

**Spontaneous Adverse Drug Reaction Reporting By Health
Consumers in Canada: A Multi-Methods Study**

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

Bismi-llāhi r-raḥmāni r-raḥīm

"In the name of God, the Most Gracious, the Most Merciful"

Dissertation Abstract

Monitoring adverse drug reactions (ADRs) through pharmacovigilance is vital to health consumer safety. Health Canada accepts ADR reports from physicians, health consumers, lawyers and manufacturer. This study uses a multi-methods approach to evaluate health consumers ADR reporting to pharmacovigilance programs.

Methods:

Guided by Risk Perception Theory, this study involved three phases.

- 1) A systematic review to identify factors influencing health consumer ADR reporting
- 2) An observational study to compare health consumer and physician ADR reports received by Health Canada from 2000-2014 to determine differences in seriousness, system organ class, and anatomical therapeutic class.
- 3) A qualitative study to explore health consumers' experiences with ADR reporting and usability of the Canadian Vigilance ADR system.

Results:

- 1) Of 1435 citations identified, 22 studies were eligible. Common barriers for health consumers to report ADRs were poor awareness and confusion on who should report. Common motives were preventing ADRs in others and wanting feedback.
- 2) Of 198,781 ADR reports, 57,078 (29.0 %) were from health consumers and 52,843 (27.0%) from physicians. Compared to physicians, health consumers reported significantly more ADRs (serious and non-serious) ($p < 0.0001$) and reported differently for organ systems affected and by types of medication.
- 3) Interviews from 15 adult health consumers revealed barriers (e.g., poor awareness about the available reporting systems) and motives for reporting ADRs (e.g., intolerable side effect impacting daily activities). Few were aware of the Canadian Vigilance reporting system and usability was limited by the number and complexity of questions.

Conclusion:

Health consumer role in directly reporting ADRs is influenced by several factors. In Canada, most were unaware of the Canadian Vigilance System and unclear about their role in reporting ADRs. Quarters of Canadian ADRs are reported by health consumers and their ADRs had different characteristics from physicians. These findings are relevant to policymakers, public health officials, and regulatory agencies for improving medication safety in Canada and worldwide.

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List of Abbreviations

ADRs	Adverse Drug Reactions
AMSTAR	Assessment of Multiple Systematic Reviews
CASP	Critical Appraisal Skills Program
CIOMS	Council for International Organizations of Medical Sciences
EMA	European Medical Agency
FDA	Food and Drug Administration
HCPs	Healthcare Professionals
ICH	International Conference on Harmonization
MAH	Manufacturing Authorization Holders
MedDRA	The Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
PICO	Population, Intervention, Comparator, and Outcomes
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
TGA	Therapeutic Good Administration
UK	United Kingdom
US	United State
WHO	World Health Organization
YCS	Yellow Card Scheme

Chapter One. Introduction

Introduction

This chapter describes the statement of problem, the study objectives and the dissertation format.

1.1. Statement of Problem

Drug safety is a serious issue and adverse drug reactions (ADRs) are a common aspect of drug therapy due to extensive use of medications (Jarernsripornkul, Krska, Capps, Richards, & Lee 2002). Over the past two decades, 3.9% to 4.4% of the drugs approved in each 5-year period were eventually withdrawn from the market by Health Canada for safety reasons (Lexchin, 2014). In 2011, 1 in 200 Canadian seniors and 1 in 1000 Canadian non-seniors were identified as having an ADR-related hospitalization (CIHI, 2013). ADRs are a worldwide problem that affects different populations. ADRs can result in significant disabilities or mortalities and are associated with an economic drain of the healthcare system (Oshikoya & Awobusuyi, 2009).

