05. Given the number of comparisons of a similar nature, the issue of multiple comparisons arose. Furthermore, since multiple hypotheses were tested, the chance of incorrectly rejecting a null hypothesis (Type I error) was increased (Mittelhammer, Judge, & Miller, 2000). Therefore, to counteract these issues, I employed the Bonferroni correction, which tested each individual hypothesis at a significance level of α/m, where α was the desired overall alpha level and m was the number of hypotheses (see Miller, 1966). In this study, I adjusted for multiple comparisons by dividing my criterion of significance (0.05) by the number of tests (8), which yielded 0.006 (i.e. 0.05/8=0.006). Subsequently, I employed this number (0.006) as a benchmark to determine whether any comparison was statistically significant.

The *OR*, which is another measure of association for categorical data, as well as an additional appropriate method to employ in this study, was also used in conjunction with logistic regression models (see Gertsman, 2008). The chi-square test illustrated that an association exists, while the *OR* displayed the strength of the association. The confidence intervals were calculated at 95% for each *OR*. Statistical analysis were performed using a statistical software package (SPSS v25).

Methodology

Population

In this study, the target population were the reporters, consumers and physicians, who both submitted ADR reports (cases) to the FDA. ADRs voluntarily reported by consumers and physicians can be made directly to the market authorization holders of the product, which is mandated by law to subsequently report these events to the FDA (FDA, 2017). ADRs reported by consumers can also be made directly to such regulatory agencies as the FDA without making the initial report to their physicians (Health Action International, 2015).

Sampling and Sampling Procedures

I hypothesized that the two groups, consumers and physicians, were independent, and that the sample size of physician and consumer groups were unequal. Moreover, I hypothesized that the number of ADRs at case and event level reported by consumers and physicians were not the same. Furthermore, I hypothesized that physicians would report a lower number of ADRs at case and event level in comparison to consumers. To ascertain that the reporting differences between consumers and physicians were statistically significant and were not due to chance, the difference between two independent proportions (with unequal sample size per group) sample size calculation was performed. Hence, the following sample size formula was employed: $n_1 = [\sqrt{p}(1-p)\,(1 + 1/k)\, z_{\alpha/2} + \sqrt{p_1(1-p_1) + p_2(1-p_2)/k}\, z_{ß}]^2 /(p_1-p_2)^2$, $n_2 = kn_1$ (see Ott & Longnecker, 2008), where $z_{\alpha/2}$ corresponds to a two-tailed significance level and is the critical value of the Normal distribution at α/2 (for a confidence level of 95%, α is 0.05 and the critical value is

1.96); Z_β corresponds to power and is the critical value of the Normal distribution at β (for a power of 80%, β is 0.2 and the critical value is 0.84); p_1 and p_2 were the expected sample proportions of the two groups of participants (consumer versus physician); and, k = ratio of larger group (consumers) to smaller group (physicians) of participants (see Ott & Longnecker, 2008).

A total of 87,807 ADR reports and 143,399 ADRs (consumer [83,009 ADRs] and physician [60,390 ADRs]) for the 2nd quarter of the year 2016 were analyzed. Spontaneous ADRs were reported by consumers and physicians with α = 0.05 (two-tailed) and the minimum required power level β = 0.80. For the difference between two independent proportions (with unequal sample size per group) analysis, G*Power was used to calculate the appropriate sample size based on the following criteria: *z*-test (a two-tailed test)*;* proportion for group 2 (consumers = 83,009/143,399 =.58); proportion for group 1 (physicians = 60,390/143,399 =.42); an allocation ratio of n_2/n_1, which is the ratio of larger group (consumers) to smaller group (physicians) of participants (83,009/60,390 = 1.37); an 80% power; and, an alpha level of .05. Based on the aforementioned assumptions, the appropriate total sample size needed for this particular test was 312, with 132 and 180 sample sizes needed for each consumer and physician group, respectively. Hence, the total sample size of 312 represented the minimum sample size needed for sufficient power.

Data Collection Procedures

This study included ADRs at case and event level that were submitted by consumers and physicians to the FDA via the FDA's FAERS database, which contains

the latest quarterly data files that were extracted for analysis. Data were collected subsequent to Institutional Review Board (IRB) approval in April 2018. The data containing the spontaneous ADR reports from the FAERS database were accessed and downloaded from the quarterly data file data selection time period: 01 April 2016 through 30 June 2016. The quarterly data files were available in two different formats: ASCII and SGML. In the ASCII files, the data elements were separated from each other by a "$" sign ("$ delimited") (FDA, 2016b). The SGML files conform to the ICH guidelines regarding transmission of individual case safety reports (FDA, 2016b). The data files included, but were not limited to, the following data: demographic and administrative information and the initial report image identification (ID) number; drug information from the case reports; reaction information from the reports; patient outcome information from the reports; information on the source of the reports; and, a "README" file containing a description of the files (FDA, 2016).

The spontaneous ADR reports were initially collected in the form of raw data via the MedWatch program, which is the FDA's Safety Information and AE Reporting Program that gathers reports of ADRs, medication or product use errors, and quality issues associated with human medical products, medical devices, vaccines and other biologics, dietary supplements, and cosmetics (FDA, 2017). Under MedWatch, HCPs, including physicians, and consumers may voluntarily submit reports to the FDA when they discover an issue or an adverse reaction with a drug, medical device, biologic, or other FDA-regulated products. Subsequently, these data were thoroughly cleaned, recorded, recoded, redacted, and stored as an electronic file in the FAERS database by

the FDA for accessibility (Hyman, 2000). Since the data had been previously coded and redacted, the data were anonymously encrypted in form, with no personal identifiers present. The data were in a line listing format in which a unique number known as the individual safety report (ISR) was assigned for identifying an AER report (FDA, 2015). A case number, which consists of one or more ISR, was assigned for identifying an AERS case, and served as a link to the necessary variables for research. Once the ADR data had been collected, spontaneous reports from consumers and physicians were compared for ADRs at case and event level.

Instrumentation and Operationalization of Constructs

ADRs were coded using MedDRA, and ADRs at case and event level were determined by the Council for International Organizations of Medical Sciences criteria (EMEA, 1995). All ADR terms had been previously coded to the PT within FAERS, and the PT was used to obtain the correct SOC. The codes for outcomes in the FAERS ASCII files were as follows: DE = Death; LT = Life-Threatening; HO = Hospitalization−Initial or Prolonged; DS = Disability; CA = Congenital Anomaly; RI = Required Intervention to Prevent Permanent Impairment/Damage; and, OT = Other. SOC was retrieved from the quarterly output and the PT was entered into the MedDRA database (if necessary) to determine SOC category. Reporter demographics were coded M= male and F= female or NR= Not Reported.

The reporters in this study were consumers (non-HCPs) and physicians, and the codes for reporter's type of occupation in the AERS ASCII files were as follows: MD = Physician and CN = Consumer.

Data Analysis Plan

In this study, I analyzed secondary data, specifically, ADRs that were submitted by consumers and physicians to the FDA, from the FAERS database, which contains quarterly data files that were extracted for analysis (FDA, 2016b). The data containing the spontaneous ADR reports from the FAERS database were accessed and downloaded from the quarterly data file data selection time period: 01 April 2016 through 30 June 2016. Once the ADR data had been collected, spontaneous reports from consumers and physicians were assessed. A total of 87,807 ADR reports (cases) and 143,399 ADRs (events) (consumer [83,009 ADRs] and physician [60,390 ADRs]) reported by consumers and physicians for the 2nd quarter of the year 2016 (01 April 2016 through 30 June 2016) were analyzed. The distinction between ADR reports and ADRs could be made in the following manner: ADR reports (or cases) are singular and can have multiple ADRs (or events) within them. In my study, 87,807 ADR cases referred to the number of cases that contain 143,399 events. The numbers in brackets signifies that consumers reported 83,009 events while physicians reported 60,390 events (please note: the remaining number of events that were reported from other sources that are not relevant to this study include, but are not limited to, pharmacists, other HCPs, and lawyers). Spontaneous US ADRs were analyzed in an effort to compare consumer and physician reporting of ADRs. These reports were examined on the basis of the reporter type and patient outcome (which determines the severity of the event).

The FAERS reporting system data contained seven files. The element that connected the files data was the Primary ID. The files were as follows: Demographic,

Outcome, Drug, Reaction, Report Sources, Indication, and Therapy. The "Outcome" file contains all outcomes, in other words "all" events, that occurred to a patient after drug administration and reported by a medical doctor or a consumer. The "Demographic" file contained and described the cases, which were identified through IDs (every case had a single ID). As for a single patient (a case) could be reported with one or more outcomes (events), there were IDs that were associated with more than one outcome. In an analysis focused on cases and outcomes simultaneously, only those IDs that had a single outcome could be used (FDA, n.d.).

Prior to commencing secondary data collection, approval from the IRB was sought and obtained (04-18-18-0523354). Upon receipt of approval, the quarterly data file data as described above were extracted from the FDA's FAERS database (April 2018).

The following research questions will be addressed:

Primary Research Questions

Research Question 1A: Is there a statistically significant difference in the distribution of ADRs by reporter (consumer versus physician) and patient outcome?

$H_0$1A: There is no statistically significant difference in the distribution of ADRs by reporter (consumer versus physician) and patient outcome.

H_a1A: There is a statistically significant difference in the distribution of ADRs by reporter (consumer versus physician) and patient outcome.

Research Question 1B: Is there a statistically significant difference in the distribution of ADRs by reporter when comparing by severity of outcome?

$H_0$1B: There is no statistically significant difference in the distribution of ADRs by reporter when comparing by severity of outcome.

H_a1B: There is a statistically significant difference in the distribution of ADRs by reporter when comparing by severity of outcome.

Exploratory Research Questions

Research Question 2: Is there a statistically significant difference in the distribution of ADRs by reporter (consumer versus physician) and SOC?

$H_0$2: There is no statistically significant difference in the distribution of ADRs by reporter (consumer versus physician) and SOC.

H_a2: There is a statistically significant difference in the distribution of ADRs by reporter (consumer versus physician) and SOC.

Research Question 3: Is there a statistically significant difference in the distribution of ADRs by reporter (consumer and physician) and demographics?

$H_0$3: There is no statistically significant difference in the distribution of ADRs by reporter (consumer versus physician) and demographics.

H_a3: There is a statistically significant difference in the distribution of ADRs by reporter (consumer versus physician) and demographics.

The primary objective in this study was to test the association between the type of reporter reporting the ADR and patient outcome, with exploratory objectives of evaluating total ADRs (events) and total ADR cases (reports) reported by consumers and physicians versus SOC and reporter demographics. Once data were downloaded from the FDA's FAERS database, they were analyzed for type of reporter and patient outcome, as

well as SOC, and reporter demographics. This study contains several tables, specifically for the distribution of ADRs based on patient outcome, as well as SOC and reporter demographics. The independent variable was the reporter (consumer versus physician whereas patient outcome, SOC, and reporter demographics was the dependent variables. The unit of analysis was the total number of ADR cases and reported ADRs. A statistical software package (SPSS v.25) was employed to manage and set up the data, as well as to perform bivariate and multivariate analyses. Bivariate analyses, specifically, the chi-square test for independence, *OR*, and logistic regression was conducted to assess statistically significant differences between the categorical independent variable (the reporter) and the seven different levels of the categorical dependent variable (patient outcome) (see Ott & Longnecker, 2008). The seven different levels of the patient outcome variable were as follows: death (DE); LT; initial or prolonged existing inpatient hospitalization (HO); persistent or significant disability or incapacity (DS); a congenital anomaly or birth defect (CA); necessary intervention to inhibit permanent damage (RI); or, other (important) medical outcome, event, or reaction (OT) (FDA, 2016b). As previously mentioned, SOC was categorized by PT within MedDRA. Reporter demographics were categorized as male versus female since this information was readily available within the dataset.

In this study, I employed quantitative methods, which are frequently used to analyze spontaneous data (see Aagaard et al., 2009). Chi-square test and *OR*s, as the most appropriate statistical methods, were conducted unless otherwise specified to investigate the relationship between reporter and reported ADRs. The chi-square test, as the most

appropriate analytical strategy to employ in this study, was used to test for association between two categorical variables (see Gerstman, 2008). The statistical significance in association between reporter and total number of reported ADRs, as well as patient outcome, were shown with a *p*-value of less than 0.006. The *OR*, which is another measure of association for categorical data, as well as an additional appropriate method to employ in this study, was also used in conjunction with logistic regression models (see Gertsman, 2008). The chi-square test illustrated that an association existed, while the *OR* displayed the strength of the association. The confidence intervals were calculated at 95% for each *OR*.

After bivariate analyses were conducted, the results were presented via tables. It is important to mention that the tables presented had to be clear and concise. Table titles had to be understandable without reading the chapter text (see Diether, 2016). All relevant results were noted, even those that were contrary to the alternative hypotheses, or those that tended to distract from clear determinations. Furthermore, statements of the results were rendered without any implication, speculation, assessment, evaluation, or interpretation (see van Hunsel et al., 2009). In conducting research for this study, the area of examination and the research questions allowed me to determine the research method that was be followed. The research method entailed the manner in which the researcher gathered, assessed, and deciphered the data in this study (see Creswell, 2014). One of the most important aspects of secondary data analysis is the implementation of theoretical knowledge and conceptual skills within existing data in an effort to address the research questions. Since a secondary data analysis was performed, which is a systematic method

with procedural and evaluative steps, this process was commenced with the development of the research questions, which enabled identification of datasets for analysis (see Creswell, 2014).

The main research question was as follows: is there a statistically significant difference in the distribution of ADRs by reporter (consumer versus physician) and patient outcome? To address this research question, seven logistic regression analyses were conducted in which the dependent variable, patient outcome, were dichotomized for seven distinct categories: fatal and non-fatal; LT and non-LT; hospitalized and non-hospitalized; with and without the outcome of initial or prolonged disability; with and without the outcome of congenital anomaly; with and without the outcome of required intervention to prevent permanent impairment/damage; and, with and without the outcome of other (important medical event). The results were presented in a tabular fashion, thereby producing several tables comparing consumer versus physician to the aforementioned seven distinct categories of the dependent variable patient outcome. Secondary questions included reporter versus SOC and reporter demographics.

Threats to Validity

Since the correlational cross-sectional research design was utilized, the secondary data led to under-reporting and recall bias, which yielded misclassification or information bias (see Gualano et al., 2015). Furthermore, the use of this particular design only provided a rather limited amount of information of the sample (see Gualano et al., 2015). The correlational cross-sectional research design presented challenges regarding the determination of causal relationships between the distribution of case and event level

ADRs by reporter (consumer versus physician) and patient outcome, SOC, and reporter demographics. The correlational cross-sectional design contained several limitations that were significant to examine, including internal validity, which was only germane to such a design as experimental that attempts to establish a causal relationship (see Frankfort-Nachmias, 2014). Since researchers do not alter the independent variables, they must render logical or theoretical inferences in terms of the direction of the causation by taking into account that correlation between variables does not imply causation (see Field, 2013). Hence, it is challenging for researchers to make causal inferences.

To overcome several methodological limitations of correlational cross-sectional designs, researchers frequently employ statistical analyses, including cross-tabulation, for the purpose of organizing, describing, and summarizing their observations, as well approximating some of the processes inherent within experimental designs (see Frankfort-Nachmias, 2014). When the data are categorized, researchers are able to make contrasts between the categorical groups (see Frankfort-Nachmias, 2014).

Despite the disadvantages of correlational cross-sectional research designs, in particular, the threat to internal validity, these designs have advantages inherent within them. Despite this design's internal weaknesses, it manages the threats to external validity (see Campbell & Stanley, 1963). However, researchers using the cross-sectional design must sacrifice internal validity in order to achieve greater generalizability or external validity (see Research Design, n.d.). Correlational cross-sectional designs usually have a high level of external validity, which enables researchers to generalize their findings to a larger population (see Carlson & Morrison, 2009). Furthermore, these

designs enable the researchers to perform studies in natural, real-life settings utilizing probability samples, thereby increasing the external validity of their studies (see Frankfort-Nachmias, 2014).

Additionally, correlational cross-sectional designs do not require the random assignment of individual cases to comparison groups, which is particularly useful in situations where the random assignment of individuals to a treatment or control group may be unethical or improbable (see Frankfort-Nachmias, 2014). Although correlational cross-sectional designs prevent researchers from making causal inferences, these non-experimental designs nonetheless play a pivotal role in research efforts by allowing researchers to establish a statistical relationship between variables and, subsequently, paving the way for future studies in which researchers can utilize experimental designs to confirm the statistical relationship as a causal one (Price, 2012).

Ethical Procedures

Given that the ADR data from the FDA's FAERS database have been de-identified, it is not possible to trace back to the consumers and physicians from whom the data were originally collected. Since these data will no longer identifiable, the subsequent use of these data would not constitute research on human subjects (University of Chicago, 2014). Moreover, since this study employed secondary data analysis, recruitment of the participants were not made, especially those in vulnerable populations, including, but not limited to the following: minors (age 17 and under); adult students of the researcher; subordinates of the researcher; patients of the researcher; nursing home residents; prisoners; mentally impaired or disabled individuals; emotionally impaired or

disabled individuals; physically impaired or disabled individuals; individuals residing within the US who may not be fluent in English; undocumented immigrants; victims/witnesses of violent crime or other trauma (e.g. natural disasters); active duty military personnel; and, any other individuals who may not be able to protect their own rights or interest (Walden University, n.d.).

Furthermore, this study did not involve the following sensitive topics, which would pose ethical challenges in doctoral research and, consequently, entail early ethics consultation with the Walden University IRB: questions about professional work that might lead to disclosure of behavior(s) or standpoints that may lead to someone being terminated from their position or passed over for promotion (e.g., lack of compliance with policy, disagreement with leadership decisions, etc.); questions regarding substance use, mental state, or violence that may necessitate a referral or intervention to eschew violence to the participant (addiction, severe depression, suicidality, eating disorders, bullying, physical threats, etc.); illicit activities in which the participant may inculpate him or herself via research data (e.g. illegal drug use, illegal immigration, child neglect, insider trading, harassment, assault, bullying, cyberbullying, etc.); personal issues that may cause anxiety to an individual if framed in a judgmental, non-inclusive, dismissive, or otherwise insensitive fashion (ethnicity, body image, religion, etc.); race or ethnicity as a variable or inclusion criterion; and, outcomes of a new intervention or program in an education, psychological, or clinical environment (Walden University, n.d.).

While doctoral research and other projects that necessitate secondary data analysis do not entail interactions or interventions with humans, they still require IRB review, as

per the Code of Federal Regulations 45 CFR 46.102(f), which defines 'human subject' as a living individual about whom a researcher collects data via intervention or interaction with the individual or identifiable private information for the purpose of research (U.S. Department of Health & Human Services, 2010). The secondary data analysis does not require IRB review when it falls outside of the regulatory definition of research involving human subjects (University of Chicago, 2014). Although secondary data analysis in this study will not jeopardize the privacy of the participants in the manner that primary data collection and analysis may (Purdue Online Writing Lab, 2016), the rights of participants will still need to be protected by ensuring that all identifiers have been removed from the dataset (Walden University, n.d.). Furthermore, since the data from the FAERS database was readily available to the public, no additional approval (other than Walden University IRB approval) was needed. Hence, prior to commencing secondary data collection, approval from the Walden University IRB was sought and obtained (04-18-18-0523354).

Summary

This study was quantitative in nature, and the cross-sectional research design was employed. Secondary analysis of these data was performed by utilizing the chi-square test, as well as the *OR*. I discussed the methodology and analytical strategies in this chapter and provided greater insight into the significance of including consumer reports within SRSs, as well as comparing the rates of case and event level ADR reporting between consumers and physicians for the purpose of increasing awareness of the rate of under-reporting. The ADR data was obtained from the FDA's FAERS database in order to assess ADRs submitted as reports by consumers and physicians and patient outcome,

SOC, and reporter demographics. Chi-square test of association, *OR*, and logistic regression analyses was employed for comprehending the nature of these categorical secondary data. Statistical analysis was conducted via a statistical software package (SPSS v.25). Next, in Chapter 4, I provide the results of the study. Lastly, in Chapter 5, I provide a discussion of the results, study limitations, recommendations for future research, and the implications for social change.

Chapter 4: Results

Introduction

The purpose of this quantitative study was to examine whether a statistically significant difference exists in the distribution of ADRs within the FAERS database by reporter (consumer versus physician) and patient outcome, while also evaluating reporter differences in SOC and reporter demographics. The reporter was the independent variable consisting of two levels: consumer and physician. Patient outcome, SOC, and reporter demographics were the dependent variables. The unit of analysis was the total number of ADR cases and reported ADRs. Within the exploratory research questions, I evaluated the total number of ADR cases and reported ADRs of reporters (consumer and physician; independent variable) compared to SOC (dependent variable), and I also evaluated the total number of ADR cases and reported ADRs of reporters (consumer and physician) compared to demographics. The findings of this study are represented in tables in this chapter. The following research questions and hypotheses were addressed during the analysis:

Primary Research Questions

Research Question 1A: Is there a statistically significant difference in the distribution of ADRs by reporter (consumer versus physician) and patient outcome?

$H_0$1A: There is no statistically significant difference in the distribution of ADRs by reporter (consumer versus physician) and patient outcome.

H_a1A: There is a statistically significant difference in the distribution of ADRs by reporter (consumer versus physician) and patient outcome.

Research Question 1B: Is there a statistically significant difference in the distribution of ADRs by reporter when comparing by severity of outcome?

$H_0$1B: There is no statistically significant difference in the distribution of ADRs by reporter when comparing by severity of outcome.

H_a1B: There is a statistically significant difference in the distribution of ADRs by reporter when comparing by severity of outcome.

Exploratory Research Questions

Research Question 2: Is there a statistically significant difference in the distribution of ADRs by reporter (consumer versus physician) and SOC?

$H_0$2: There is no statistically significant difference in the distribution of ADRs by reporter (consumer versus physician) and SOC.

H_a2: There is a statistically significant difference in the distribution of ADRs by reporter (consumer versus physician) and SOC.

Research Question 3: Is there a statistically significant difference in the distribution of ADRs by reporter (consumer and physician) and demographics?

$H_0$3: There is no statistically significant difference in the distribution of ADRs by reporter (consumer versus physician) and demographics.

H_a3: There is a statistically significant difference in the distribution of ADRs by reporter (consumer versus physician) and demographics.

Data Collection

I conducted the analysis by using data publicly available from the FAERS database. The AEs and medication error were coded in the FAERS database to terms in

the MedDRA terminology. The FAERS database contained its data in seven tables linked through cases reports identifications (IDs), which could be found within the following data tables: Demographic, Outcome, Report sources, Reaction, Drug, and Therapy and Indication (FDA, n.d.).

The data employed in the current analysis covered the cases of AEs reported or updated in the second quarter of 2016 (from 01 April 2016 to 30 June 2016), and the analysis was performed from the case perspective (case-based analysis) and events perspective (event-based analysis). This type of approach was necessary due to the fact that a significant number of cases are associated with multiple events. Consequently, the analysis based on ADR cases was performed using only those case IDs that were associated with only one event. Therefore, the samples used in the analysis of cases and events had different sizes. Furthermore, since the number of events is greater than the number of cases, the set of case IDs that was used to build the dataset with all necessary variables and observations for the statistical analyses (along with the associated events from the "outcome" table) was used as a starting point in the development of the dataset.

With regards to the analysis of ADRs by reporter and SOC, the drug consumption outcomes and, more precisely, their associated reactions, were grouped according to the SOC by matching the PTs for reactions from the FAERS "Reaction" table. Subsequently, the matched terms were coded using the MedDRA terminology with the outcomes from FAERS "Outcome" table based on the case identifiers (IDs). The conversion of the existent PTs into SOCs was made using the 2016 release, which covers the first half of the year, from The Protect Adverse Drug and Product Reaction Database, which is

provided by The European Medicines Agency and PROTECT Partners (FDA, n.d.). The above-mentioned database contains drugs names (trade and active ingredient name), the PTs for reactions (coded via MedDRA), and the SOC group for each PT. Given that not all PTs from the "Reaction" table could be matched with a SOC group based on the PTs from The Protect Adverse Drug and Product Reaction Database, and since the manual matching may lead to bias (systematic or random), the analysis was limited to those PTs for which the exact SOC group can be identified. Concurrently, since the intended analysis was event outcome-based and multiple reactions (PTs) could be associated with one or more outcomes, the analysis was also limited to only those case IDs associated with a single reaction (PT) reported. Hence, this particular analysis was based on approximately 25% of the total reported ADRs, namely, cases (IDs) with a single reaction (PT) and one or more events.

All *p*-values were calculated using the chi-square (χ^2) test and a significance level of .006. Given the number of comparisons of a similar nature, the issue of multiple comparisons arose. Furthermore, since multiple hypotheses were tested, the chance of incorrectly rejecting a null hypothesis (Type I error) was increased (see Mittelhammer, Judge, & Miller, 2000). Therefore, to counteract these issues, I employed the Bonferroni correction, which tested each individual hypothesis at a significance level of α/m, where α was the desired overall alpha level and m was the number of hypotheses (see Miller, 1966). In this study, I adjusted for multiple comparisons by dividing my criterion of significance (0.05) by the number of tests (8), which yielded 0.006 (i.e. 0.05/8=0.006).

Subsequently, I employed this number (0.006) as a benchmark to determine whether any comparison was statistically significant.

The same significance level was used for *OR* confidence intervals. The *p*-value from the chi-square test was calculated for only the categorical data contained in the 2x2 contingency tables. Therefore, the test was conducted to determine whether statistically significant differences exist between two groups. A significant *p*-value (less than .006) indicated that a statistically significant difference exists between consumers and physicians in reporting of an ADR case or event. The *OR* represented how much more likely consumers were to report an ADR case or event in comparison to physicians. A post-hoc power analysis was also computed. For the difference between two independent proportions analysis, G*Power was used to calculate the power based on the following criteria: *z*-test (a two-tailed test)*;* a medium effect size of 0.33; proportion for group 1 (physicians = 60,390/143,399 = .42); an alpha level of .05; a sample size of 60,390 for group 1, which represents physicians; and, a sample size of 83,009 for group 2, which represents consumers. Based on the aforementioned criteria, the post-hoc power for this analysis was 1.0.

Results

Research Question 1A

The first part of the research question, I examined whether a statistically significant difference exists in the distribution of ADRs based on reporter (consumer versus physician) and patient outcome. The case-based and event-based analyses were performed, and the chi-square test was conducted for both types of analyses. Since the

response variable (patient outcome) contains seven categories, a reference category is needed to compute *OR*s and compare reporter and patient outcome. Therefore, other medical event (OME) was selected as a reference category; the results are shown in Tables 1 and 2. As can be seen in Table 1, for the case-based analysis, the results from the chi-square test revealed a statistically significant association between reporter and patient outcome, χ^2 (6, N = 87,807) = 406.74, p <.001, ϕ_C = .07. Cramer's V value of .07, which was less than a value of .20, signified a relatively weak relationship between reporter and patient outcome. The *ORs* for the six categories of patient outcome (congenital, fatal, disability, hospitalization, intervention, and LT) were computed and compared to the reference category of OME.

For the patient outcome category of congenital, the odds ratio for reporter (*OR* = 0.39) was less than 1, thereby indicating a negative relationship between reporter and patient outcome category of congenital. The odds of consumers reporting congenital ADR reports versus OME ADR reports were 0.39 times the same odds among physicians.

For the patient outcome category of fatal, the odds ratio for reporter (*OR* = 0.86) was less than 1, thereby indicating a negative relationship between reporter and patient outcome category of fatal. The odds of consumers reporting fatal ADR reports versus OME ADR reports were 0.86 times the same odds among physicians.

For the patient outcome category of disability, the odds ratio for reporter (*OR* = 0.77) was less than 1, thereby indicating a negative relationship between reporter and

patient outcome category of disability. The odds of consumers reporting disability ADR reports versus OME ADR reports were 0.77 times the same odds among physicians.

For the patient outcome category of hospitalization, the odds ratio for reporter (*OR* = 0.87) was less than 1, thereby indicating a negative relationship between reporter and patient outcome category of fatal. The odds of consumers reporting hospitalization ADR reports versus OME ADR reports were 0.87 times the same odds among physicians.

For the patient outcome category of intervention, the odds ratio for reporter (*OR* = 0.13) was less than 1, thereby indicating a negative relationship between reporter and patient outcome category of intervention. The odds of consumers reporting intervention ADR reports versus OME ADR reports were 0.13 times the same odds among physicians.

For the patient outcome category of LT, the odds ratio for reporter (*OR* = 0.29) was less than 1, thereby indicating a negative relationship between reporter and patient outcome category of LT. The odds of consumers reporting LT ADR reports versus OME ADR reports were 0.29 times the same odds among physicians. Based on these results, the null hypothesis would be rejected in favor of the alternative hypothesis.

Table 1 also illustrates the distribution of ADR reports (cases) by reporter and the seven categories of patient outcome. A total of 87,807 reports were received for the 01 April 2016 through 30 June 2016 period of the quarterly data file data selection time period: 01 April 2016 through 30 June 2016. According to Table 1, in comparison to

physicians, consumers reported more ADR reports for the following categories of patient outcome: death, disability, hospitalization, and OME.

Table 1

Distribution of Adverse Drug Reactions (ADRs) Reports in the US (01 April 2016 through 30 June 2016) by Reporter and Patient Outcome

Reporter Type	Congenital *N*	Death *N*	Disability *N*	Hospitalization *N*	Intervention *N*	Life-threatening *N*	Other Medical Event *N*	Total *N*
Both Reporters	181	7,903	978	26,416	12	753	51,564	87,807
Consumer	70 (38.7)	4,564 (57.8)	539 (55.1)	15,362 (58.2)	2 (16.7)	236 (31.3)	3,1683 (61.4)	52,456 (59.7)
Physician	111 (61.3)	3,339 (42.2)	439 (44.9)	11,054 (41.8)	10 (83.3)	517 (68.7)	19,881 (38.6)	3,5351 (40.3)

Note. $\chi^2 = 406.74$, $df = 6$, $p < .001$. Numbers in parentheses indicate column percentages. $p < .006$

As can be seen in Table 2, for the event-based analysis, the results from the chi-square test revealed a statistically significant association between reporter and patient outcome, χ^2 (6, N = 143,399) = 1,299.37, $p < .001$, $\phi_C = .09$. The Cramer's V value of .09, which was less than a value of .20, signified a relatively weak relationship between reporter and patient outcome. The *ORs* for the six categories of patient outcome (congenital, fatal, disability, hospitalization, intervention, and LT) were computed and compared to the reference category of OME.

For the patient outcome category of congenital, the odds ratio for reporter (*OR* = 0.58) was less than 1, thereby indicating a negative relationship between reporter and patient outcome category of congenital. The odds of consumers reporting congenital ADRs versus OME ADRs were 0.58 times the same odds among physicians.

For the patient outcome category of fatal, the odds ratio for reporter (*OR* = 0.89) was less than 1, thereby indicating a negative relationship between reporter and patient outcome category of fatal. The odds of consumers reporting fatal ADRs versus OME ADRs were 0.89 times the same odds among physicians.

For the patient outcome category of disability, the odds ratio for reporter (*OR* = 0.76) was less than 1, thereby indicating a negative relationship between reporter and patient outcome category of disability. The odds of consumers reporting disability ADRs reports OME ADRs were 0.76 times the same odds among physicians.

For the patient outcome category of hospitalization, the odds ratio for reporter (*OR* = 0.85) was less than 1, thereby indicating a negative relationship between reporter and patient outcome category of fatal. The odds of consumers reporting hospitalization ADRs versus OME ADRs were 0.85 times the same odds among physicians.

For the patient outcome category of intervention, the odds ratio for reporter (*OR* = 0.12) was less than 1, thereby indicating a negative relationship between reporter and patient outcome category of intervention. The odds of consumers reporting intervention ADRs versus OME ADRs were 0.12 times the same odds among physicians.

For the patient outcome category of LT, the odds ratio for reporter (*OR* = 0.33) was less than 1, thereby indicating a negative relationship between reporter and patient outcome category of LT. The odds of consumers reporting LT ADRs versus OME ADRs were 0.33 times the same odds among physicians. Based on these results, the null hypothesis would be rejected in favor of the alternative hypothesis.

Table 2 also shows the distribution of ADRs (events) by reporter and patient outcome. A total of 143,399 ADRs were received for the 01 April 2016 through 30 June 2016 period of the quarterly data file data selection time period: 01 April 2016 to 30 June 2016. According to Table 2, in comparison to physicians, consumers reported more ADRs for the following categories of patient outcome: death, disability, hospitalization, and OME.

Table 2

Distribution of Adverse Drug Reactions (ADRs) in the US (01 April 2016 through 30 June 2016) by Reporter and Patient Outcome

Reporter Type	Congenital *N*	Death *N*	Disability *N*	Hospitalization *N*	Intervention *N*	Life-threatening *N*	Other Medical Event *N*	Total *N*
Both Reporters	507	16,178	2,866	46,149	19	4,154	73,526	143,399
Consumer	237 (46.7)	8,346 (57.8)	1,535 (53.6)	26,074 (56.5)	3 (15.8)	1,394 (33.6)	44,420 (60.4)	83,009 (57.9)
Physician	270 (53.3)	6,832 (42.2)	1,331 (46.4)	20,075 (43.5)	16 (84.2)	2,769 (66.4)	29,106 (39.6)	60,390 (42.1)

Note. $\chi^2 = 1{,}299.37$, $df = 6$, $p < .001$. Numbers in parentheses indicate column percentages.
$p < .006$

Research Question 1B

The second part of the research question, I examined whether a statistically significant difference exists in the distribution of ADRs based on reporter (consumer versus physician) and severity of patient outcome. For the severity of patient outcome analysis, I grouped patient outcomes into a dichotomous variable by severity (serious versus nonserious) and tested this first. For this particular analysis, the seven categories of the patient outcome variable were grouped into a dichotomous variable by severity (serious versus nonserious) and the relationship was first tested. The reason for grouping

the seven categories of patient outcome variable into two categories is to create a severity variable consisting of two levels: serious and nonserious in order to determine whether there is a statistically significant association between reporter and severity of patient outcome.

As shown in Tables 3 and 4, the serious outcomes ("Serious" column) were grouped as death and LT ADRs, and the nonserious outcomes ("Nonserious" column) were grouped as hospitalization, disability, congenital anomaly, intervention (required to prevent permanent impairment/damage), and OME. The case-based and event-based analyses were performed and the chi-square test was conducted for both types of analyses; the results are shown in Tables 3 and 4. As can be seen in Table 3, for the case-based analysis, the results from the chi-square test revealed a statistically significant association between reporter and patient outcome severity, χ^2 (1, N = 87,807) = 73.39, p <.001, ϕ_C =.03. The Cramer's V value of .03, which was less than a value of .20, signified a relatively weak relationship between reporter and severity of patient outcome. The odds ratio for reporter (OR = 0.82) was less than 1, thereby indicating a negative relationship between reporter and patient outcome severity. The odds of consumers reporting serious ADR reports versus nonserious ADR reports were 0.82 times the same odds among physicians. Based on these results, the null hypothesis would be rejected in favor of the alternative hypothesis.

Table 3 also illustrates the distribution of ADR reports (cases) by reporter and patient outcome severity. A total of 87,807 reports were received for the 01 April 2016 through 30 June 2016 period of the quarterly data file data selection time period: 01 April

2016 through 30 June 2016. Of these, consumers reported 52,456 (59.7%) ADR reports and physicians reported 35,351 (40.3%) ADR reports. Of the total ADR reports, 8,656 reports were serious and 79,151 reports were nonserious. Of the 8,656 serious reports, consumers reported 4,800 (55.5%) serious reports and physicians reported 3,865 (44.5%) serious reports. Therefore, consumers reported more ADR reports and more serious ADR reports in comparison to those reported by physicians.

Table 3

Distribution of Adverse Drug Reactions (ADRs) Reports in the US (01 April 2016 through 30 June 2016) by Reporter and Patient Outcome Severity

Patient Outcome Severity	Serious *N*=8,656	Nonserious *N*= 79,151	Total *N*= 87,807
Consumer	4,800 (55.5)	47,656 (60.2)	52,456 (59.7)
Physician	3,856 (44.5)	31,495 (39.8)	35,351 (40.3)

Note. χ^2 = *73.39, *df* = 1, *OR* = 0.82. *p* <.001. Numbers in parentheses indicate column percentages. *p* <.006

According to Table 4, for the event-based analysis, the results from the chi-square test revealed a statistically significant association between reporter and patient outcome severity, χ^2 (1, *N* = 143,399) = 249.18, *p* <.001, ϕ_C =.04. The Cramer's V value of .04, which was less than a value of .20, signified a relatively weak relationship between reporter and severity of patient outcome. The odds ratio for reporter (*OR* = 0.79) was less than one, thereby indicating a negative relationship between reporter and patient outcome severity. The odds of consumers reporting serious ADRs versus nonserious ADRs were

0.79 times the same odds among physicians. Based on these results, the null hypothesis would be rejected in favor of the alternative hypothesis.