ADRs are monitor by most countries and by the World Health Organization (WHO) using spontaneous reporting systems. Spontaneous reporting systems are a key component of pharmacovigilance, which encompasses the science and activities related to monitoring, detecting, assessing, understanding, and preventing ADRs (Aagaard, Nielsen, & Hansen, 2009). Pharmacovigilance methods include post-marketing surveillance, interrogation of large electronic data sets, and spontaneous ADR reporting (Sharrar & Dieck, 2013). Spontaneous reporting (volunteer reporting) is the most common method used for data collection and monitoring of ADR. In spontaneous reporting systems, physicians, pharmacists, and health consumers voluntarily report any suspected reaction due to the use of health product (Harmark, 2008). The main advantage of spontaneous reporting is that its scope is national and able to cover diverse populations. In post marketing surveillance, the most severe and unexpected cases are reported which is helpful in detecting signals more rapidly. The major disadvantages of this system include underreporting and poor quality of reports.

In the beginning of ADR monitoring, only doctors and dentists were allowed to submit ADR reports to pharmacovigilance databases (Aagaard et al., 2009). However, in 1995 when health agencies started focusing more on health consumers' safety, all drug manufacturers worldwide were mandated to report ADRs (WHO, 2011). Later, other healthcare professionals (HCPs), pharmacists, and health consumers were allowed to report ADRs in the hopes that this would increase the volume and quality of ADR reports (Aagaard et al., 2009).

Pharmacovigilance organizations' interest in involving health consumers as reporters appears to be influenced by underreporting of ADRs by HCPs (Golomb, McGraw, Evans, & Dimsdale, 2007). Health Consumers reports are not universally accepted in pharmacovigilance, but lately, and because of the elevation in the number of national pharmacovigilance schemes, there has been an increase in the acceptance rate of health consumer reports (van Hunsel, van der Welle, Passier, van Puijenbroek, & van Grootheest, 2010). Around 46 countries accept health consumer ADR reports to their national pharmacovigilance schemes; while fear of added noise or confusion and the potential difficulty in identifying serious ADRs has delayed other countries from accepting health consumer's reports (Blenkinsopp, Wilkie, Wang, & Routledge, 2007).

There is an ongoing debate about the benefits of direct health consumer reporting of ADRs to pharmacovigilance and signal detection. Some health authorities feel that health consumers create messy reports and that they lack the medical background necessary to make adequate additions to the surveillance systems (Mitchell, Henry, Sanson-Fisher, & O'Connell, 1988). Others confirm that health consumer reporting is essential for good pharmacovigilance practices and signal detection and should therefore be included (van Grootheest, de Graaf, & Berg, 2003). Although recent research has tentatively shown validity and benefits in direct health consumer reporting (Basch, 2010), there is a lack of published literature to support or deny these claims. Furthermore, the literature is deficient when we target factors influencing reporting ADR by health consumers.

The acceptance of spontaneous ADR health consumer reports' has been in effect in Canada since 1965, but little is known about health consumer experience and the usability of the ADR

reporting system. No studies were found using the Canadian ADR Reporting System in comparing reports from physicians and health consumers.

1.2. Study Objectives

The overall aim of this dissertation is to evaluate the involvement of health consumer ADR reporting on pharmacovigilance activities using a multi-methods study. Specific objectives were focused on the following:

1. To conduct a systematic review to determine the factors influencing health consumer reporting of ADRs.
2. To conduct a retrospective observational study to compare ADRs reported by health consumers with ADRs reported by physicians based on seriousness, system organ class (SOC), and anatomical therapeutic chemical (ATC).
3. To conduct an interpretive description, qualitative study to explore health consumers' experiences reporting ADRs and the usability of the Canadian Vigilance reporting system.