Table 4 also shows the distribution of ADRs (events) by reporter and patient outcome severity. A total of 143,399 ADRs were received for the 01 April to 30 April 2016 period of the quarterly data file data selection time period: 01 April 2016 to 30 June 2016. Of these, consumers reported 83,009 (57.9%) ADRs and physicians reported 60,390 (42.1%) ADRs. Of the total ADRs, 20,332 ADRs were serious and 123,067 ADRs were nonserious. Of the 20,332 serious ADRs, consumers reported 10,740 (52.8%) serious ADRs, and physicians reported 9,592 (47.2%) serious ADRs. Therefore, consumers reported more ADRs and more serious ADRs in comparison to those reported by physicians.

Table 4

Distribution of Adverse Drug Reactions (ADRs) in the US (01 April 2016 through 30 June 2016) by Reporter and Patient Outcome Severity

Patient Outcome Severity	Serious *N*=20,332	Nonserious *N*= 123,067	Total *N*= 143,399
Consumer	10,740 (52.8)	72,269 (58.7)	83,009 (57.9)
Physician	9,592 (47.2)	50,798 (41.3)	60,390 (42.1)

Note. $\chi^2 = 249.18$*, $df = 1$, $OR = 0.79$. $p < .001$. Numbers in parentheses indicate column percentages. $p < .006$

Given that the results from the severity of patient outcome analysis were statistically significant, I subsequently proceeded to test specific dyads (e.g. fatal versus non-fatal, LT versus non-LT, etc.) to further characterize the relationship between

reporter and patient outcome. For both the case-based and event-based analyses, seven separate standard logistic regression models (thereby totaling 14 standard logistic regression models for both types of analyses) were generated and run to determine whether reporter was a statistically significant predictor of patient outcome. The results from the logistic regression analyses as shown in Tables 5-18.

As can be seen in Table 5, for the case-based analysis, the results from the logistic regression analysis revealed that reporter was a statistically significant predictor of patient outcome of fatal (Wald $\chi^2 = 14.3$, $p < .001$). The odds ratio for the patient outcome of fatal ($OR = .91$) was less than one, thereby indicating a negative relationship between reporter and patient outcome of fatal. The odds of consumers reporting fatal ADR cases versus non-fatal ADR cases were 0.91 times the same odds among physicians. Based on these results, the null hypothesis would be rejected in favor of the alternative hypothesis.

Table 5

Logistic Regression Predicting Reporting Cases of Patient Outcome of Fatal versus Non-Fatal

	B	SE_B	*OR*	95% CI
Reporters (all)	-.09	.02	.91	[.87,.96]

Note. CI = confidence interval for odds ratio (*OR*). $N = 87{,}807$, $p < .001$.
$p < .006$

As can be seen in Table 6, for the event-based analysis, the results from the logistic regression analysis revealed that reporter was not a statistically significant predictor of patient outcome of fatal (Wald $\chi^2 = .10$, $p = .75$). The odds ratio for the patient outcome of fatal ($OR = 1.00$) was equal to one, thereby indicating that as reporter

changes from 0 (physician) to 1 (consumer), the odds of consumers reporting fatal ADRs versus non-fatal ADRs were no different than the odds among physicians. Based on these results, the null hypothesis would be retained.

Table 6

Logistic Regression Predicting Reporting ADRs Resulting in Patient Outcome of Fatal versus Non-fatal

	B	SE_B	*OR*	95% CI
Reporters (all)	-.005	.02	1.00	[.96, 1.03]

Note. CI = confidence interval for odds ratio (*OR*). $N = 143{,}399$, $p = .75$.
$p < .006$

For testing the relationship between reporting and patient outcome of LT, the ADR cases and events were partitioned into two groups: LT or non-LT. ADR cases and events that resulted in death were excluded for this particular analysis. Therefore, the analysis was limited to only the non-fatal outcomes.

As can be seen in Table 7, for the case-based analysis, the results from the logistic regression analysis revealed that reporter was a statistically significant predictor of patient outcome of LT (Wald $\chi^2 = 230.73$, $p < .001$). The odds ratio for the patient outcome of LT ($OR = .30$) was less than one, thereby indicating a negative relationship between reporter and patient outcome of LT. The odds of consumers reporting LT ADR cases versus non-LT ADR cases were 0.30 times the same odds among physicians. Based on these results, the null hypothesis would be rejected in favor of the alternative hypothesis.

Table 7

Logistic Regression Predicting Reporting Cases of Patient Outcome of Life-Threatening versus Non-Life-Threatening

	B	SE_B	*OR*	95% CI
Reporter (all)	-1.20	.08	.30	[.26,.35]

Note. CI = confidence interval for odds ratio (*OR*). $N = 79{,}904$, $p < .001$.
$p < .006$

As can be seen in Table 8, for the event-based analysis, the results from the logistic regression analysis revealed that reporter was a statistically significant predictor of patient outcome of LT (Wald $\chi^2 = 963.39$, $p < .001$). The odds ratio for the patient outcome of LT (*OR* = .36) was less than one, thereby indicating a negative relationship between reporter and patient outcome LT. The odds of consumers reporting LT ADRs versus non-LT ADRs were 0.36 times the same odds among physicians. Based on these results, the null hypothesis would be rejected in favor of the alternative hypothesis.

Table 8

Logistic Regression Predicting Reporting ADRs Resulting in Patient Outcome of Life-Threatening versus Non-Life-Threatening

	B	SE_B	*OR*	95% CI
Reporter (all)	-1.04	.03	.36	[.33,.38]

Note. CI = confidence interval for odds ratio (*OR*). $N = 127{,}221$, $p < .001$.
$p < .006$

As can be seen in Table 9, for the case-based analysis, the results from the logistic regression analysis revealed that reporter was a statistically significant predictor of patient outcome of hospitalization (Wald $\chi^2 = 39.5$, $p < .001$). The odds ratio for the

patient outcome of hospitalization (*OR* = .91) was less than one, thereby indicating a negative relationship between reporter and patient outcome of hospitalization. The odds of consumers reporting hospitalization ADR cases versus non-hospitalization ADR cases were 0.91 times the same odds among physicians. Based on these results, the null hypothesis would be rejected in favor of the alternative hypothesis.

Table 9

Logistic Regression Predicting Reporting ADR Cases of Patient Outcome of Hospitalization versus Non-Hospitalization

	B	SE_B	*OR*	95% CI
Reporter (all)	-.09	.02	.91	[.88,.94]

Note. CI = confidence interval for odds ratio (*OR*). $N = 87{,}807$, $p < .001$.
$p < .006$

As can be seen in Table 10, for the event-based analysis, the results from the logistic regression analysis revealed that reporter was a statistically significant predictor of patient outcome of hospitalization (Wald $\chi^2 = 53.7$, $p < .001$). The odds ratio for the patient outcome of hospitalization (*OR* = .92) was less than one, thereby indicating a negative relationship between reporter and patient outcome of hospitalization. The odds of consumers reporting ADRs resulting in hospitalization versus those not resulting in hospitalization were 0.92 times the same odds among physicians. Based on these results, the null hypothesis would be rejected in favor of the alternative hypothesis.

Table 10

Logistic Regression Predicting Reporting ADRs Resulting in Patient Outcome of Hospitalization versus Non-Hospitalization

	B	SE_B	*OR*	95% CI
Reporter (all)	-.08	.01	.92	[.90,.94]

Note. CI = confidence interval for odds ratio (*OR*). $N = 143{,}399$, $p < .001$.
$p < .006$

As can be seen in Table 11, for the case-based analysis, the results from the logistic regression analysis revealed that reporter was a statistically significant predictor of patient outcome of disability (Wald $\chi^2 = 8.8$, $p = .003$). The odds ratio for the patient outcome of disability ($OR = .83$) was less than one, thereby indicating a negative relationship between reporter and patient outcome of disability. The odds of consumers reporting disability ADR cases versus non-disability ADR cases were 0.83 times the same odds among physicians. Based on these results, the null hypothesis would be rejected in favor of the alternative hypothesis.

Table 11

Logistic Regression Predicting Reporting ADR Cases of Patient Outcome of Disability versus Non-Disability

	B	SE_B	*OR*	95% CI
Reporter (all)	-.19	.07	.83	[.73,.94]

Note. CI = confidence interval for odds ratio (*OR*). $N = 87{,}807$, $p < .001$.
$p < .006$

As can be seen in Table 12, for the event-based analysis, the results from the logistic regression analysis revealed that reporter was a statistically significant predictor of patient outcome of disability (Wald $\chi^2 = 22.4$, $p < .001$). The odds ratio for the patient outcome of disability (*OR* = .84) was less than one, thereby indicating a negative relationship between reporter and patient outcome of disability. The odds of consumers reporting ADRs resulting in disability versus those not resulting in disability were 0.84 times the same odds among physicians. Based on these results, the null hypothesis would be rejected in favor of the alternative hypothesis.

Table 12

Logistic Regression Predicting Reporting ADRs Resulting in Patient Outcome of Disability versus Non-Disability

	B	SE_B	*OR*	95% CI
Reporter (all)	-.18	.04	.84	[.78,.90]

Note. CI = confidence interval for odds ratio (*OR*). $N = 143{,}399$, $p < .001$.
$p < .006$

As can be seen in Table 13, for the case-based analysis, the results from the logistic regression analysis revealed that reporter was a statistically significant predictor of patient outcome of congenital (Wald $\chi^2 = 31.5$, $p < .001$). The odds ratio for the patient

outcome of congenital (*OR* = .42) was less than one, thereby indicating a negative relationship between reporter and patient outcome of congenital. The odds of consumers reporting congenital ADR cases versus non-congenital ADR cases were 0.42 times the same odds among physicians. Based on these results, the null hypothesis would be rejected in favor of the alternative hypothesis.

Table 13

Logistic Regression Predicting Reporting ADR Cases of Patient Outcome of Congenital versus Non-Congenital

	B	SE_B	*OR*	95% CI
Reporter (all)	-.86	.15	.42	[.31,.57]

Note. CI = confidence interval for odds ratio (*OR*). $N = 87{,}807$, $p < .001$.
$p < .006$

As can be seen in Table 14, for the event-based analysis, the results from the logistic regression analysis revealed that reporter was a statistically significant predictor of patient outcome of congenital (Wald $\chi^2 = 25.5$, $p < .001$). The odds ratio for the patient outcome of congenital (*OR* = .64) was less than one, thereby indicating a negative relationship between reporter and patient outcome of congenital. The odds of consumers reporting ADRs resulting in congenital versus those not resulting in congenital were 0.64 times the same odds among physicians. Based on these results, the null hypothesis would be rejected in favor of the alternative hypothesis.

Table 14

Logistic Regression Predicting Reporting ADRs Resulting in Patient Outcome of Congenital versus Non-Congenital

	B	SE_B	*OR*	95% CI
Reporter (all)	-.45	.09	.64	[.54,.76]

Note. CI = confidence interval for odds ratio (*OR*). $N = 143{,}399$, $p < .001$.
$p < .006$

As can be seen in Table 15, for the case-based analysis, the results from the logistic regression analysis revealed that reporter was not a statistically significant predictor of patient outcome of intervention (Wald $\chi^2 = 6.7$, $p = .01$). The odds ratio for the patient outcome of intervention ($OR = .14$) was less than one, thereby indicating a negative relationship between reporter and patient outcome intervention. The odds of consumers reporting intervention ADR cases versus non-intervention ADR cases were 0.14 times the same odds among physicians. Based on these results, the null hypothesis would be retained.

Table 15

Logistic Regression Predicting Reporting ADR Cases of Patient Outcome of Intervention versus Non-Intervention

	B	SE_B	*OR*	95% CI
Reporter (all)	-2.00	.78	.14	[.03,.62]

Note. CI = confidence interval for odds ratio (*OR*). N = 87,807, p =.01.
p <.006

As can be seen in Table 16, for the event-based analysis, the results from the logistic regression analysis revealed that reporter (Wald $\chi^2 = 10.03$, $p = .002$) was a statistically significant predictor of patient outcome of intervention. The odds ratio for the patient outcome of intervention (*OR* = .14) was less than one, thereby indicating a negative relationship between reporter and patient outcome of intervention. The odds of consumers reporting ADRs resulting in intervention versus those not resulting in intervention were 0.14 times the same odds among physicians. Based on these results, the null hypothesis would be rejected in favor of the alternative hypothesis.

Table 16

Logistic Regression Predicting Reporting ADRs Resulting in Patient Outcome of Intervention versus Non-Intervention

	B	SE_B	*OR*	95% CI
Reporter (all)	-2.00	.63	.14	[.04,.47]

Note. CI = confidence interval for odds ratio (*OR*). N = 143,399, p =.002.
p <.006

As can be seen in Table 17, for the case-based analysis, the results from the logistic regression analysis revealed that reporter was a statistically significant predictor

of patient outcome of OME (Wald $\chi^2 = 150.7$, $p < .001$). The odds ratio for the patient outcome of OME ($OR = 1.19$) was greater than one, thereby indicating a positive relationship between reporter and patient outcome of OME. The odds of consumers reporting OME ADR cases versus non-OME ADR cases were 1.19 times higher than the odds among physicians. Based on these results, the null hypothesis would be rejected in favor of the alternative hypothesis.

Table 17

Logistic Regression Predicting Reporting ADR Cases of Patient Outcome of OME versus Non-OME

	B	SE_B	*OR*	95% CI
Reporter (all)	.17	.01	1.19	[1.16, 1.22]

Note. CI = confidence interval for odds ratio (*OR*). $N = 87{,}807$, $p < .001$.
$p < .006$

As can be seen in Table 18, for the event-based analysis, the results from the logistic regression analysis revealed that reporter was a statistically significant predictor of patient outcome of OME (Wald $\chi^2 = 394.95$, $p < .001$). The odds ratio for the patient outcome of OME ($OR = 1.24$) was greater than one, thereby indicating a positive relationship between reporter and patient outcome of OME. The odds of consumers reporting ADRs resulting in OME versus those not resulting in OME were 1.24 times higher than the odds among physicians. Based on these results, the null hypothesis would be rejected in favor of the alternative hypothesis.

Table 18

Logistic Regression Predicting Reporting ADRs Resulting in Patient Outcome of OME versus Non-OME

	B	SE_B	*OR*	95% CI
Reporter (all)	.21	.01	1.24	[1.21, 1.26]

Note. CI = confidence interval for odds ratio (*OR*). $N = 143{,}399$, $p < .001$.
$p < .006$

Research Question 2

The second research question examined whether a statistically significant difference exists in the distribution of ADRs between reporters and SOC. The event-based analysis was performed, and the chi-square test was conducted; the results are shown in Table 19. As can be seen in Table 19, the results from the chi-square test revealed a statistically significant association between reporter and SOC (25, $N = 36{,}665) = 3{,}157.04$, $p < .001$)). Based on these results, the null hypothesis would be rejected in favor of the alternative hypothesis.

To further characterize the relationship between reporter and SOC, 26 separate logistic regression analyses were performed to determine whether a statistically significant relationship exists between the reporter and each individual SOC. The results from the event-based analyses can be seen in Table 19. According to the results in Table 19, there was a statistically significant difference between the reporter and the ADRs (events) grouped by the SOCs of their associated reactions. Hence, reporter was a predictor for a majority of the SOCs that were analyzed. Moreover, there are ADRs grouped by SOCs that were more frequently reported by consumers in comparison to

those reported by physicians. The odds of consumers reporting ADRs were higher than the odds of physicians for the following six SOCs: Gastrointestinal disorders (*OR* = 2.85, *p* <.001); General disorders and administration site conditions (*OR* = 1.99, *p* <.001); Injury, poisoning and procedural complications (*OR* = 1.36, *p* =.001); Psychiatric disorders (*OR* = 1.26, *p* = .001); Reproductive system and breast disorders (*OR* = 3.30, *p* <.001); and, Vascular disorders (*OR* = 1.44, *p* <.001).

However, the odds of consumers reporting ADRs were lower than the odds of physicians for the following 14 SOCs: Blood and lymphatic system disorders (*OR* = .23, *p* <.001); Cardiac disorders (*OR* = .74, *p* <.001); Endocrine disorders (*OR* = .30, *p* <.001); Hepatobiliary disorders (*OR* =.30, *p* <.001); Immune system disorders (*OR* =.61, *p* <.001); Infections and infestations (*OR* = .85, *p* <.001); Investigations (*OR* = .83, *p* = 0.005); Metabolism and nutrition disorders (*OR* = .52, *p* <.001); Musculoskeletal and connective tissue disorders (*OR* = .50, *p* <.001); Neoplasms benign, malignant and unspecified (*OR* = .61, *p* <.001); Nervous system disorders (*OR* = .78, *p* <.001); Renal and urinary disorders (*OR* = .62, *p* <.001); Respiratory, thoracic and mediastinal disorders (*OR* = .61, *p* <.001); and, Skin and subcutaneous tissue disorders (*OR* = .30, *p* <.001).

An evaluation was not made for the SOC Social circumstances due to the fact that a single event was reported by the consumers and zero events were reported by the physicians. Out of the 25 evaluable SOCs, a statistically significant difference between reporter and SOC was not found for the following five SOCs: Congenital, familial and genetic disorders (*p* = .11); Ear and labyrinth disorders (*p* = .79); Eye disorders (*p* = .37);

Pregnancy, puerperium and perinatal conditions (p = .81); and, Surgical and medical procedures (p = .07).

Table 19 also shows the distribution of ADRs (events) by reporter and SOC. A total of 36,665 ADRs were received for the quarterly data file data selection time period: 01 April 2016 to 30 June 2016.