1.3. Dissertation Format

This is a manuscript-based dissertation (see Table 1.1). Chapter 1 describes the research problem and organization of the dissertation. Chapter 2 is a literature review findings about ADR reporting by health consumers. Chapter 3 presents the dissertation's methodologies in detail. Chapter 4 is a systematic review, which aimed to determine the factors influencing reporting of ADRs by health consumers. Chapter 5 is a retrospective observational study, which compared ADRs reported to the Canadian Vigilance System by health consumers with ADRs reported by physicians based on seriousness, system organ class (SOC), and anatomical therapeutic chemical (ATC). Chapter 6 is an interpretive description qualitative study, which explored Canadian health consumers' experiences reporting ADRs and the usability of the Canadian Vigilance Reporting System. Chapter 7 provides an integrated discussion of the dissertation findings. Finally, Chapter 8 describes the role of the co-authors of the manuscript.

Table 1.1 Summary of Dissertation Organization

Chapter #	Chapter title	Objective(s)	Methods	Manuscript Format
1	Introduction	Describe the research problem, and explain the organization of the dissertation	N/A	American Psychological Association
2	Literature Review	Examine adverse drug reaction reporting by health consumers	Literature review	American Psychological Association
3	Methodology	Discuss dissertation methodologies in details	N/A	American Psychological Association
4	Factors Affecting Health consumer Reporting of Adverse Drug Reactions: A Systematic Review	Determine factors influencing health consumer reporting of adverse drug reactions	Systematic Review	British Journal of Clinical Pharmacology
5	Adverse Drug Reaction Reporting in Canada: A Retrospective Observational Analysis of Health Canada Adverse Drug Reaction Database from 2000 to 2014	Compare ADRs reported by health consumers with ADRs reported by physicians based on seriousness, system organ class (SOC), and anatomical therapeutic chemical (ATC)	Retrospective observational study- Cross-sectional	Drug Safety
6	Explore health consumer views and experiences on reporting ADRs to the Canadian Vigilance Database: A Qualitative Study	Explore health consumers' experiences reporting adverse drug reactions and the usability of the Canadian Vigilance Reporting System	Interpretive description qualitative study	Drug Safety
7	Integrated Discussion	Provide an integrated discussion of the dissertation findings	Descriptive Synthesis	American Psychological Association
8	Contributions	Describe the role of manuscript authors	N/A	American Psychological Association

**Chapter Two. Adverse Drug Reporting by Health consumer: Literature
Review**

Literature Review

The review of the literature is divided into six parts. Section, 2.1 presents countries where direct health consumer adverse drug reactions (ADRs) reporting is accepted and gives examples on which countries accept direct health consumer reporting and when they started accepting direct reporting. Section, 2.2 provide information on ADRs in Canada. The third section, 2.3 presents an overview of the Canadian Vigilance ADR Online Database that is further described in the current available online database from Health Canada. Section 2.4, reviews the ADR reports submitted internationally by health consumers versus those submitted by healthcare professionals to the post-market surveillance databases. Furthermore, section 2.5 introduces direct health consumer-reporting effect on signal detection in which comparative analysis was used internationally. Section 2.6, presents an overview of the Medical Dictionary for Regulatory Activities (MedDRA). The last section, 2.6, summarizes the literature.

2.1 Countries that Accept Direct Health consumer ADR Reporting

ADRs are monitored by many countries including the World Health Organization (WHO) since the 1960s using spontaneous reporting systems, also called 'early warning' systems (Stricker & Psaty, 2004) . During the first years of reporting systems' existence, only doctors and dentists were allowed to submit reports (Herxheimer, Crombag, & Alves, 2010). As of 2011, around 46 countries accept health consumer ADR reports to their national spontaneous reporting databases (Avery et al., 2011). Allowing health consumers to report ADRs directly to health authorities was seen by the European Commission as a way to improve pharmacovigilance (van Hunsel, Harmark, Pal, Olsson, & van Grootheest, 2012). The potential benefits of health consumer reporting, as summarized at the First International Conference on Consumer Reports on Medicines in 2000, included the promotion of health consumer rights and equity, acknowledging that health consumers have unique perspectives and experiences and that healthcare organizations would benefit from health consumer involvement (Anderson, Krska, Murphy, Avery, 2011).

Table 2.1 shows the countries that were identified as having health consumer reporting schemes. Countries such as France, China, Spain, and Portugal do not accept health consumer reports into their pharmacovigilance activities or signal detection (Herxheimer, Crombag, & Alves, 2010).

Table 2.1 National Pharmacovigilance Schemes that Include Health Consumer Reporting

Country	Pharmacovigilance System	Year Of Start Accepting Health Consumers Reporting	Reporting Methods
Australia (Avery et al., 2011)	Therapeutic Good Administration	2003	Hard copy form 'Blue card', online, post, telephone
Belgium (Herxheimer et al., 2010)	Federal Agency for Medicines and Health Products (FAMHP)	2006	Hard copy form 'Yellow card',
Canada (Health Canada, 2008)	Health Canada Vigilance Program	1965	Post, fax, telephone, online method launched in 2005
Denmark (Aagaard et al., 2009)	Danish Medicines Agency	2003	E-mail, post, online, fax
Italy (Herxheimer et al., 2010)	Italian Drug Regulatory Agency	2004	Form downloaded from internet; electronic form also available
Netherlands (Avery et al., 2011)	The Netherlands Pharmacovigilance Centre Lab (Lareb)	2003	Post, e-mail, fax, online, telephone
New Zealand (Avery et al., 2011)	Medicines and Medical Devices Safety Authority	1970	Report forms available online or as hard copy For submission by freepost, fax or e-mail; telephone reports also accepted
Sweden (Herxheimer et al., 2010)	Swedish Drug Information system	1978	Forms, e-mail, electronic method launched in 2008
UK (Inch et al., 2012)	The Yellow Card Scheme	2003, pilot; 2005, full introduction)	Hard copy form 'Yellow Card', post, e-mail, fax, telephone, online
USA (Avery et al., 2011)	US Food and Drug Administration (FDA)	1960	Post, online, telephone

2.2. Health Consumer versus Healthcare Professional Reports

Health consumers' reports add another rich source from which data may be extracted. They provide insight into the impact on daily living activities and express descriptive details of the ADRs (van Hunsel et al., 2012). Van Grootheest et al (2003) have argued that health consumer ADR reports will cause a shift in the number and the types of ADR reports submitted to health authorities.

When comparing ADR reports from both health consumers and HCPs, it was noted that the quality of reports was almost similar (Aagaard et al., 2009). In 2006, a systematic review of seven studies, which compared HCP reports with health consumer reports, found that the quality of reports appeared to be similar. It was also found that health consumers were more likely to report ADRs if they felt that HCPs had not acknowledged their concerns (Blenkinsopp et al., 2007).

One of the studies that compared reports from health consumers and reports from HCPs noted that both parties reported the same number of serious reports, but health consumers reported more life threatening ADRs and disability outcomes than HCPs (de Langen, van Hunsel, Passier, Berg, & van Grootheest, 2008). Gawert et al., (2011) concluded that in Germany: physicians reported smaller numbers of ADRs as compared to health consumers but health consumer reports of ADRs should not replace physician reports due to the inconsistencies that exist between physician and health consumer reports (Gawert, Hierse, & Zink 2011). Jarernsiripornkul et al., (2002) informed that health consumers report more ADRs than physicians and physicians did not report all the ADRs that were recorded or reported by the health consumers.

2.3. Direct Health Consumer Reporting Effect on Signal Detection

The Working Group VIII of the Council for International Organizations of Medical Sciences (CIOMS VIII) defined a drug safety signal as information that arises from one or multiple sources (including observations and experiments), which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify taking action (Shibata & Hauben, 2011). In general, more than one report is required for signal generation (van Puijenbroek, van Grootheest, Diemont, Leufkens, & Egberts, 2001).