Table 19

Analysis of Adverse Drug Reactions in the United States (01 April to 30 April 2016) by System Organ Class (SOC) and Reporter

SOC	*Consumers*	*Physicians*	**p*	*OR*	95% CI
Blood and lymphatic system disorders	300 (25.2)	891 (74.8)	<.001	.23	[.21, .27]
Cardiac disorders	1,149 (50.7)	1,118 (49.3)	<.001	.74	[.68, .80]
Congenital, familial and genetic disorders	5 (35.7)	9 (64.3)	.11	.40	[.14, 1.20]
Ear and labyrinth disorders	68 (56.7)	52 (43.3)	.79	.95	[.66, 1.37]
Endocrine disorders	24 (28.9)	59 (71.1)	<.001	.30	[.18, .48]
Eye disorders	367 (56.1)	287 (43.9)	.37	.93	[.79, 1.09]
Gastrointestinal disorders	3,797 (77.6)	1,099 (22.4)	<.001	2.85	[2.65, 3.06]
General disorders and administration site conditions	5,743 (70.3)	2,430 (29.1)	<.001	1.99	[1.89, 2.10]
Hepatobiliary disorders	213 (29.8)	502 (70.2)	<.001	.30	[.25, .35]
Immune system disorders	203 (45.9)	239 (54.1)	<.001	.61	[.51, .74]
Infections and infestations	1,624 (54.4)	1,364 (45.6)	<.001	.85	[.79, .93]
Injury, poisoning and procedural complications	327 (65.0)	176 (35.0)	.001	1.36	[1.13, 1.64]
Investigations	468 (53.2)	411 (46.8)	.005	.83	[.73, .94]
Metabolism and nutrition disorders	358 (42.2)	490 (57.8)	<.001	.52	[.46, .60]
Musculoskeletal and connective tissue disorders	441 (41.0)	635 (59.0)	<.001	.50	[.44, .56]
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	832 (46.2)	967 (53.8)	<.001	.61	[.56, .67]
Nervous system disorders	1,715 (52.2)	1,568 (47.8)	<.001	.78	[.73, .84]
Pregnancy, puerperium and perinatal conditions	15 (55.6)	12 (44.4)	.81	.91	[.43, 1.96]
Psychiatric disorders	580 (63.2)	337 (36.8)	.001	1.26	[1.10, 1.45]
Renal and urinary disorders	475 (46.4)	549 (53.6)	<.001	.62	[.55, .70]
Reproductive system and breast disorders	327 (81.1)	73 (18.3)	<.001	3.30	[2.56, 4.26]

Respiratory, thoracic and mediastinal disorders	846 (46.2)	986 (53.8)	<.001	.61	[.56, .67]
Skin and subcutaneous tissue disorders	282 (29.7)	667 (70.3)	<.001	.30	[.26, .34]
Social circumstances	1 (100)	0 (0)	1.00	NE	NE
Surgical and medical procedures	17 (77.3)	5 (22.7)	.07	2.48	[.91, 6.72]
Vascular disorders	1,032 (66.1)	530 (33.9)	<.001	1.44	[1.29, 1.60]

Note. χ^2 = *3,157.04, *df* = 25, **p* <.006. Numbers in parentheses indicate column percentages. CI = confidence interval for odds ratio (*OR*). NE= Not Evaluable.

Research Question 3

The third research questions examined whether a statistically significant difference exists in the distribution of ADRs by reporter (consumer versus physician) and reporter demographics (gender). The case-based and event-based analyses were performed and the chi-square test was conducted for both types of analyses; the results are shown in Tables 20 and 21. As can be seen in Table 20, for the case-based analysis, the results from the chi-square test revealed a statistically significant association between the reporter and the reporter gender (male versus female) (χ^2 = 118.48, p <.001, N = 77,025). The odds ratio for the reporter gender (*OR* = 1.18) was greater than one, thereby indicating a positive relationship between reporter and reporter gender. The odds of consumers reporting ADR cases were 1.18 times higher for females versus males than the odds of physicians. Moreover, the odds of physicians reporting ADR cases were 1.18 times higher for males versus females than the odds of consumers. Based on these results, the null hypothesis would be rejected in favor of the alternative hypothesis.

Table 20 also illustrates the distribution of ADR reports (cases) by reporter and reporter gender. A total of 77,025 ADR reports were received from the quarterly data file data selection time period: 01 April 2016 to 30 June 2016. Of these, 32,534 reports were

reported by male reporters and 44,491 reports were reported by female reporters. Of the 32,534 reports from male reporters, male consumers reported 18,529 (57%) ADR reports and male physicians reported 14,005 (43%) ADR reports. Of the 44,491 reports from female reporters, female consumers reported 27,075 (60.9%) ADR reports and female physicians reported 17,416 (39.1%) ADR reports. Regardless of gender, consumers reported more ADR reports in comparison to those reported by physicians (59.2% vs 40.8%, respectively).

Table 20

Distribution of Adverse Drug Reactions (ADRs) Reports in the US (01 April 2016 through 30 June 2016) by Reporter and Gender

Reporter	Male *N*= 32,534	Female *N*= 44,491	Total *N*= 77,025
Consumer	18,529 (57.0)	27,075 (60.9)	45,604 (59.2)
Physician	14,005 (43.0)	17,416 (39.1)	31,421 (40.8)

Note. χ^2 = *118.48, *df* = 1, *OR* = 1.18. *p* <.001. Numbers in parentheses indicate column percentages. *p* <.006

As can be seen in Table 21, for the event-based analysis, the results from the chi-square test revealed a statistically significant association between reporter and the reporter gender (χ^2 = 258.47, *p* <.001, *N* = 128,100). The odds ratio for the reporter gender (*OR* = 1.20) was greater than one, thereby indicating a positive relationship between reporter and reporter gender. The odds of consumers reporting ADRs were 1.20 times higher for females versus males than the odds of physicians. Moreover, the odds of physicians reporting ADRs were 1.20 times higher for males versus females than the

odds of consumers. Based on these results, the null hypothesis would be rejected in favor of the alternative hypothesis.

Table 21 also illustrates the distribution of ADRs (events) by reporter and reporter gender. A total of 128,100 ADRs (events) were received from the quarterly data file data selection time period: 01 April 2016 to 30 June 2016. Of these, 56,841 ADR were reported by male reporters and 71,259 ADRs were reported by female reporters. Of the 56,841 ADRs reported by male reporters, male consumers reported 31,212 (54.9%) ADRs and male physicians reported 25,629 (45.1%) ADRs. Of the 72,259 ADRs reported by female reporters, female consumers reported 42,315 (59.4%) ADRs and female physicians reported 28,944 (40.6%) ADRs. Regardless of gender, consumers reported more ADR reports in comparison to those reported by physicians (57.4% vs 42.6%, respectively).

Table 21

Distribution of Adverse Drug Reactions (ADRs) in the US (01 April 2016 through 30 June 2016) by Reporter and Gender

Reporter	Male *N*=56,841	Female *N*= 71,259	Total *N*= 128,100
Consumer	31,212 (54.9)	42,315 (59.4)	73,527 (57.4)
Physician	25,629 (45.1)	28,944 (40.6)	54,573 (42.6)

Note. χ^2 = *258.47, *df* = 1, *OR* = 1.20. *p* <.001. Numbers in parentheses indicate column percentages. *p* <.006

Summary

For the quarterly data file data selection time period: 01 April 2016 to 30 June 2016, a total of 87,807 ADR reports with 143,399 ADR events were examined in this

study. For the case and event-based analyses, the findings from the study revealed that consumers reported more ADR reports and more ADRs in comparison to those reported by physicians. Moreover, consumers reported more serious ADR reports and more serious ADRs in comparison to those reported by physicians. For the first research question, the results from both the case- and event-based analyses revealed statistically significant differences between consumers and physicians with regards to the distribution of ADR cases and events by patient outcome, as well as by the severity of patient outcome in the US. For the second research question, the results from the event-based analysis showed a statistically significant difference between consumers and physicians with regards to the distribution of ADR events by SOC. For the third research question, the results from both the case- and event-based analyses revealed a statistically significant difference between consumers and physicians with regards to the distribution of ADR cases and events by reporter gender. Female consumers and male physicians were more likely to report ADR cases and events in comparison to their respective opposite gender counterparts. For the case-based analysis, the findings from the study revealed that female consumers reported more ADR cases than female physicians. Next, in Chapter 5, I provide a discussion of these results, study limitations, recommendations for future research, and the implications for social change.

Chapter 5: Discussion, Conclusions, and Recommendations

Introduction

To date, no studies have been conducted within the US in which the FDA FAERS database was employed to compare reporting of ADRs by reporter (consumers and physicians) and patient outcome, as well as by SOC and reporter demographics at case and/or event levels (Sakaeda et al., 2013). In this quantitative study, in an effort to fill the gap in the literature, I examined the statistical difference in the distribution of case and event level ADRs within the FAERS database by reporter (consumers and physicians) and patient outcome, while also evaluating reporter differences in SOC and demographics. The factors explored and compared included the differences in under-reporting of consumers compared to physicians, thereby elucidating whether consumer reporting played a pivotal role in AE reporting.

In this study, I analyzed secondary data, specifically, ADRs that were submitted by consumers and physicians to the FDA from the FAERS database, which contained quarterly data files that were extracted for analysis (FDA, 2016b). The data containing the spontaneous ADR reports from the FAERS database were accessed and downloaded from the quarterly data file data selection time period containing one quarter of data: 01 April 2016 through 30 June 2016. Once the ADR data were collected, spontaneous reports from consumers and physicians were assessed for ADRs. The reporter was the independent variable and consisted of two levels: consumer and physician. Patient outcome, SOC, and reporter demographics were the dependent variables. The unit of analysis was the total number of ADR cases and reported ADRs. Because this study was

quantitative in nature, secondary data analysis was performed by utilizing the chi-square test, the *OR*, and logistic regression.

For both the case- and event-based analyses, the findings from the study revealed that consumers reported significantly more ADR reports (59.7% versus 40.3%, respectively) and more serious ADR reports (55.5% versus 44.5%, respectively) in comparison to those reported by physicians. Moreover, consumers reported significantly more ADRs (57.9% versus 42.1%, respectively) and more serious ADRs (52.8% versus 47.2%, respectively) in comparison to those reported by physicians.

Furthermore, the results from the event-based analysis showed that a statistically significant difference exists between consumers and physicians with regards to the distribution of ADR events by SOC. Additionally, the results from both the case- and event-based analyses revealed a statistically significant difference between consumers and physicians with regards to the distribution of ADR cases and events by reporter gender. Based on these findings, I provide in this chapter a discussion, recommendation for action and further research, and implications for positive social change.

Interpretation of Findings

In an effort to assess ADRs and ADR reports from physicians and consumers, as well as to compare the findings among those from other studies, researchers from European countries and the US have conducted studies using their respective databases for collecting ADRs. The findings from such studies suggest the significance of including ADR reports from consumers. Alatawi and Hansen (2017) also evaluated the FAERS database. However, the aforementioned study involved the comparison of reporting rates

in the FAERS database to expected rates of known ADEs by examining three groups of drugs (statins, biologics, and narrow therapeutic index drugs) in order to determine the difference in sensitivity to reporting. The results from the authors' research revealed that most drug-ADE pairs were statistically significantly under-reported by both consumers and physicians.

In my study, I did not aim at determining the statistical significance of under-reporting of drug-ADE pairs by consumers and physicians. Rather, I focused on the comparison of the two reporter types, thereby showing that consumers reported more ADRs and ADR reports in comparison to those reported by physicians, similar to the findings from the European studies conducted by Aagaard et al. (2009) and de Langen, et al. (2008). Currently, no studies have been conducted within the US in which the FDA FAERS database was employed to compare under-reporting of ADRs by reporter (consumers and physicians) and patient outcome, as well as by SOC and reporter demographics at case and/or event level (Sakaeda et al., 2013).

The studies performed by Aagaard et al. (2009) and de Langen et al. (2008) used a similar type of data collection and/or data analysis methods in relation to my study. Aagaard et al. (2009) utilized the Danish ADR database to compare ADR reports between consumers and other sources, including physicians, pharmacists, lawyers, pharmaceutical companies and other HCPs. The same authors analyzed the data from these reports in terms of the reporter category, severity of the ADRs, the category of ADRs by SOC, and the suspected medicines on level 1 of the ATC classification system. Based on the results from the study of Aagaard et al. (2009), statistically significant

differences existed between reporter types and distribution of ADRs. Consumers reporting of serious ADRs was analogous to that of physicians (approximately 45%), although lower than that of pharmacists and other HCPs.

Similar to the study by Aagaard et al. (2009), my study involved the analysis of data from the ADR reports collected by FAERS database with respect to the following: the distribution of ADR cases and events by patient outcome and reporter (consumer versus physician); the distribution of ADR cases and events by the severity of patient outcome (serious versus nonserious) and reporter; the distribution of ADR events by SOC and reporter; and, the distribution of ADR cases and events by reporter and reporter gender (male versus female). However, unlike the study by Aagaard et al. (2009), my study did not analyze data with regards to ATC.

In my study, the results from both the case- and event-based analyses revealed statistically significant differences between consumers and physicians with regards to the distribution of ADR cases and events by patient outcome as well as by the severity of patient outcome in the US. The results of ADR reporting by consumers and physicians from my study differed from those reported by Aagaard et al. (2009) due to the characteristics of the sample and methodology. The study by Aagaard et al. (2009) was conducted in Denmark with a significantly smaller sample size in comparison to that of my study. Moreover, the same authors did not investigate patient outcome or sample demographics.

With regards to reporting ADRs and serious ADRs, for the case-based analysis, the findings from my study have revealed that consumers reported more ADR cases than

physicians. The results have shown that consumers reported nearly 60% of ADR cases, while physicians reported about 40% of ADR cases. Furthermore, consumers reported nearly 56% of serious ADR cases, while physicians reported nearly 45% of serious ADR cases. Therefore, consumers reported more ADR reports and more serious ADR reports in comparison to those reported by physicians.

With regards to SOC, the results from the study by Aagaard et al. (2009) revealed a statistically significant difference between reporter types in terms of the distribution of ADRs by SOC. The same authors claimed that, in comparison to other sources, consumers were more likely to report ADRs from the following SOCs: Nervous system disorders (*OR* = 1.27); Psychiatric disorders (*OR* = 1.70); and, Reproductive system and breast disorders (*OR* = 1.27). In my study, the findings from the event-based analysis also showed a statistically significant difference between consumers and physicians with regards to the distribution of ADR events by SOC. Similar to the results from the Aagaard et al. (2009) study, the findings from my study have revealed that the odds of consumers reporting ADRs were higher than those of physicians for the SOCs Psychiatric disorders (*OR* = 1.26, *p* = .001) and Reproductive system and breast disorders (*OR* = 3.30, *p* <.001). Unlike the results from Aagaard et al. (2009), the results from my study have also shown that the odds of consumers reporting ADRs were higher than those of physicians for the following SOCs: Gastrointestinal disorders (*OR* = 2.85, *p* <.001); General disorders and administration site conditions (*OR* = 1.99, *p* <.001); Injury, poisoning and procedural complications (*OR* = 1.36, *p* =.001); and, Vascular disorders (*OR* = 1.44, *p* <.001).

According to Aagaard et al. (2009), compared with other sources, consumers were less likely to report ADRs from the SOCs Blood and lymphatic system disorders (*OR* = .22) and Hepatobiliary system disorders (*OR* = .14). Similar to the findings from my study, the odds of consumers reporting ADRs were lower than those of physicians for the SOCs Blood and lymphatic system disorders (*OR* = .23, *p* <.001) and Hepatobiliary disorders (*OR* = .30, *p* <.001). Additionally, unlike the findings from Aagaard et al. (2009), the results from my study have also shown that the odds of consumers reporting ADRs were lower than those of physicians for the following SOCs: Cardiac disorders (*OR* = .74, *p* <.001); Endocrine disorders (*OR* = .30, *p* <.001); Immune system disorders (*OR* = .61, *p* <.001); Infections and infestations (*OR* = .85, *p* <.001); Investigations (*OR* =.83, *p* = 0.005); Metabolism and nutrition disorders (*OR* = .52, *p* <.001); Musculoskeletal and connective tissue disorders (*OR* = .50, *p* <.001); Neoplasms benign, malignant and unspecified (*OR* = .61, *p* <.001); Nervous system disorders (*OR* = .78, *p* <.001); Renal and urinary disorders (*OR* = .62, *p* <.001); Respiratory, thoracic and mediastinal disorders (*OR* = .61, *p* <.001); and, Skin and subcutaneous tissue disorders (*OR* = .30, *p* <.001).

The study conducted by Aagaard et al. (2009) revealed statistically significant findings suggesting that, in comparison to other literature reviewed, consumers reported different categories of ADRs for different types of SOC and ATC groups. Similarly, the findings from my study have revealed that consumers had also reported different categories of ADRs for different types of SOCs in comparison to physicians (although my study did not focus on ATC). Therefore, when comparing and contrasting the results

from Aagaard et al. (2009) and those from my study, it can be concluded that consumers should be active participants within systematic drug surveillance systems, including clinical settings, and their reports should be treated with as much importance as those from other sources.

The study conducted by de Langen et al. (2008) involved the comparison of ADR reports between patients and HCPs collected from the Netherlands database. The authors analyzed the data from these reports with regards to the age and gender of the reporters, the attributes of the most frequently reported drugs and the attributes of the most frequently reported ADRs, their seriousness, and their outcome. Although this study is very similar to mine, I focused on the US and the FDA FAERS database as well as on consumers and physicians. de Langen et al. (2008) discovered statistically significant differences between patient reports and reports from HCPs with regards to the seriousness and outcome of reported ADRs in the Netherlands. In comparison to HCPs, patients reported a significantly higher number of LT ADRs (5.2% vs 2.7%) and disability (2.3% vs 0.4%). Conversely, the findings from my study have shown that, for the case-based analysis, the odds of consumers reporting ADR cases were lower than those of physicians corresponding to the following patient outcomes: death (OR = .91, p <.001); LT (OR = .30, p <.001); hospitalization (OR = .91, p <.001); disability (OR = .82, p = .003); and, congenital (OR = .42, p <.001). However, unlike the results from de Langen et al. (2008), the results from my study have demonstrated that the odds of consumers reporting ADR cases corresponding to OME were higher than those of physicians (OR = 1.19, p <.001).

The findings from de Langen et al. (2008) have shown that patients reported significantly fewer ADRs leading to death (0.6% vs 1.5%) and hospitalization or prolongation of hospitalization (9.8% vs 12.0%). Similarly, the findings from my study have shown that, for the event-based analysis, the odds of consumers reporting LT ADRs (OR = .36, p <.001) and those resulting in hospitalization (OR = .92, p <.001) were lower than those of physicians. Additionally, unlike the findings from de Langen et al. (2008), the results from my study have demonstrated that, in comparison to physicians, consumers were less likely to report the following patient outcomes: disability (OR = .84, p <.001); congenital (OR = .64, p <.001); and, intervention (OR = .14, p =.002). However, unlike the results from de Langen et al. (2008), the results from my study have demonstrated that the odds of consumers reporting ADRs resulting in OME were higher than the odds of physicians (OR = 1.24, p <.001).

The findings from the same authors revealed that no statistically significant differences were determined between patient reports and reports from HCPs with regards to patient characteristics (age and gender). Conversely, the findings from my study from both the case- and event-based analyses have shown a statistically significant difference between consumers and physicians with regards to the distribution of ADR cases and events by reporter gender. Female consumers and male physicians were more likely to report ADR cases and events in comparison to their respective opposite gender counterparts. Prior research has divulged findings suggesting that females are 1.5 to 1.7 times more susceptible to ADRs in comparison to males (Rademaker, 2001; Luca, Ramesh, & Ram, 2017). Researchers have discovered that possible risk factors attributed

to pharmacokinetics, pharmacodynamic, pharmacogenetics, and immunological and hormonal factors are responsible for females' predisposition to ADRs. Furthermore, researchers have determined an additional risk factor linked to the difference in prescribed drug consumption between females and males Rademaker, 2001; Luca et al., 2017). Therefore, female consumers may be more inclined to report ADRs in comparison to their male counterparts.

Results from previous literature have shown that the rate of burnout for female physicians is twice as high as that of male physicians within the US (Medscape, 2017). Moreover, the suicide rate among US female physicians is 2.5 to 4 times as high in comparison to that of the general US population (Schernhammer & Colditz, 2004). Additionally, high ranking leadership positions within hospital and academic settings in the US are occupied by male physicians given that only 15% of medical school dean-level (decanal) positions are held by female physicians (Schor, 2018). Findings from prior research have also demonstrated a salary gap between male and female physicians in the US, thereby suggesting that female physicians earn less than their male counterparts (Jagsi et al., 2012; Jenna, Olenski, & Blumenthal, 2016). Researchers have discovered that, even after controlling for such factors as faculty ranking, years in practice, and graduation from a top medical university, female physicians earned nearly $20,000 less in comparison to male physicians (Jenna et al., 2016). Therefore, female physicians may be less inclined to report ADRs compared to male physicians.

For the case-based analysis, the findings from my study revealed that female consumers reported more ADR cases than female physicians (61% versus 39%,

respectively). The odds of consumers reporting ADR cases were higher for females versus males than the odds of physicians (*OR* = 1.18, *p* <.001). For the event-based analysis, the findings from my study showed that female consumers reported more ADRs than female physicians (60% versus 40%, respectively). The odds of consumers reporting ADRs were higher for females versus males than the odds of physicians (*OR* = 1.20, *p* <.001). Therefore, irrespective of gender, from both the case- and event-based analyses, consumers reported more ADR reports and more ADRs in comparison to those reported by physicians.

de Langen et al. (2008) also stated that no statistically significant differences were determined between patient reports and reports from HCPs with regards to the most frequently reported ADRs from the following five most involved SOCs: Nervous system disorders, Psychiatric disorders, Gastrointestinal disorders, Musculoskeletal disorders, and General disorders/administration site conditions. Conversely, the results from my study have revealed statistically significant differences between consumer reports and reports from physicians with regards to the ADRs that were reported for the aforementioned SOC categories.

The study conducted by de Langen et al. (2008) revealed statistically significant findings suggesting that patients reported ADRs differently from HCPs with respect to the seriousness and outcome of reported ADRs. Similarly, the findings from my study have revealed that consumers have reported ADRs in a different manner than that reported by physicians with regards to the patient outcome and the severity of patient outcome. Therefore, when comparing and contrasting the results from de Langen et al.

(2008) and those from my study, it can be concluded that consumer reporting should not substitute physician reporting (as physicians are a reliable source for ADR reporting). Hence, consumer reporting may nonetheless serve as a crucial component in healthcare, thereby placing patient safety and greater access to efficacious drugs at the forefront of pharmacovigilance.

The theoretical foundation that was employed this study is known as SARF, which stems from the perception of risk framework. The theory maintains that risk interconnects with the psychological, social, institutional, and cultural viewpoints of individuals in a way that may increase of decrease individuals' responses to the risk or risk event (Kasperson & Ratick, 1988). These variations in the perception of risk evoke behavioral responses from individuals that change the social and economic aspects of society, thereby magnifying or diminishing the actual physical risk (Kasperson & Ratick, 1988).

Similar to the theoretical framework used in this study, Bongard et al. (2002) and Durrie et al. (2009) conducted studies in which the SARF theoretical framework was used. The findings from both studies have shown the difference in risk perception between consumers and physicians. In the study conducted by Bongard et al. (2002), study participants consisting of 400 HCPs and 153 non-HCPs were requested to assess their risk perception of ADRs related to 13 different drug classes. Based on the findings from the study, anticoagulants and NSAIDs were ranked by HCPs as the first and second most dangerous drugs, respectively. Contrarily, aspirin, anticoagulants, and NSAIDs were ranked by consumers as the least dangerous drugs, with aspirin ranking as the least

harmful. Moreover, sleeping pills, tranquillizers, and antidepressant drugs were ranked by consumers as the most dangerous, with psychotropic drugs ranking as the most harmful. The consumer's perception of the safety of aspirin may in part be linked to the insufficient information regarding the risk of aspirin and the abundance of information given to the consumer via advertisements, Internet, and commercials (Durrie et al., 2009). Hence, the authors concluded that the consumer was unaware of such ADRs and, therefore, underestimated the risk related to NSAIDs (Bongard et al., 2002).

Bongard et al. (2002) claimed that the mass media's portrayal of psychotropic drugs and its association with frequent suicide attempts may have greatly affected the public's high-risk perception of these drugs. Given the difference in the drug class perception between the consumers and HCPs, the authors concluded that consumers and HCPs have differing risk perceptions of ADRs. Hence, the results from the study conducted by Bongard et al. (2002) bolster the claim that risk perception of ADRs varies between consumers and HCPs, which is crucial for my study and which may explain why physicians reported ADRs less frequently than consumers.

In the study performed by Durrie et al. (2009), study participants comprised of 92 medical students were asked to evaluate their risk perception of ADRs related to 13 different drug classes before and after taking pharmacology courses. Based on the findings from the study, before taking pharmacology courses, hypnotics were ranked by medical students as the most dangerous drug, followed by antidepressants and anticoagulants, while contraceptive pills were ranked as the least dangerous. After taking pharmacology courses, antidepressants were ranked by medical students as the most

dangerous drugs, followed by anticoagulants and hypnotics. Furthermore, Durrie et al. (2009) discovered a statistically significant increase in perceived risk for other classes of drugs. The highest increases were observed for contraceptive pills, NSAIDs, and aspirin, while the lowest increases were observed for hypocholesterolaemic and antidepressant drugs. The authors concluded that after completion of the pharmacology courses, medical students became more aware of potentially serious ADRs that are associated with drugs deemed relatively safe by non-HCPs, such as NSAIDs and aspirin. Therefore, the findings from the study conducted by Durrie et al. (2009) revealed that the perceived risk of ADRs by medical students was different after taking pharmacology courses. The lack of adequate training and education for physicians can greatly influence their risk perception with regards to different drug classes and the various levels of risk associated with each drug class. Hence, the findings from the study conducted by Durrie et al. (2009) are critical to this study and may explain the need for efficacious training and preparation, as well as adequate information for physicians on ADRs, which may explain the under-reporting of ADRs, including both serious and nonserious, by physicians in comparison to consumers.

The SARF theory may elucidate the difference in risk perception between consumers and physicians. Consumers may perceive any ADR, whether nonserious or serious, as a risk based on media, marketing, advertisement, promotional materials, Internet, and even anecdotal evidence (Durrie et al. (2009). For instance, traditional media (television, newspaper, magazine, radio) coverage affects the propagation of drug safety information, thereby influencing warnings, alerts, and label changes to the drugs

that are issued by the FDA (Yong et al., 2009). According to findings from prior research, 100% of newspaper articles referenced a salubrious effect of a recently approved medicine, while only 32% mentioned at least one deleterious adverse effect from this drug (Cassels et al., 2003). Moreover, the Internet can serve a crucial role in contributing to behavioral changes to drug safety information, thereby influencing the risk perception of consumers since the message delivered by regulatory authorities, such as the FDA, is not akin to the one conveyed by the media (Cassels et al., 2003; Yong et al., 2009).

Additionally, direct-to-consumer (DTC) advertising, which is as an effort undertaken by pharmaceutical companies to promote their prescription products directly to patients (currently only allowed in the US and New Zealand), plays a pivotal role in impacting the risk perception of consumers. Results from previous research have suggested that an increase in consumer reporting of ADRs to the FDA was evident thanks to the 2007 enactment of the print advertising requirement (Du et al., 2012), which mandated DTC advertisements to contain, in clear and conspicuous text, the following statement: "You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088." (Kessler & Vladeck, 2007).

While investments have been made in digital promotion via Web sites, online display advertising, search engine marketing, social media campaigns, and mobile advertising, nearly two-thirds of promotional expenditure has been distributed to traditional media (television, newspaper, magazine, radio), including DTC advertising

(Gilchrist, 2016). Findings from the study conducted by Du et al. (2012), which investigated the relationship between DTC advertising expenditure and ADR reporting, have shown a positive relationship between the two variables (Du et al., 2012). According to the same authors, after the ratification of the Title IX of the Food and Drug Administration Amendments Act (FDAAA) in 2008, spending on DTC print ads resulted in more reports per drug on a monthly basis, of which nearly 65% might have resulted from the MedWatch enactment of the print advertisement requirement that mandates manufacturers to include toll-free reporting numbers in print DTC advertisements (Du et al., 2012). Furthermore, the same authors claimed that, based on their findings, a positive, statistically significant association existed between the number of patients and ADR reporting. According to the same authors, the influx of DTC ads contributed to an increase in ADR reporting by patients, which increased nearly 40% (from 1.28 monthly reports per drug to 1.74 monthly reports per drug) (Du et al., 2012).

The difference in consumer reporting of ADRs to the FDA prior and subsequent to the 2007 print advertisement requirement was apparent. In 2004, nearly 18% of consumers submitted ADR reports to the FDA. One decade later, ADR reports were submitted to the FDA by approximately 42% of consumers (Aikin, et al., 2016). Hence, due to the collaborative efforts between the media and the FDA, the contribution of consumer reporting has been steadily increasing, as more consumers have been reporting ADRs. Therefore, the influence of media may explain the large amount of serious and nonserious ADR cases and events reported by the consumers in comparison to those reported by physicians, which was evident in this study.

Moreover, consumers may also perceive an ADR as a risk based on the communication gap (either lack of or poor communication) between them and their physicians. The results from the study conducted by Golomb et al. (2007) have suggested that 87% of patients initiated communication with their physicians regarding a potential association between an AE and a drug that they were consuming. However, the physicians were less likely to corroborate the possible relationship and, therefore, were more reticent to report ADRs (Golomb et al., 2007). Even if physicians and their patients engaged in conversations regarding drug safety risks, which was evident in the study conducted by Enger et al. (2013), poor or insufficient communication still existed, thereby potentially contributing to a change in risk perception among consumers. The findings from the study performed by Enger et al. (2013) have suggested that only 33% of patients (who were using the anti-smoking patch varenicline reported having conversations with their physicians regarding the drug safety risks and the adverse effects they were experiencing from the drug (Enger, et al., 2013). Consequently, consumers were more likely to report ADRs while physicians were less likely to report them. Therefore, improper communication between consumers and their physicians may justify the large amount of nonserious ADR cases and events reported by the consumers in comparison to those reported by physicians, which was evident in my study.

Moreover, consumers may also perceive an ADR as a risk based on consumers' reporting behaviors, which arise from consumers' perception and experience of ADRs, especially serious ADRs, as well as their experiences in reporting ADRs directly to PV centers. In several studies conducted within the Netherlands and the UK, researchers have

explored the differences between ADR reports from patients and HCPs regarding the perception of the importance of ADR reporting, as well as the perception of the severity of the reported ADRs (van Hunsel et al., 2010; Anderson et al., 2011; & Krska et al., 2011). The findings from the study conducted by Anderson et al. (2011) have suggested that patients perceived reporting ADRs directly to a PV center as significant, thereby resulting in more ADRs being reported in comparison to those reported by physicians. The findings from the studies performed by Anderson et al. (2011) and Krska et al. (2011) have demonstrated a difference in viewpoints between consumers and physicians with regards to the severity of the ADR. The same authors argued that the definition of "seriousness" or severity of the ADR may be dissimilar between patients and HCPs. For instance, patients considered ADRs resulting in disability as serious ADRs and, therefore, reported more ADRs resulting in disability in comparison to those reported by HCPs. Interestingly, the findings from my study have revealed that consumers also reported more ADR disability reports and ADRs resulting in disability than those reported by physicians. Therefore, the perception of seriousness of ADRs may justify the large amount of serious ADR cases and events reported by consumers in comparison to those reported by physicians, which was evident in my study.

Additionally, the findings from these studies conducted by van Hunsel et al. (2010) and Anderson et al. (2011) have suggested that patient reporting of ADRs is not only a consequence of patients' perception of the seriousness of the ADR, but also the necessity to share their experiences of an ADR with others, especially the manner in which an ADR influences their quality-of-life on a daily basis. The same authors argued

that patients are eager to divulge their experiences of ADRs, as well as their perceptions and viewpoints regarding the significance of ADR reporting to a PV center. Hence, the authors concluded that altruism, viz., patients' selfless concern for the well-being of others, was the primary motivation for reporting ADRs. Therefore, the potential inclination for consumers to report ADR cases and events out of sheer altruism may explain the large amount of serious and nonserious cases and events reported by consumers in comparison to those reported by physicians, which was evident in my study.

The SARF theory may also justify the reason physicians reported less ADR reports and ADRs, including both serious and nonserious, in comparison to those reported by consumers. The findings from a systematic review performed by Lopez-Gonzalez et al. (2009), which sought to identify knowledge and attitudes associated with ADR reporting, revealed that the lack of knowledge and certain reporting behaviors of HCP seem to be associated with under-reporting in over 90% of studies (Lopez-Gonzalez, Herdeiro, & Figueriras, 2009). Specifically, the lack of knowledge regarding the functionality of SRS, as well as the attitudes (ignorance, in particular) to report ADRs, appear to be linked to under-reporting of ADRs by physicians. Findings from prior studies have suggested that numerous HCPs deemed that the sole purpose of SRS was to identify serious ADRs. Consequently, these HCPs Therefore, the ignorance of the ADR reporting requirements was prevalent among physicians, thus suggesting that insufficient knowledge and an oblivious attitude of physicians was evident.

Furthermore, Lopez-Gonzalez et al. (2009) claimed that certain attitudes of HCPs, such as diffidence, insecurity, complacency, lethargy, and fear, appeared to be related to the under-reporting of ADRs. The results from the same authors' systematic reviewed have shown that diffidence (fear of appearing ridiculous) was an attitude related to under-reporting in more than 70% of the studies reviewed. Moreover, insecurity, which may also be linked to diffidence, appeared in more than 65% of the studies reviewed by these same authors as a potential factor for under-reporting. The aforementioned attitudes are based on the inability for an HCP to establish a causal relationship between a drug and an ADR. The same authors stated that most HCPs are inclined to believe that only a causal relationship between a drug and an AE necessitates reporting of ADRs to an SRS. Therefore, such HCPs may be reluctant to report ADRs if they deem a non-causal drug-ADR association.

According to Lopez-Gonzalez et al. (2009), the attitude of fear may be aligned with the attitude of lack of confidence about confirming drug-ADR associations since HCPs may be less inclined to report an ADR when they feel less confident about the existence of a causal relationship between drugs and ADRs. This attitude may reflect the apprehensions of reporters "not to appear foolish", a perception that may explain the reason why physicians reported less ADRs in comparison to those reported by consumers in my study.

Lopez-Gonzalez et al. (2009) also claimed that the attitude of complacency, the belief that all ADRs of a drug are known when a drug enters the market and that only safe medications are marketed, seemed to be linked to under-reporting in about 67% of studies

they reviewed. This perception may be attributed to the lack of adequate or proper training and education received by HCPs, especially in epidemiology and pharmacology and at the clinical levels in undergraduate and medical schools.

Moreover, Lopez-Gonzalez et al. (2009) identified the attitude of lethargy, viewed as a set of factors, including, lack of time and interest in rendering a diagnosis and reporting, which may impede or rationalize non-reporting of ADRs. The perception of the reporting process as a bureaucratic and challenging one was also identified as part of the attitude of lethargy and an additional factor contributing to under-reporting of ADRs by HCPs. If reporters are incognizant of the usefulness of the ADR data that may be reported to the system, then it is understandable, and perhaps to some extent justifiable that, despite any guarantee of confidentiality, those who were unfamiliar with the system would be less likely/less inclined to report ADR, due to an aversion to disclosing confidential information. Therefore, the findings from Lopez-Gonzalez et al. (2009) have shown that training and medical specialty appear to be related to reporting in nearly three-fourths of the studies that they reviewed. The same authors contended that such findings may yield the following insights: the greater the training, the better the attitudes toward ADR reporting (Lopez-Gonzalez et al., 2009). Hence, the findings from the study conducted by Lopez-Gonzalez et al. (2009) are critical to this study and may explain the need for adequate and necessary training and preparation, which may increase the knowledge and attitudes of physicians on ADR reporting, thereby potentially contributing to an increase in physician reporting of ADRs. These results may explain the under-reporting of ADRs, including both serious and nonserious, by physicians in comparison

to those reported by consumers in my study. Thus, the increase in knowledge of physicians and the amelioration in physician attitudes may lead to an increase in ADR reporting.

In my study, I identified variations between physicians and consumers in terms of reporting ADRs (Aagaard et al., 2009). SARF was employed to elucidate the differences between HCPs and consumers' reporting of ADRs. The perception of risk as it applies to the present issue involved the premise that different groups (HCPs and non-HCPs, researchers and the public, or HCPs and consumers) hold different views on the possible risks associated with some action or environment. In my study, I discovered that several factors contribute to the perception of risk, including factors related to the individual, the presentation of the risk, and the attributes of the risk (Aagaard et al., 2009). The findings from the studies conducted by Bongard et al. (2002), Durrie et al. (2009), and Lopez-Gonzalez et al. (2009), which also employed the SARF framework and confirmed the aforementioned factors contributing to the risk perception, are important to my study and may explain the need for adequate education and training for physicians, as well as an educational intervention designed to ameliorate attitudes associated with under-reporting, especially among physicians, which may explain the differences in reporting of ADRs by physicians and consumers found in my study. Furthermore, the results from the study performed by Du et al. (2012), are also significant to my study and may justify the need to launch initiatives for consumers and physicians aimed at ameliorating patient-physician communications, which may also explain the differences in ADR reporting between consumers and physicians found in my study. Hence, with respect to ADR

reporting and drug therapy, consumers frequently have contrasting views in their perception of risk versus HCPs (Aronson, 2006). Therefore, the SARF framework was appropriate for this study with regards to identifying under-reporting of ADRs since it was assumed that the consumer's perception of risk differed from that of the physician.