One side of a vigorous debate, particularly in Europe, about the usefulness of health consumer reports in signal detection, argues that European national centers for monitoring adverse drug reactions should resist pressures to accept ADR reports directly from the public (Egberts, Smulders, de Koning, Meyboom, & Leufkens, 1996). One reason cited in the objections is that: health

consumers report ADR that are related to the natural history of their diseases and not necessarily related to the drug. Another reason is that health consumer reports are poorly documented and, as a result, do not lend themselves to further evaluation. A last concern is that health consumer reports can increase the number of signals and background noise (Egbert et.al, 1996).

However, few studies are published that analyze direct health consumer reporting and its impact on signal detection. Nevertheless, these few studies have shown that direct reporting by health consumers has an important and positive effect on signal detection. One of the studies, by Hammond, Rich, and Gibbs (2007), used disproportionality analysis to determine the impact of health consumer reports on signal detection. The researchers found that the signal was identified earlier when health consumer reports were included in the data and it concluded that ADR reports submitted directly to pharmaceutical companies by health consumers can help significantly in the early detection of safety signals (Hammond, Rich, & Gibbs, 2007).

2.4. Adverse Drug Reaction (ADR) Reporting in Canada

There are over 22,000 human drug products and 40,000 medical devices available on the Canadian market (Health Canada, 2007). ADR reporting was introduced in Canada in 1965. Health consumer ADR reports were accepted by Health Canada through the Canada Vigilance Program (Inch, Watson & Anakwe-Umeh, 2012). Health Canada monitors the safety, effectiveness and quality of health products after they reach the marketplace. Market Authorization Holders (MAHs) (manufacturers and distributors) are required to submit ADRs in accordance with the requirements of the Food and Drugs Act and Regulations within 15 days from occurrence. All reports of serious ADRs that have occurred in Canada (domestic) and all reports of serious unexpected ADRs that have occurred outside Canada (foreign) must be reported to the Canada Vigilance Program (Health Canada, 2011).

ADR reporting is increasing in Canada. In 2010, a total of 32,921 ADR reports were submitted to the Canadian Vigilance Program. Of these reports, 5727 (17.4%) were submitted by health consumers, and 1120 (3.4%) were submitted by health care professionals (HCPs). The number

of domestic reports for ADRs in Canada has approximately tripled between 2001 and 2010, and was 19.7% higher in 2010 compared with 2009 (Marielle & Melanie, 2011).

2.5. The Canada Vigilance Program and Online Database Overview

The Canada Vigilance Program is a post-marketing surveillance program that collects and assesses reports of suspected ADRs to health products marketed in Canada. This program enables Health Canada to monitor the safety profile of health products once they are marketed to ensure that the benefits of the products continue to outweigh the risks.

The Canada Vigilance Program has collected reports of suspected ADRs since 1965. These reports are voluntarily submitted to Health Canada by health consumers and HCPs as well as by market authorization holders (MAHs), whom are required to submit reports according to the Food and Drugs Regulations (Health Canada, 2012).

Seven regional offices support the Canada Vigilance Program, providing local points of contact for HCPs and health consumers. Adverse reaction reports are collected regionally and forwarded to the national office for further analysis. MAHs send reports directly to the national office (Health Canada, 2011).

Health consumers, HCPs, and MAHs can view the types of adverse reactions that have been reported to Health Canada via the Canada Vigilance Program Online Database, MedEffect, which contains over 225,000 suspected adverse reaction reports that have occurred in Canada since 1965 (Health Canada, 2011). The database is updated quarterly to reflect new information received by Health Canada. Only suspected adverse reactions to Canadian marketed health products that occur in Canada are found in the database (Health Canada, 2012).

2.6. Summary of the literature

Adverse drug reactions are a worldwide problem that affects all drugs and their users. They cause significant disability and mortality, and can be associated with an economic drain on the healthcare system (Bates et al., 1995; Oshikoya & Awobusuyi, 2009).