Limitations of the Study

Despite the advantages of the FAERS database, which offers a solid structure for reporting of ADRs, the disadvantages of this system and its data are noteworthy to discuss. FAERS contains redundancies, reporting biases, and conflations (including, but not limited to, multiple entries and indications with ADRs) that are negatively impacting analysis and interpretation (McAdams et al., 2008). These biases can lead to conclusions of drug-ADR causal relationships where none exist and may also obfuscate potential drug-ADR relationships. Within the FAERs data, there is no evidence of a causal relationship between the drug and the reported event (FDA, 2017). Although consumers and HCPs are urged to submit ADR reports, the existence of the event may not necessarily be attributed to the drug, but rather to the condition being treated, other concomitant medicines or drugs, or other reasons. Therefore, the information in the ADR reports is indicative of the viewpoints of the reporter (FDA, 2017).

Additionally, the FAERS data do not lead to a precise risk estimation relating to a drug. Risk estimation necessitates sufficient information associated with drug utilization to generate a numerical figure for the denominator of the risk estimate. However, this information is typically extracted from sales data, which may exaggerate the prescription and utilization levels (Hazell & Shakir, 2006). Since the denominator (number of patients

prescribed the product) may be unknown or erroneous, it is improbable to compute the incidence rate of ADR using the FAERS data (Rodriguez, Evelyn, Staffa, & Graham, 2001). Hence, neither incidence rates nor an estimation of drug risk can be calculated from the FAERS data (FDA, 2017).

An additional limitation of the FAERS database is its bias toward serious outcomes, in particular, the conflation of ADRs and serious outcomes (Maciejewski et al., 2017). This bias may have resulted from the lack of comprehension regarding the definition of the term "death", specifically, whether death was listed as an ADR (resulting from the consumption of a medicinal product drug only) or an outcome (due to a disease). For instance, within the FAERS database, death was erroneously reported as an ADR rather an outcome resulting from the use of the drug thalidomide to treat a type of cancer known as complex myeloma multiplex (Maciejewski et al., 2017). Moreover, there are instances where the patient outcome of death may be over-reported, in relation to its prevalence among ADRs. Hence, the aforementioned limitation may contribute to over-reporting, especially among consumers.

Since FAERS is a voluntary reporting system, not all reports for every AE or medication error that occurs with a product are submitted to the FDA. Moreover, duplicate reports may exist in which the same report was submitted by a consumer and/or by another reporter (the physician). Hence, the aforementioned limitations may result in an increase in risk associated with a product or drug (Chedid, Vijayvargiya, & Camilleri, 2018).

An additional limitation of the study that needs to be discussed is that one reporter may report more than one ADR event per case (report), thereby resulting in ADRs not being truly independent. Since my study was conducted at the ADR case and event level (modeled after the Danish study conducted by Aagaard et al. (2009)), the findings from these analyses were not at the patient/consumer level. Therefore, it was impossible to differentiate between ADRs, as the ADR events are identified by an ISR number instead of by reporter. Moreover, it was not possible to differentiate ADR events by reporter type and, consequently, it was not possible to designate an ADR event as primary (or secondary) for a reporter. Therefore, a reporter level analysis was not performed in this study.

Limitations of the correlational cross-sectional research design, as well as the secondary data analysis in this study, must also be acknowledged. Since quantitative methods were employed, consumer perception of ADRs was not analyzed given that the latter requires qualitative methods. Qualitative data analysis of consumer reports would have been advantageous to this study in an effort to garner a fresh and alternate perspective of the consumer's experience of ADRs. Since the correlational cross-sectional research design was employed in this study, the secondary data may have resulted in implicit bias, reporting bias, and recall bias, which may yield misclassification or information bias (Gualano et al., 2015). Implicit bias among physicians may occur, thereby propagating disparities in healthcare and rendering clinical decisions, especially physicians' inclination for certain drugs versus other drugs (Gawron & Bielefeldt, 2018). Under-reporting not only impacts older medicines and products as well as nonserious

ADRs, but also affects new drugs and serious ADRs (Hazell & Shakir, 2006). Reporting rate is also subject to fluctuate gradually and, therefore, be impacted by such aspects as media coverage, thereby contributing to reporting bias (Hazell & Shakir, 2006). Moreover, it can prove challenging to render statistical decisions on the relative risk of one product or indication versus another given that the rate of under-reporting may be different between the two medicines, thereby potentially concealing or overstating any statistically significant difference in toxicity profile (Hazell & Shakir, 2006).

Furthermore, the use of this particular design provided a rather limited amount of information of the sample (Gualano et al., 2015). The correlational cross-sectional research design presented challenges regarding the determination of causal relationships between the distribution of ADRs by reporter (consumer versus physician) and patient outcome, as well as SOC and reporter demographics. The correlational cross-sectional design contained several limitations that are significant to examine, including internal validity, which is only germane to experimental designs, which attempt to establish a causal relationship (Frankfort-Nachmias, 2014). Since researchers do not alter the independent variables, they must render logical or theoretical inferences in terms of the direction of the causation by taking into account that correlation between variables does not imply causation (Field, 2013). Hence, in my study, it was challenging to make causal inferences when working with FAERS data for which quantitative methods were

Recommendations

With regards to the case- and event-based analyses performed in this study, in addition to analyzing consumer and physician ADR reports for severity of ADRs, it is

also noteworthy to assess such reports for nonserious ADRs in order to determine into which SOC groups they would fall and compare the findings to those with serious ADRs. Furthermore, it would be beneficial to assess the serious and nonserious ADRs based on ATC groups, which was not addressed or performed in my study. Additionally, it would be worthwhile to examine and analyze the chronological trends in spontaneous reporting of ADRs to the FAERS database by computing and comparing over time the reporting proportions for both serious and nonserious events, as well as the serious to nonserious ratio (Moulis et al., 2012). Although the seriousness of ADRs is a crucial factor to investigate in ADR reporting, the trends in reporting of serious versus nonserious ADRs have not been scrutinized, especially within the FAERS database. Therefore, additional research is needed and it is recommended that an observational, descriptive study is employed (Moulis et al., 2012).

Additional research is needed to assess the quality of spontaneous reports, which is consequential for the precise assessment of drug safety signals. Crucial information that allows researchers to render causal inferences may potentially be omitted from ADR reports with inferior quality and those that contain insufficient details (Hazell & Shakir, 2006). Moreover, ADR reports can be confounded by concurrent diseases or conditions, concomitant medication, or other factors. Consequently, "background noise" can emerge within the FAERS database, thereby rendering signal detection difficult or impossible or potentially creating false positive signals (Hazell & Shakir, 2006).

To reduce the "noise" within the FAERS database, it may be worthwhile to map drug identifiers in FAERS to the chemical structures of these drugs' ingredients, which

may yield information on the complete drug profile rather than the incomplete profile consisting of merely drug names and synonyms (Maciejewski et al., 2017). Moreover, given the millions of reports that are submitted to the FAERS database, it may be necessary to automate this process by utilizing machine learning methods. As a result, such an automated process may facilitate the identification of conflations in the data, such as multiple reports for the same ADR and consumer, or cases where ADRs were confounded with the conditions that the medicines or products are treating. For instance, diabetes was previously recorded as a side effect for medicines that treat diabetes (Maciejewski et al., 2017).

Signals in FAERS database are obfuscated by redundancies in the chemical name, which yields incorrect statistical associations that lead to statistical insignificance on synonym aggregation, thereby concealing associations that would otherwise be statistically significant on aggregation (Maciejewski et al., 2017). To counteract this issue, it may be necessary to represent the active ingredients of drugs by their unique chemical structures by creating and embedding a readily searchable form within FAERS that enables users to easily search by the drugs' chemical structures (Maciejewski et al., 2017). Therefore, additional research is needed in this respect.

Given the conflation of ADRs and outcomes, particularly the serious outcome of "death", it is recommended to create a feature within FAERS that distinguishes between disease- and drug-related outcomes in an effort to correct the confusion as to when a medicinal product is utilized in different indications with distinct symptoms and outcomes (Moulis et al., 2012). Moreover, an additional feature to build and integrate

within the FAERS database is to automatically send an alert to the investigator to common indication biases, including high death rate in cancer, or baseline metabolic anomalies in diabetes (Moulis et al., 2012). Therefore, additional research is needed on this topic and subsequent statistical analysis on ADR reporting is recommended to distinguish between the outcomes associated with the disease or with the drug (Maciejewski et al., 2017).

Additionally, within FAERS, the trends and biases, such as the conflation of ADRs and serious outcomes, in ADR reporting may hinder the reliability of drug-ADR associations (Maciejewski et al., 2017). Consequently, additional research on detecting drug-ADR associations is needed to monitor fluctuations in reporting patterns and trends. Since FAERS contains numerous types of conflation, these may be discovered via statistical analyses, such as a chemical structure and time-resolve analyses of ADR reporting (comparing ADR reports over time) (Maciejewski et al., 2017). Such analyses may be necessary to calculate time-resolved profiles of drug-ADR associations, which may divulge significant drug safety information relating to the comorbidities and similarities of ADRs between drugs and AEs across ATC, as well as their time evolution (the numbers of reports per month for individual ADRs observed across FAERS database for certain drugs) (Maciejewski et al., 2017). Moreover, the use of correlative studies may divulge additional features of the potential discrepancies between the clinical profiles of medicines or products that possess similar chemical structures (Maciejewski et al., 2017).

Consequently, ADR signals and their evolution can be observed and compared over time in an attempt to unveil biases that were otherwise difficult to detect. Furthermore, the use of time-resolved statistical analysis for drug-ADR associations can yield potential benefits in identifying biased reporting trends and biases within the ADR data (Maciejewski et al., 2017). Therefore, additional research is needed to demonstrate the value of performing chemical structure analysis and comparative analysis of ADRs over time (time-resolved analysis) in an effort to potentially divulge factors that have previously been undetected.

The results from such additional research may provide unbiased classification of ADRs, indications, and drugs with similar clinical profiles. Once these biases and conflations are rectified, the molecular mechanism of previously hidden ADRs may ultimately be unveiled (Maciejewski et al., 2017). Therefore, the findings from such additional research may prompt investigators to avoid confounding associations based on chemical compounds and reporting biases in FAERS.

Since FAERS is an instrumental database for consumers, physicians, pharmaceutical representatives and scientists, and other reporters, it can nonetheless be ameliorated in several ways to improve postmarketing pharmacovigilance. As was previously discussed in this chapter, it was recommended that an automated process is created to map drugs and synonyms to their unique chemical ingredients (Maciejewski et al., 2017). Moreover, alerts could be provided for indications where serious outcomes are frequent and challenging or impossible to detect or differentiate from ADRs. However, definitive drug-ADR associations necessitate exposure data, as the information on dosage

application and related pharmacokinetics (PK) data are crucial (Maciejewski et al., 2017). Currently, dosage information is not provided, and PK data can only be acquired from various sources, such as PharmaPendium, which contains both FAERS data and PK information (Maciejewski et al., 2017). However, these data are not directly mapped, and this resource cannot be accessible by the public. However, FAERS database could be linked to such public databases as DailyMed or drugs.com, which may yield information on PK, drug labels, formulations, and approved indications (Maciejewski et al., 2017). Therefore, it is recommended to invest in and perform additional research on acquiring information and performing statistical analyses that may offer further insight into drug-ADR associations based on dose and PK data.

One of the current disadvantages of the FAERS database is the lack of commentary by any reporter when submitting ADR reports. Several EU countries, including, but not limited to, Sweden and UK, enable any reporter to add free text case narratives of their ADR experiences when submitting suspected ADR reports online (Vilhelmsson, 2015). Therefore, it would be of utmost significance to ameliorate the FAERS surveillance system by introducing a feature that includes free text comments from all reporter types, especially consumers. Hence, such a feature may yield greater insight into consumer experiences with the drug and ADR.

It would be beneficial to improve the FAERS database by creating and incorporating an automated reporting mechanism in FAERS that not only collects ADR information in a manner that would diminish inaccuracies and other errors relating to misclassification of ADRs and indications, but also interacts with the reporters in a user-

friendly manner, especially with those who do not possess technical competence. Consequently, such qualities within the FAERS system would enable reporters to acquire feedback after submitting their entries, particularly with cases on the same or similar suspect drug, indication, patient population, and treatment programs that are most frequent or challenging. In addition to other advantages, the inclusion of such features may also assist investigators, physicians, and scientists to determine and define the "suspect drug" in treatment regimens, irrespective of the aim of the submitters/reporters (Maciejewski et al., 2017). Although such a development within the FAERS database would certainly necessitate funding, it is recommended that such a commitment and investment be a concerted public and private sector effort that would not only be advantageous to legislature and the scientific community, but also to the health and well-being of the public.

Under-reporting has been a significant problem that has plagued PV activities not only at a national scale, but also at a global scale. Although the reporting rate of ADRs has gradually improved over the years, ADRs are still under-reported in SRSs by consumers and physicians. Results from prior research have revealed that lack of training and education, as well as the lack of knowledge and certain attitudes on the part of physicians, contribute to under-reporting of ADRs by physicians (Lopez-Gonzalez et al., 2009). Consequently, such findings may have potential significant impact given that knowledge and attitudes are factors that can be modified through proper trainings and educational efforts. HCPs, especially physicians, are encouraged to continue enhancing their comprehension regarding the objective and significance of PV in an effort to not

only submit ADR reports, but to ameliorate the amount and quality of ADR reports. If physicians are properly educated on the purpose of SRS and the benefits of ADR reporting, then it is possible that they may impart their knowledge upon their patients. Moreover, if physicians are thoroughly educated by the FDA and other regulatory agencies on the postmarketing safety risks, then they can also impart their teachings upon their patients and consumers on such risks. Therefore, it is recommended that physicians undergo additional training, especially at the undergraduate level of pre-medical education, that enhances their knowledge regarding observing and detecting ADRs at the clinical level, as well as increases their comprehension regarding the significance of ADR reporting.

If an educational intervention is created to bridge the gap between HCPs' knowledge and attitudes and under-reporting of ADRs, then the reporting rate among physicians may be ameliorated (Lopez-Gonzalez et al., 2009). Therefore, in an effort to increase reporting, it is recommended that observational studies be conducted to explore the utility and effectiveness of such interventions, and to assess whether a statistically significant relationship exists between attitudes and reporting. Subsequently, it is recommended to design and launch an educational initiative to ameliorate attitudes associated with under-reporting, particularly among physicians. Consequently, such an effort may contribute to an increase in signal detection, thereby allowing the health authorities and regulatory agencies to address and combat health disparities in a rapid fashion.

Prior research has shown findings suggesting the need for educational initiatives to foster efficient patient-physician communication in an effort to improve the poor communication between patients and their physicians. Findings from previous literature have demonstrated that efficacious communication between patients and their providers stems from the ability of HCPs to convey important information regarding their patients' health, as well as the benefits and risks of drugs that patients may be consuming, in a manner that is precise, well-timed, thorough, and clear (Marcus, 2014). With regards to drug safety information, results from prior research have shown that a majority of patients prefer to have such information relayed to them in a manner and format that is accessible, easy to read, and facilitates comprehension of the material learned, with any new safety information clearly identified or marked. Accordingly, such a method may enable patients to be cognizant of new information regarding the advantages and jeopardizes of the drugs they are consuming, specifically for those who have been consuming medications for a long time and, therefore, do not feel the need to repeatedly check for new drug safety information (Marcus, 2014). Consequently, patients will be motived to actively partake in their care, thereby resulting in increased patient satisfaction, greater adherence to treatment guidelines and medication usage instructions, an amelioration in health outcomes, and a reduction in treatment times and expenditures associated with administering care (Marcus, 2014).

Additionally, results from prior research have shown that physicians are more engaged during their conversations with their patients regarding their health when these physicians have drug safety information that is relayed to them in a well-timed, concise,

and authentic fashion, thus yielding stronger and more efficient patient-physician communications (Van de Wiel et al., 2011). Therefore, it is recommended to implement educational interventions that target efficient patient-physician communication in an effort to improve the poor communication between patients and their physicians.

Previous literature findings have demonstrated findings that, although consumer reporting has increased globally, awareness of ADR reporting, especially among consumers, is still rather low (Margraff & Bertram, 2014). Findings from the UK study conducted by Avery et al. (2011) have revealed that only 8.5% of patients were cognizant of ADR reporting to SRS YCS despite patient contribution to ADR reporting since 2005 within the UK (Avery et al., 2011). The duration between the inception of direct consumer reporting and the frequency of consumer ADR reporting to SRSs appeared to impact the reporting rate. Results from prior research have shown that those countries that have allowed for direct consumer reporting for a long period of time, including, the Netherlands, Denmark, and the UK, had a higher reporting rate (de Langen et al., 2008; Aagaard et al., 2009; Avery et al., 2011). Contrarily, those countries that have recently introduced direct patient reporting, such as Portugal, Malta, and Hungary, had a lower reporting rate (Inch, Watson, Anakwe-Umeh, & YC Study Collaboration, 2012; Margraff & Bertram, 2014). Although not the aim of the present study, it is unclear the manner in which physician reporting is evolving in the countries that have introduced patient reporting. Increasing consumer and physician awareness of ADR reporting should be at the forefront of national regulatory agencies, especially in countries with a low reporting rate. Therefore, additional research is needed to investigate the attributes of consumer

reporters, in particular, the psychological features that may elucidate the willingness to partake in consumer reporting.

A recommended method to ameliorate under-reporting is to advertise the SRS to the general public and to stimulate not only HCPs, but also the consumers and their families who have experience with ADRs to submit ADR reports to regulatory health agencies, such as the FDA. Findings from a study conducted Arnott et al. (2013) have shown that promoting greater participation in pharmacovigilance activities will depend on raising public awareness, which should commence with strengthening patient-physician communication and promoting education among consumers and HCPs, especially regarding drug safety risks and ADR reporting. Moreover, it is essential to embolden consumers to submit ADR reports and to encourage them that their actions will yield significance and value to their reports (Arnott et al., 2013). If communications between patients and their physicians are strengthened, then these conversations will involve discussions on the importance and value of ADR reporting, especially if both parties are aware of ADR reporting and its significance. While educational efforts may not necessarily lead to a change in reporting behaviors, such initiatives may nonetheless provide a better understanding of reporting behaviors among consumers and physicians. Thus, it may be possible to combat discrepancies in healthcare and improve the well-being and safety of the public if concerted efforts are undertaken by researchers working with regulatory agencies, legislators, pharmaceutical companies, and the public.

Implications

The results from this study have shown that consumer reports may not only have potential impact for positive social change at the individual level, but also at the greater level of public health. ADR reports from consumers are typically commensurate with the number of consumers who consume medication (Du et al, 2012). Irrespective of reporting an ADR, the chances of consumers being impacted by other consumers who experienced the same ADRs (particular if the occurrence of the ADR is infrequent and reportage of it has not been presented by the media) are rather low. Conversely, ADR reports from HCPs for a particular medicinal product may decline over time, which may be a consequence of HCPs' failure to report the same ADR experienced by other patients (Du et al, 2012). Although the FDA mandates pharmaceutical companies to submit ADR reports, pharmaceutical companies may oftentimes be exempt by FDA for reporting certain nonserious ADRs. Therefore, the findings from this study have confirmed that consumer reporting is imperative to successful pharmacovigilance, especially in submitting ADR reports to SRSs, such as FAERs.

Findings from this study have shown that consumer ADR reports may contribute to the early detection of safety issues (Hammond et al., 2007; Egberts et al., 1996). In a study conducted by Hammond et al. (2007), of a total 23 safety issues, 12 safety issues were detected by consumers at an early stage, eight issues were identified simultaneously, and only three issues were identified after analyzing ADR reports from consumers and HCPs (Hammond et al., 2007). Moreover, consumer reported ADRs may deter misdiagnosis and the potential exacerbation of potentially grave and fatal disorders

(Vihelmsson, 2015). Hence, by gathering as many consumer and patient experiences as possible, new and suspected ADRs may be detected, thereby enabling the analysis of potential causation at the population level in an effort to counteract unwarranted harm and suffering to levels, including, but not limited to, individual, family, organizational, and societal/policy (Vihelmsson, 2015).

Additionally, the results from this study have corroborated findings from previous research suggesting that consumer ADR reports may yield novel insight and information different from that provided by reports from physicians and other HCPs. In the study conducted by Aagaard et al. (2009) in which an analysis of 6,319 ADR reports was performed, results from the study have revealed that, in comparison to other sources, patients were more likely to report ADRs associated with the following SOCS: "nervous system disorders," "psychiatric disorders," and "reproductive system and breast disorders." (Aagard et al., 2009).

Findings from this study have supported results from previous literature suggesting that consumer reporting may contribute to a greater amount of spontaneous ADR report submission, thereby augmenting SRSs and contributing to positive social change (Aagaard et al., 2009; de Langen et al., 2008; Blenkinsopp et al., 2007; van Hunsel et al., 2009). Results from published research have shown that consumers and patients are inclined to detect and report more ADRs in comparison to HCPs (Aagaard et al., 2009; de Langen et al., 2008; Blenkinsopp et al., 2007; van Hunsel et al., 2009). Similarly, the findings from my study have also demonstrated that consumers reported more ADRs and submitted more ADR reports than physicians. Since the number of

ADRs reported by consumers is higher in comparison to that of HCPs and other reporters (Van Grootheest, & de Graaf, 2003; Blenkinsopp, et al., 2007), and since the inclusion of consumer reports can provide value and additional insight beyond those reports submitted by HCPs, as evidenced in this study and previous studies, it would be justifiable to include consumer reports in the pharmacovigilance and signal detection activities of other countries in addition to those that currently accept consumer reporting of ADRs (Health Action International, 2015). Thus, by merging the reports from consumers with those of physicians and other HCPs, and injecting them into SRSs in a manner that enables causal relationships to be detected between the drugs and ADRs (and compared over time), the SRSs may ultimately contain informative and crucial data regarding ADRs, thereby contributing to the detection of signals and overall improvement in pharmacovigilance and drug safety (Health Action International, 2015).

The findings from this study have an impact for positive change at the societal level. The FAERS SRS plays an integral role in postmarket surveillance. However, the system is in dire need of updates and standardizations in an effort to respond to, depict, and disseminate information contained within the dynamic environment and the digital age consisting of the Internet and social media (ISMP, 2018). To date, the FDA has stated that it continues to revise its critical guidelines for reporting ADRs, which is a document that previously updated circa 2001. No drafts for discussion have been released. Therefore, the results from this study may attract the attention of regulatory agencies to release important instructions regarding the proper and effective means of ADR

reporting, which may inevitably stimulate reporting of ADRs to regulatory health agencies by both consumers and physicians.

Consequently, consumer reporting may actively be promoted to the general public not only through the official websites of drug regulatory agencies and via pamphlets and drug product information leaflet (for those who may not have access to the Internet), but also via public information. As indicated by the WHO, consumer reporting should be as easy and cheap as possible with, for instance, easy access to prepaid reporting forms (Vihelmsson, 2015). Findings from prior research have confirmed that consumer reporting leads to an increase in the frequency of ADRs reported to PV centers, thereby leading to signal detection (Vihelmsson, 2015). Furthermore, consumers who are cognizant of voluntary, SRSs, appeared to be knowledgeable and equipped in using such systems to directly report ADRs. However, increased promotion of and adequate training on how to utilize such systems, as well as accurate and precise ADR reporting requirements, are nonetheless needed (Vihelmsson, 2015). For instance, active promotion and increasing awareness of ADR reporting can be made at local pharmacies via brochures and information when a medicine that is prescribed or over-the-counter is purchased. These brochures may also contain easy accessible information of consumer ADR reports from which data have already been amassed and assessed, thereby presenting additional insight into potential drug-ADR associations. Within the current digital epoch, the utilization of social media data that is available for ADR monitoring is being increasingly discussed by researchers (Vihelmsson, 2015). The use of social media, especially Facebook and Twitter, has been recommended as one of the methods to

increase spontaneous ADR reporting (Vihelmsson, 2015). Currently, specific applications, such as MedWatcher, are available and accessible by consumers for reporting adverse effects resulting from drugs, vaccines, and medical devices (Vihelmsson, 2015). Hence, the results from this study can encourage additional research that may yield further insight and greater understanding of the aforementioned factors, which will ultimately transform into positive developments and practices given the necessity for more consumers to report their experienced suspected ADRs.

Conclusion

This study has shown that consumers reported more ADR reports and ADRs as well as more serious ADR reports and serious ADRs in comparison to those reported by physicians. Additionally, the study has revealed that consumers reported a large amount of nonserious ADR reports and ADRs in comparison to those reported by physicians. Moreover, the results from this study have revealed that female consumers reported more ADRs in comparison to female physicians. The results from this study have also demonstrated that consumers reported on different SOC groups than physicians. Based on the results from previous studies and from this study, consumer reports yield insight into not only the limitations of surveillance systems, but also the under-reporting of ADRs, both of which are persistent problems, especially in foreign countries and in those countries not currently accepting consumer reporting. The results from prior research have revealed that a majority of ADRs are under-reported, and the overall reporting rate of ADRs is circa 1% (although the rate considerably fluctuates due to the severity and type of reaction, as well as the characteristics of the drug). Additional findings from

studies have shown that only 6% of all ADRs are reported in the US (Alatawi & Hansen, 2017). The information from consumer reports may offer additional understanding of the ADR experiences that consumers may have. Given the higher number of ADRs reported by consumers in comparison to those reported by physicians, which was evident from the results in this study, it would be judicious to incorporate consumer reports in the PV and signal detection processes, especially in foreign countries that are not currently accepting such reporting. Hence, the findings from this study may reveal the significance of consumer reporting in providing a deeper understanding and awareness of ADRs, thereby encouraging regulators and legislators from foreign countries to accept consumer reports and integrate them with physician reports within their PV practices.

References

Aagaard, L, Nielsen, L.H., & Hansen, E.H. (2009). Consumer reporting of adverse drug reactions. A retrospective analysis of the Danish adverse drug reaction database from 2004 to 2006. *Drug Safety*, *32*(11), 1067-1074. Retrieved from http://adisonline.com/drugsafety/Pages/default.aspx

Abraham, J., & Ballinger, R. (2012). The neoliberal regulatory state, industry interests, and the ideological penetration of scientific knowledge: Deconstructing the redefinition of carcinogens in pharmaceuticals. *Science, Technology, & Human Values*, *37*(5), 443-477. doi:10.1177/0162243911424914

Adams, J. (1995). *Risk*. London: UCL Press. doi: 10.1002/sim.4780141513

Aikin, K. J., O'Donoghue, A. C., M. Squire, C., Sullivan, H. W., & Betts, K. R. (2016). An empirical examination of the FDAAA-mandated toll-free statement for consumer reporting of side effects in direct-to-consumer television advertisements. *Journal of Public Policy & Marketing*, *35*(1), 108-123. doi:10.1509/jppm.14.077

Alatawi, Y. M., & Hansen, R. A. (2017). Empirical estimation of under-reporting in the US Food and Drug Administration Adverse Event Reporting System (FAERS). *Expert Opinion on Drug Safety*, 1-7. doi:10.1080/14740338.2017.1323867

Anderson, C., Krska, J., Murphy, E., Avery, A., & Yellow Card Study Collaboration. (2011). The importance of direct patient reporting of suspected adverse drug

reactions: a patient perspective. *British Journal of Clinical Pharmacology*, *72*(5), 806-822. doi: 10.1111/j.1365-2125.2011.03990.x

Arnott, J., Hesselgreaves, H., Nunn, A. J., Peak, M., Pirmohamed, M., Smyth, R. L.,... & Young, B. (2013). What can we learn from parents about enhancing participation in pharmacovigilance?. *British Journal of Clinical Pharmacology*, *75*(4), 1109-1117. doi: 10.1111/j.1365-2125.2012.04441.x

Aronson, J. K. (2006). A prescription for better prescribing. *British Journal of Clinical Pharmacology*, *61*(5), 487-491. doi: 10.1111/j.1365-2125.2006.02649

Avery, A. J., Anderson, C., Bond, C. M., Fortnum, H., Gifford, A., Hannaford, P. C.,... & Murphy, E. (2011). Evaluation of patient reporting of adverse drug reactions to the UK 'Yellow Card Scheme': Literature review, descriptive and qualitative analyses, and questionnaire surveys. *Health Technology Assessment*. doi: 10.3310/hta15200

Biagi, C., Montanaro, N., Buccellato, E., Roberto, G., Vaccheri, A., & Motola, D. (2013). Underreporting in pharmacovigilance: an intervention for Italian GPs (Emilia–Romagna region). *European Journal of Clinical Pharmacology*, 1-8. doi: 10.1007/s11096-015-0209-x

Blenkinsopp, A., Wilkie, P., Wang, M., & Routledge, P. A. (2007). Patient reporting of suspected adverse drug reactions: a review of published literature and international experience. *British Journal of Clinical Pharmacology, 63*(2), 148-156. doi: 10.1111/j.1365-2125.2006.02746.x

Bongard, V., Ménard-Taché, S., Bagheri, H., Kabiri, K., Lapeyre-Mestre, M., &

Montastruc, J.L. (2002). Perception of the risk of adverse drug reactions: differences between health professionals and non-health professionals. *British Journal of Clinical Pharmacology, 54*(4), 433-6. doi:10.1046/j.1365-2125.2002.01674.x

Bren, L. (2001). Frances Oldham Kelsey: FDA medical reviewer leaves her mark on history. *FDA consumer*, *35*(2), 24-29. Retrieved from http://urschristen.de/GA%20-%20Thalidomid%20-%20Frances%20Oldham%20Kelsey.pdf

Britten, N. (2009). Medication errors: the role of the patient. *British Journal of Clinical Pharmacology*, *67*(6), 646–650. doi10.1111/j.1365-2125.2009.03421.x

Brown, M. T., & Bussell, J. K. (2011). Medication adherence: WHO cares? *Mayo Clinic Proceedings*, *86*(4), 304–314. doi:10.4065/mcp.2010.0575

Brun, W. (1994). Risk perception: Main issues, approaches and findings. *Subjective Probability*, 295-320. Retrieved from doi10.1111/j.1365-2125.2009.06425.x

Campbell, D., & Stanley, J. (1963). Experimental and quasi-experimental designs for research. *Boston*. Retrieved https://books.google.com/books?hl=en&lr=&id=KCTrCgAAQBAJ&oi=fnd&pg=PT4&dq=Experimental+and+quasi-experimental+designs+for+research&ots=Mdp2DSuH-I&sig=mRXgDmc6bXGSmCFOw55j6kysChU#v=onepage&q=Experimental%20and%20quasi-experimental%20designs%20for%20research&f=false

Carlson, M. D., & Morrison, R. S. (2009). Study design, precision, and validity in

observational studies. *Journal of Palliative Medicine, 12*(1), 77-82. doi: 10.1089/jpm.2008.9690

Cassels, A., Hughes, M. A., Cole, C., Mintzes, B., Lexchin, J., & McCormack, J. P. (2003). Drugs in the news: an analysis of Canadian newspaper coverage of new prescription drugs. *Canadian Medical Association Journal*, *168*(9), 1133-1137. Retrieved from http://www.cmaj.ca/content/168/9/1133.short

Chedid, V., Vijayvargiya, P., & Camilleri, M. (2018). Advantages and limitations of the federal adverse events reporting system in assessing adverse event reporting for eluxadoline. *Clinical Gastroenterology and Hepatology*, *16*(3), 336-338. Retrieved from https://www.cghjournal.org/article/S1542-3565(17)31362-9/abstract

Cobert, B. (2011). *Cobert's manual of drug safety and pharmacovigilance*. Jones & Bartlett Publishers.

Creswell, J. (2014). The Selection of a Research Design. In *Research Design: Qualitative, Quantitative, and Mixed Methods Approaches* (p. 3). London: Sage Publications. Retrieved from http://www.sagepub.com.proxy1.athensams.net/upm-data/22780_Chapter_1.pdf

de Langen, J., van Hunsel, F., Passier, A., de Jong-van den Berg, L., & van Grootheest, K. (2008). Adverse drug reaction reporting by patients in The Netherlands three years of experience. *Drug Safety*, 31(6), 515-524. Retrieved from https://rd.springer.com/article/10.2165/00002018-200831060-00006

Diether, v. (2016, December 5). *Writing Chapter 4: The results of your research study*. Retrieved from http://dissertationwriting.com/write-dissertation-results-chapter/

Di Maio, M., Gallo, C., Leighl, N. B., Piccirillo, M. C., Daniele, G., Nuzzo, F., ... & Ceribelli, A. (2015). Symptomatic toxicities experienced during anticancer treatment: agreement between patient and physician reporting in three randomized trials. *Journal of Clinical Oncology*, *33*(8), 910-915. Retrieved from https://iris.unito.it/handle/2318/1572016#.W9H9w8_rt9M

Drottz-Sjöberg, B. M. (1991). *Non-expert definitions of risk and risk perception*. Center for Risk Research, Stockholm School of Economics. Retrieved from https://books.google.com/books?id=DC34skLhI90C&pg=PA758&dq=Non-expert+definitions+of+risk+and+risk+perception.+Center&hl=en&sa=X&ved=0ahUKEwiZ5orhj6LeAhXSUt8KHS1eBRMQ6AEIKDAA#v=onepage&q=Non-expert%20definitions%20of%20risk%20and%20risk%20perception.%20Center&f=false

Du, D. T., Goldsmith, J., Aikin, K. J., Encinosa, W. E., & Nardinelli, C. (2012). Despite 2007 law requiring FDA hotline to be included in print drug ads, reporting of adverse events by consumers still low. *Health Affairs*, *31*(5), 1022-1029. Retrieved from https://www.healthaffairs.org/doi/abs/10.1377/hlthaff.2010.1004

Durrie, G., Hurault, C., Damase-Michel, C., & Montastruc, J.L. (2009). Perception of risk of adverse drug reactions: A 3-year follow-up of a cohort of medical students. *Fundamental and Clinical Pharmacology*, 24(4), 423-427. doi:10.1111/j.1472-8206.2009.00783.x

Egberts, T. C., Smulders, M., De Koning, F. H., Meyboom, R. H., & Leufkens, H. G. (1996). Can adverse drug reactions be detected earlier? A comparison of reports by patients and professionals. *BMJ*, *313*(7056), 530-531. Retrieved from https://www.bmj.com/content/313/7056/530.short

EMEA. (1995). *ICH Topics E 2 A Clinical Safety Data Management Definitions and Standards for Expedited Reporting*. Retrieved from http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002749.pdf

Enger, C., Younus, M., Petronis, K. R., Mo, J., Gately, R., & Seeger, J. D. (2013). The effectiveness of varenicline medication guide for conveying safety information to patients: a REMS assessment survey. *Pharmacoepidemiology and Drug Safety*, *22*(7), 705-715. Retrieved from https://onlinelibrary.wiley.com/doi/full/10.1002/pds.3400

European Medicines Agency. (2010). *Regulations.* Retrieved April 23, 2017, from Office Journal of the European Union: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=%20OJ:L:2010:348:0001:0016:EN:PDF

Farquhar, C., Armstrong, S., Kim, B., Masson, V., & Sadler, L. (2015). Under-reporting of maternal and perinatal adverse events in New Zealand. *BMJ open*, *5*(7), e007970. Retrieved from https://bmjopen.bmj.com/content/5/7/e007970.short

FDA. (n.d.). *FAERS Public Dashboard*. Retrieved from https://fis.fda.gov/sense/app/777e9f4d-0cf8-448e-8068-f564c31baa25/sheet/7a47a261-d58b-4203-a8aa-6d3021737452/state/analysis

FDA. (2015). *Instructions for Requesting Individual Case Reports*. Retrieved January 18, 2016, from http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm345338.htm

FDA. (2016a). Preventable Adverse Drug Reactions: A Focus on Drug Interactions Retrieved November 5, 2017, from https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm110632.htm

FDA. (2016b). *FDA Adverse Event Reporting System (FAERS): Latest Quarterly Data Files*. Retrieved January 18, 2016, from http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm082193.htm

FDA. (2017). Questions and Answers on FDA's Adverse Event Reporting System. Retrieved October 7, 2017, from https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/surveillance/adversedrugeffects/

Field, A. (2013). *Discovering Statistics using IBM SPSS Statistics.* SAGE Publications, Ltd.

Frankfort-Nachmias, C. (2014). *Research Methods for the Social Sciences.*Worth Publishers.

Gawron, A. J., & Bielefeldt, K. (2018). Risk of pancreatitis following treatment of irritable bowel syndrome with eluxadoline. *Clinical Gastroenterology and Hepatology*, *16*(3), 378-384. Retrieved from https://www.sciencedirect.com/science/article/pii/S1542356517309357

Gerstman, B. B. (2008). Basic biostatistics: Statistics for health practice. Sudbury, MA: Jones and Bartlett.