Much controversy remains among experts concerning the utility and efficacy of incorporating health consumer ADR reports into pharmacovigilance guidelines and protocols (Hazell, Cornelius, Hannaford, Shakir, & Avery, 2013; Mitchell et al., 1988). Some researchers believe that health consumer ADR reporting is detrimental to pharmacovigilance activities while others fully support it and agree that direct health consumer reporting is necessary for good pharmacovigilance since health consumers as users of medications have first-hand knowledge of their experiences with ADRs (Aagaard et al., 2009; Grootheest, De Graaf, & Berg, 2003). Spontaneous direct health consumer reporting may prove to be essential for continuous improvement and successful pharmacovigilance. However, the literature is deficient regarding the role of direct health consumer reporting, and its effects, on pharmacovigilance activities (Herxheimer, 2012).

Furthermore, by allowing direct health consumers spontaneous reporting, we are allowing the health consumer to be actively involved in their treatment. With the added health consumer reports to those of HCPs, the spontaneous surveillance database can acquire data rich in additional information about ADRs (Hammond, Rich & Gibbs, 2007). It could be argued that this only speeds up the drug alert detection process.

The literature review has demonstrated a gap in knowledge of the Canadian Vigilance Reporting System, one of the earliest safety reporting system active since 1965 in some countries. No studies were found that compared and contrasted health consumer reports against HCP reports in Canada using the Canadian Vigilance Online Database. Understanding how health consumers are involved in ADR reporting can provide new insights into the importance and limitations of integrating health consumer-generated ADR reports into pharmacovigilance approaches which might help in improving medication use safety in Canada.

Chapter Three. Methodology

Methodology

The overall purpose of the dissertation was to evaluate the involvement of health consumer ADR reporting on pharmacovigilance activities using a multi-method study. This chapter provides a detailed description with rationale for the methods used for the systematic review, the quantitative study and the qualitative study. It describes each phase of study with their objectives, study design, data collection and data analysis.

3.1. Systematic Review

A systematic review of the literature brought to light the range of studies on health consumer ADR reporting. Section 3.1 describes the objective, methods, search protocol, selection and analyses processes undertaken for the systematic review.

3.1.1. Objective.

The systematic review aimed to determine the factors that influence reporting of ADRs by health consumers. Specific research questions that guided the review were:

- What are the barriers influencing ADR reporting by health consumers?
- What are motives for health consumers to report ADRs?

3.1.2. Methods.

The systematic review was designed based on the methods proposed by the Cochrane Handbook for Systematic Reviews of Interventions (Higgins & Green, 2008) and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses criteria (PRISMA) (Shamseer et al., 2015). The systematic review protocol was developed a priori to minimize risk of bias in the review process related to, for example, authors' selection and inclusion of studies and outcome reporting (Moher, Liberati, Tetzlaff, & Altman, 2009). In accordance with PRISMA guidelines, our systematic review was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on December 4, 2014 and was last updated on January 19, 2015 (registration number CRD42014015310) (Shamseer et al., 2015).

3.1.3. Search Strategy.

A comprehensive search was conducted using hand and electronic searching in electronic databases and grey literature. The search strategy was developed by a University of Ottawa Librarian (EW) and the primary investigator (RD) using the inclusion exclusion criteria listed in Table 3.1. Literature search strategies relied on medical subject headings (MeSH) and text terminology related to health consumer reporting of ADRs. The following databases were searched without language restriction: MEDLINE, EMBASE, and PSYCHINFO (all Ovid interface); CINAHL; PUBMED; Cochrane Database of Systematic Reviews; and Grey Literature. The PROSPERO registry was also searched for ongoing or recently completed pertinent systematic reviews.

First, search terms were identified to include the following: health consumers, consumers, patients, public, adverse drug reactions, report, reporting, spontaneous, pharmacovigilance, and surveillance. A broad search was conducted in MEDLINE (see Appendix B). Citations published from inception of spontaneous ADR reporting in 1964 to December 5, 2014 were searched. Reference lists of qualifying studies were also scanned. The search strategies are provided in Appendix B to allow others to replicate the search as per PRISMA guidelines.

3.1.4. Selection Process.

The citations identified by the search strategy had duplicates removed using standard software (ENDNOTE 7). Blind assessment was conducted by two reviewers to enhance the quality of the systematic review by ensuring relevant studies were not rejected and minimizing risk bias from individual reviewers' judgment (Shamseer et al., 2015).

The two independent reviewers (RD, RS) conducted three levels of screening. Level one screening, using citation titles only, was used to determine study relevance to the overall objectives of the systematic review. Only citations judged as 'exclude' by both reviewers were removed. Level two screening using titles and abstracts was to determine if citations met the inclusion criteria. Level three screening using the full text was to determine if citations met inclusion criteria. The two reviewers (RD, RS) independently extracted data with disagreement resolved through discussion.

Study inclusion and exclusion criteria were created to guide the identification and selection of citations eligible for the systematic review. Studies were eligible for inclusion if they: (1) addressed health consumers' perceptions on ADR reporting and (2) focused on factors influencing reporting of ADRs by health consumers. No language requirements were imposed, although only non-English publications amenable to Google Translate conversion were included due to resource limitations (see Table 3.1).

Table 3.1 Criteria for Inclusion and Exclusion of Studies

	Inclusion Criteria	Exclusion Criteria
Study Design	Regardless of methodology, qualifying studies: addressed health consumers' perceptions on ADR reporting and; focused on factors influencing reporting of ADRs by health consumers.	Letters, editorials, and narrative reviews were excluded.
Participants	All studies addressing health consumers' perceptions of ADR reporting were included	Studies addressing health consumers and HCPs role in pharmacovigilance; perception of HCPs on ADR reporting; studies comparing frequencies of reported ADR by health consumers versus HCPs; frequencies of ADR reported by health consumers; and studies addressing role of regulators on pharmacovigilance
Language	Studies reported in all languages if able to translate	Unable to translate

3.1.5. Data Extraction

To extract data from included studies, reviewers used a modified form based on the Cochrane Effective Practice and Organization of Care Review Group (EPOC) data collection tool (Cochrane et al., 2008). The form was modified to extract data on factors influencing ADR reporting by health consumers and identification of the barriers and motives for health consumers to report ADR. The modified data collection form was piloted on five randomly selected included studies before its actual use. Using an extraction form ensured a systematic review process for data extraction and facilitated opportunities for re-assessing studies for inclusion (Higgins & Green, 2008). The following data were

extracted from each study: (a) characteristics of included studies (country, setting, design, and number of participants), (b) characteristics of data collection procedures used (self-administered structured questionnaire, focus group, and semi-structured telephone and face to face interviews), (c) outcomes (barriers and motives influencing ADR reporting by health consumers), (d) quality appraisals were conducted by the two reviewers (RD, RS) using the Critical Appraisal Skills Program (CASP) criteria for the descriptive observational studies (Public Health, 2009). Disagreements about data extraction were resolved by discussion. As needed, we contacted the authors of included studies to obtain further information.

3.1.6. Data Analysis.

The data collected were entered into an Excel database. The total number of studies identified from all information sources was presented in a flow diagram according to the PRISMA (Moher et al., 2009). The data was synthesized by classifying the different study types and by comparing study findings. Characteristics of included studies were analyzed descriptively and the results were presented in a narrative format as recommended by the PRISMA statement. The systematic review allowed us to determine several key barriers and motives for health consumers reporting ADR.

Studies were considered high quality if they scored 80% or above, medium quality if they scored 67 – 79.9%, and low quality if they scored <60% of the criteria listed by CASP.