Gilchrist, A. (2016). *Bill to restrict DTC ads introduced in house commitee*. Retrieved September 26, 2018, from Pharmacy Times: https://www.pharmacytimes.com/news/bill-to-restrict-dtc-ads-introduced-in-house-committe

Goldsmith, J., Aikin, K. J., Encinosa, W. E., & Nardinelli, C. (2012). Despite 2007 law requiring FDA hotline to be included in print drug ads, reporting of adverse events by consumers still low. *Health Affairs*, *31*(5), 1022-1029. Retrieved from https://www.healthaffairs.org/doi/abs/10.1377/hlthaff.2010.1004

Golomb, B., McGraw, J., Evans, M., & Dimsdale, J. (2007). Physician response to patient reports of adverse drug effects: implications for patient-targeted adverse effect surveillance. *Drug Safety, 30*, 669-675. Retrieved from https://rd.springer.com/article/10.2165/00002018-200730080-00003

Gualano, M. R., Gili, R., Scaioli, G., Bert, F., & Siliquini, R. (2015). General population's knowledge and attitudes about antibiotics: a systematic review and meta-analysis. *Pharmacoepidemiology and Drug Safety*, *24*(1), 2-10. Retrieved from https://onlinelibrary.wiley.com/doi/full/10.1002/pds.3716

Hammond, I. W., Rich, D. S., & Gibbs, T. G. (2007). Effect of consumer reporting on signal detection: using disproportionality analysis. *Expert Opinion on Drug Safety*, *6*(6), 705-712. Retrieved from https://www.tandfonline.com/doi/abs/10.1517/14740338.6.6.705

Hauben, M., & Aronson, J. K. (2009). Defining a signal and its subtypes in pharmacovigilance based on a systematic review of previous definitions. *Drug Safety*, *32*(2), 99. Retrieved from https://rd.springer.com/article/10.2165/00002018-200932020-00003

Hazell, L., & Shakir, S. A. (2006). Under-reporting of adverse drug reactions. *Drug Safety*, *29*(5), 385-396. Retrieved from https://rd.springer.com/article/10.2165/00002018-200629050-00003

Health Action International. (2015). *Direct Patient Reporting in the European Union*. Retrieved December 22, 2016, from A Snapshot of Reporting Systems in Seven Member States: http://haieurope.org/wp-content/uploads/2015/09/Direct-Patient-Reporting-in-the-EU.pdf

Herdeiro, M. T., Figueiras, A., Polónia, J., & Gestal-Otero, J. J. (2005). Physicians' attitudes and adverse drug reaction reporting. *Drug Safety*, *28*(9), 825-833. Retrieved from https://rd.springer.com/article/10.2165/00002018-200528090-00007

Herxheimer, A., Crombag, R., & Alves, T. L. (2010). Direct patient reporting of adverse drug reactions: a 12-country survey. Briefing Paper. *Health Action International,*

Europe. Retrieved from https://consumers.cochrane.org/sites/consumers.cochrane.org/files/public/uploads/10%20May%202010%20Report%20Direct%20Patient%20Reporting%20of%20ADRs.pdf

Hoyert, D. L., & Xu, J. (2012). Deaths: preliminary data for 2011. *National Vital Statistics Report*, *61*(6), 1-51. Retrieved from https://www.cdc.gov/nchs/data/nvsr/nvsr61/nvsr61_06.pdf

Hyman S.E. (2000). The needs for database research and for privacy collide. *American Journal of Psychiatry*, 157(11), 1723-1724. Retrieved from http://ajp.psychiatryonline.org/article.aspx?Volume=157&page=1723&journalID=13

Jagsi, R., Griffith, K. A., Stewart, A., Sambuco, D., DeCastro, R., & Ubel, P. A. (2012). Gender differences in the salaries of physician researchers. *JAMA Internal Medicine*, *307*(22), 2410-2417. Retrieved from https://jamanetwork.com/journals/jama/fullarticle/1182859

Jena, A. B., Olenski, A. R., & Blumenthal, D. M. (2016). Sex differences in physician salary in US public medical schools. *JAMA Internal Medicine*, *176*(9), 1294-1304. Retrieved from https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2532788?linkId=26599569

Kasperson, J., & Ratick, S (1988). The social amplification of risk: a conceptual framework. *Risk Analysis* 8(2), 177–187. doi:10.1111/j.1539-6924.1988.tb01168.x

Krska, J., Anderson, C., Murphy, E., Avery, A. J., & Yellow Card Study Collaboration. (2011). How patient reporters identify adverse drug reactions. *Drug Safety*, *34*(5), 429-436. Retrieved from https://rd.springer.com/article/10.2165/11589320-000000000-00000

Inácio, P., Cavaco, A., & Airaksinen, M. (2016). The value of patient reporting to the PV system: a systematic review. *British Journal of Clinical Pharmacology*. Retrieved from https://bpspubs.onlinelibrary.wiley.com/doi/full/10.1111/bcp.13098

ICH. (2013). *Understanding MedDRA*. Retrieved from https://www.meddra.org/sites/default/files/page/documents/meddra2013.pdf

Inch, J., Watson, M. C., Anakwe-Umeh, S., & Yellow Card Study Collaboration. (2012). Patient versus healthcare professional spontaneous adverse drug reaction reporting. *Drug Safety*, *35*(10), 807-818. Retrieved from https://rd.springer.com/article/10.1007/BF03261977

Institute for Safe Medication Practices. (2015). *A Critique of a Key Drug Safety Reporting System*. Retrieved December 3, 2017, from https://www.ismp.org/quarterwatch/pdfs/2014Q1.pdf

ISMP. (2018, September). *Annual Report Issue- September 2018*. Retrieved September 28, 2018, from Quarter Watch: https://www.ismp.org/quarterwatchtm/annual-report-Sept-2018

Jarernsiripornkul, N., Krska, J., Capps, P. A. G., Richards, R. M. E., & Lee, A. (2002).

Patient reporting of potential adverse drug reactions: a methodological study. *British Journal of Clinical Pharmacology*, *53*(3), 318-325. Retrieved from https://bpspubs.onlinelibrary.wiley.com/doi/full/10.1046/j.0306-5251.2001.01547.x

Kasperson, J., & Ratick, S (1988). The social amplification of risk: a conceptual framework. *Risk Analysis* 8(2), 177–187. doi:10.1111/j.1539-6924.1988.tb01168.x

Kessler, D. A., & Vladeck, D. C. (2007). A critical examination of the FDA's efforts to preempt failure-to-warn claims. *Geo. LJ*, *96*, 461. Retrieved from https://heinonline.org/HOL/LandingPage?handle=hein.journals/glj96&div=18&id=&page=

Lazarou, J., Pomeranz, B. H., & Corey, P. N. (1998). Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. *JAMA Internal Medicine*, *279*(15), 1200-1205. Retrieved from https://jamanetwork.com/journals/jama/article-abstract/187436

Leroy, F., Dauxois, J. Y., Théophile, H., Haramburu, F., & Tubert-Bitter, P. (2014). Estimating time-to-onset of adverse drug reactions from spontaneous reporting databases. *BMC Medical Research Methodology*, *14*(1), 17. Retrieved from https://bmcmedresmethodol.biomedcentral.com/articles/10.1186/1471-2288-14-17

Lopez-Gonzalez, E., Herdeiro, M. T., & Figueiras, A. (2009). Determinants of under-reporting of adverse drug reactions. *Drug Safety*, *32*(1), 19-31. Retrieved from https://rd.springer.com/article/10.2165/00002018-200932010-00002

Lucca, J. M., Ramesh, M., & Ram, D. (2017). Gender differences in the occurrences and pattern of adverse drug reactions in psychiatric patients: a prospective observational study. *Tropical Journal of Medical Research*, *20*(1), 84. Retrieved from http://www.tjmrjournal.org/article.asp?issn=1119-0388;year=2017;volume=20;issue=1;spage=84;epage=90;aulast=Lucca

Maciejewski, M., Lounkine, E., Whitebread, S., Farmer, P., DuMouchel, B., Shoichet, B. K., & Urban, L. (2017). The importance of reverse translation for preclinical off-target mitigation: quantification and mitigation of biases in the FDA adverse event reporting system. *BioRxiv*, 068692. Retrieved from https://www.biorxiv.org/content/early/2017/01/29/068692

Marcus, C. (2014). Strategies for improving the quality of verbal patient and family education: a review of the literature and creation of the EDUCATE model. *Health Psychology and Behavioral Medicine: An Open Access Journal*, *2*(1), 482-495. Retrieved from https://www.tandfonline.com/doi/abs/10.1080/21642850.2014.900450

Margraff, F., & Bertram, D. (2014). Adverse drug reaction reporting by patients: an overview of fifty countries. *Drug Safety*, *37*(6), 409-419. Retrieved from https://rd.springer.com/article/10.1007/s40264-014-0162-y

McAdams, M. A., Governale, L. A., Swartz, L., Hammad, T. A., & Dal Pan, G. J. (2008). Identifying patterns of adverse event reporting for four members of the angiotensin II receptor blockers class of drugs: revisiting the Weber effect. *Pharmacoepidemiology and Drug Safety*, *17*(9), 882-889. Retrieved from

https://insights.ovid.com/pharmacoepidemiology-drug-safety/pads/2008/08/001/index-blame-agreement-subjective-vs-objective/37/01445491

Medscape. (2017). *Physician Lifestyle Report 2017. Retrieved September 28, 2018, from https://www.medscape.com/sites/public/lifestyle/2017*

Mezher, M. (2017, August 29). *Making Sense of FAERS: Researchers Suggest Fixes to FDA's Adverse Event Database*. Retrieved from http://raps.org/Regulatory-Focus/News/2017/08/29/28355/Making-Sense-of-FAERS-Researchers-Suggest-Fixes-to-FDAs-Adverse-Event-Database/

Medawar, C., & Herxheimer, A. (2004). A comparison of adverse drug reaction reports from professionals and users, relating to risk of dependence and suicidal behavior with paroxetine. *International Journal of Risk & Safety in Medicine*, *16*(1), 5-19. Retrieved from https://content.iospress.com/articles/international-journal-of-risk-and-safety-in-medicine/jrs295

Miller, Rupert G. (1966). *Simultaneous Statistical Inference*. Springer. Retrieved from https://www.springer.com/us/book/9781461381242

Mitchell, A., Henry, D., Sanson-Fisher, R., & O'Connell, D. (1994). Patients as a direct source of information on adverse drug reactions. *British Medical Journal, 297*, 891-893. Retrieved from https://www.bmj.com/content/297/6653/891.short

Mittelhammer, Ron C., Judge, George G., Miller, Douglas J. (2000). *Econometric Foundations.* Cambridge University Press. pp. 73–74. ISBN 0-521-62394-4.

Moore, T. J., & Bennett, C. L. (2012, November). Under-reporting of hemorrhagic and

thrombotic complications of pharmaceuticals to the US Food and Drug Administration: empirical findings for warfarin, clopidogrel, ticlopidine, and thalidomide from the Southern Network on Adverse Reactions (SONAR). In *Seminars in thrombosis and hemostasis* (Vol. 38, No. 08, pp. 905-907). Thieme Medical Publishers.

Moulis, G., Sommet, A., Durrieu, G., Bagheri, H., Lapeyre-Mestre, M., & Montastruc, J. L. (2012). Trends of reporting of 'serious' versus'non-serious' adverse drug reactions over time: a study in the French PharmacoVigilance Database. *British Journal of Clinical Pharmacology*, *74*(1), 201-204.

Ott, R. L., & Longnecker, M. T. (2008). An Introduction to Statistical Methods and Data analysis. Nelson Education.

Pal, S. N., Duncombe, C., Falzon, D., & Olsson, S. (2013). WHO strategy for collecting safety data in public health programmes: complementing SRSs. *Drug Safety*, *36*(2), 75-81. Retrieved from https://rd.springer.com/article/10.1007/s40264-012-0014-6

Parrella, A., Gold, M., Marshall, H., Braunack-Mayer, A., Watson, M., & Baghurst, P. (2012). Parental views on vaccine safety and future vaccinations of children who experienced an adverse event following routine or seasonal influenza vaccination in 2010. *Human Vaccines & Immunotherapeutics*, *8*(5), 662-667. Retrieved from https://www.tandfonline.com/doi/abs/10.4161/hv.19478

Pillans, P. I. (2008). Clinical perspectives in drug safety and adverse drug

reactions. *Expert Review of Clinical Pharmacology, 1*(5), 695-705. Retrieved from https://www.tandfonline.com/doi/abs/10.1586/17512433.1.5.695

Prescrire International. 2015. *The Reorganisation of European Pharmacovigilance*. doi 10.1111/j.1472-8206.2009.00799.x

Price, P. (2012). *Research Methods in Psychology: Core Concepts and Skills.* Retrieved March 13, 2016, from Overview of Non-experimental Research. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/25802924

Rademaker, M. (2001). Do women have more adverse drug reactions?. *American Journal of Clinical Dermatology*, *2*(6), 349-351. Retrieved from https://rd.springer.com/article/10.2165/00128071-200102060-00001

Research Design. (n.d.). Retrieved March 9, 2016, from Descriptive Studies: https://ori.hhs.gov/education/products/sdsu/res_des1.htm

Robertson, J., & Newby, D. A. (2013). Low awareness of adverse drug reaction reporting systems: a consumer survey. *The Medical Journal of Australia*, *199*(10), 684-686. Retrieved from https://www.mja.com.au/system/files/issues/199_10_181113/rob10069_fm.pdf

Rodriguez, E. M., Staffa, J. A., & Graham, D. J. (2001). The role of databases in drug postmarketing surveillance. *Pharmacoepidemiology and Drug Safety*, *10*(5), 407-410. Retrieved from https://onlinelibrary.wiley.com/doi/abs/10.1002/pds.615

Sakaeda, T., Tamon, A., Kadoyama, K., & Okuno, Y. (2013). Data mining of the public

version of the FDA Adverse Event Reporting System. *International Journal of Medical Sciences*, *10*(7), 796. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3689877/

Schernhammer, E. S., & Colditz, G. A. (2004). Suicide rates among physicians: a quantitative and gender assessment (meta-analysis). *American Journal of Psychiatry*, *161*(12), 2295-2302. Retrieved from https://ajp.psychiatryonline.org/doi/abs/10.1176/appi.ajp.161.12.2295

Schor, N. F. (2018). The decanal divide: women in decanal roles at US medical schools. *Academic Medicine*, *93*(2), 237-240. Retrieved from https://www.ingentaconnect.com/content/wk/acm/2018/00000093/00000002/art00030

Science Museum. (n.d.). *Thalidomide*. Retrieved from Brought to Life: http://broughttolife.sciencemuseum.org.uk/broughttolife/themes/controversies/thalidomide

Sen, S. (2016). Consumer reporting of adverse drug reactions: A current perspective. *International Journal of Green Pharmacy (IJGP)*, *10*(03). Retrieved from http://www.greenpharmacy.info/index.php/ijgp/article/view/671

Sultana, J., Cutroneo, P., & Trifirò, G. (2013). Clinical and economic burden of adverse drug reactions. *Journal of Pharmacology & Pharmacotherapeutics*, *4*(Suppl1), S73. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3853675/

Tadesse, W. T., Mekonnen, A. B., Tesfaye, W. H., & Tadesse, Y. T. (2014). Self-

reported adverse drug reactions and their influence on highly active antiretroviral therapy in HIV infected patients: a cross-sectional study. *BMC Pharmacology and Toxicology*, *15*(1), 32. Retrieved from https://bmcpharmacoltoxicol.biomedcentral.com/articles/10.1186/2050-6511-15-32

University of Chicago. (2014, March). *Guidance on Secondary Analysis of Existing Data Sets.* Retrieved from https://sbsirb.uchicago.edu/page/irb-guidance-documents-important-topics

U.S. Department of Health & Human Services. (2010, January 15). *Office for Human Research Protections*. Retrieved February 1, 2016, from 45 CFR 46: https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/

Van de Wiel, M. W., Van den Bossche, P., Janssen, S., & Jossberger, H. (2011). Exploring deliberate practice in medicine: how do physicians learn in the workplace?. *Advances in Health Sciences Education*, *16*(1), 81-95. Retrieved from https://rd.springer.com/article/10.1007/s10459-010-9246-3

Van Grootheest, K., & de Graaf, L. (2003). Consumer adverse drug reaction reporting. *Drug Safety*, *26*(4), 211-217. Retrieved from https://rd.springer.com/article/10.2165/00002018-200326040-00001

Van Hunsel, F., Passler, A., & Grootheest, C. (2009). Comparing patients' and healthcare professionals' ADR reports after media attention: the broadcast of a Dutch television programme about the benefits and risks of statins as an example. *British*

Journal Clinical Pharmacology, 5, 558-564. Retrieved from https://bpspubs.onlinelibrary.wiley.com/doi/full/10.1111/j.1365-2125.2009.03400.x

Van-Lierop, T., & Bunyan, C. (2008). *Strengthening Pharmacovigilance to Reduce Adverse Effects of Medicines*. Retrieved from https://ec.europa.eu/health/sites/health/files/files/pharmacovigilance/docs/2007_02_26/press-release_02_2007_en.pdf

Vilhelmsson, A. (2015). Consumer narratives in ADR reporting: an important aspect of public health? Experiences from reports to a Swedish consumer organization. *Frontiers in Public Health*, *3*, 211. Retrieved from https://www.frontiersin.org/articles/10.3389/fpubh.2015.00211/full

Vural, F., Ciftci, S., & Vural, B. (2014). The knowledge, attitude and behaviors of nurses about pharmacovigilance, adverse drug reaction and adverse event reporting in a state hospital. *Northern Clinics of Istanbul*, *1*(3), 147. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5175033/

Walden University. (n.d.). *Red flag issues that should trigger a research ethics consultation with the IRB*. Retrieved February 1, 2016, from http://academicguides.waldenu.edu/researchcenter/orec/guides

WHO. (2002). The importance of PV: safety monitoring of medicinal products. Retrieved from http://apps.who.int/medicinedocs/en/d/Js4893e/9.html

WHO. (2012). *Safety Monitoring of Medicinal Products: Reporting System for the General Public.* Retrieved April 23, 2017, from

http://www.who.int/medicines/areas/quality_safety/safety_efficacy/EMP_ConsumerReporting_web_v2.pdf

WHO. (2017). *Essential medicines and health products*. Retrieved April 23, 2017, from PV: http://www.who.int/medicines/areas/quality_safety/safety_efficacy/pharmvigi/en/

Yellowcard. (2017). *About Yellowcard*. Retrieved October 7, 2017, from https://yellowcard.mhra.gov.uk/the-yellow-card-scheme/

Yong, P. L., Bigman, C., Flynn, D. N., Mittermaier, D., & Long, J. A. (2009). Messages about Black-Box Warnings. *Drug Safety*, *32*(12), 1147-1157. Retrieved from https://rd.springer.com/article/10.2165/11318960-000000000-00000