To increase the methodological quality of the systematic review, the Assessment of Multiple Systematic Reviews (AMSTAR) tool was used (Shea et al., 2007). AMSTAR characterizes the quality of the systematic review at three levels: (8 to 11) high quality, (4 to 7) medium quality, and (0 to 3) low quality (Sharif, Sharif, Ali, & Ahmed, 2013). This systematic review protocol met 9 out of 11 criteria listed in the AMSTAR tool. Two criteria were not met including; test to assess the included studies homogeneity, and assessment of publication bias.

3.2. Cross-Sectional Description Study

3.2.1. Objective.

The overall aim of the quantitative study was to determine if health consumers' reports significantly differ from reports submitted by physicians, in term of seriousness, system organ class (SOC), and anatomical therapeutic chemical (ATC). The study analyzes reports submitted to the Canadian Vigilance Online Database, a passive surveillance system administered by Health Canada.

The following research questions and hypotheses were addressed:

1. Is there a significant difference in the distribution of ADRs based on seriousness and reporter?
2. Is there a significant difference in distribution of ADRs between reporters for system organ class (SOC)?
3. Is there a significant difference in distribution between reporters and the ATC?

Once data was downloaded from Vigilance Online database it was analyzed for type of reporter, seriousness criteria, SOC, and ATC.

3.2.2. Study Design.

This was a cross-sectional study, descriptive in nature relied on existing data (Hess, 2004). We analyzed serious ADRs reported by physicians and health consumers to Health Canada from January 1st, 2000 to December 30th, 2014. The data were quantitative in nature; secondary analysis of this data was performed. Secondary data analysis is analysis of data that were collected by someone other than the investigator for different purposes (Hox & Boeije, 2005). The analysis of data was performed to examine the relationship between the dependent (the seriousness, SOC, and ATC) and the independent (physicians and health consumers) variables (Aagaard et al., 2009).

The files were extracted from the Canadian Vigilance Online Database, MedEffect. The data files are available in ASCII format. In the ASCII files, the data elements are separated from each other by a '\$' sign (Health Canada, 2011). It is important to note that when analyzing data obtained from

Canada Vigilance Online Database causality to a certain drug cannot be assumed (Health Canada, 2007).

The Canadian Vigilance Online Database defines the HCPs as physicians, pharmacists, nurses and other paramedical professionals, and defines health consumers as health consumers, health consumers' relatives, and other members of the public. Health consumer and physicians ADR reports were compared specifically for differences in seriousness, SOC, and ATC (Aagaard et al., 2009). Only serious reactions were examined in this study. The study followed the design used by Aagaard et al. (2009) in their analysis of the Danish ADR database, The Danish Medicines Agency.

3.2.3. Study Setting.

In Canada, ADR reporting started in 1965. The Canada Vigilance ADR Reporting Database is a post marketing surveillance database used by Health Canada for collecting ADRs reported by HCPs, manufacturers, health consumers, and lawyers. These reports are submitted to the Canadian Vigilance Online Database by post, telephone or via the Internet (Health Canada, 2011). The Health Canada website contains detailed information on reporting procedures. Two different forms of ADR reporting are available for health consumers and HCPs. Both forms included: (i) health consumer information; (ii) the suspected medicine(s); (iii) health consumer outcome information; and (iv) reporter information.

An important difference exists between the two forms with respect to the categorization of seriousness of the ADR. Reports are categorized in the database by the degree of seriousness according to the Council for International Organizations of Medical Sciences criteria (CIOMS) (MedDRA, 2009). Serious ADRs are defined as reactions that are fatal, life-threatening, cause hospitalization, result in persistent or significant disability or incapacity, require intervention, or cause congenital anomalies (CIOMS, 1999). The health consumer form does not ask directly whether the health consumer considers the reaction to be serious; instead the health consumer is asked to indicate how bad the ADR was and then Health Canada codes the response as 'serious' or 'non-serious'.

3.2.4. Sampling and Data Extraction.

Many efforts were made to extract and analyze data from MedEffect, the Canadian Vigilance Online Database website. Sample sizes were determined. It was hypothesized that the number of serious ADRs between physicians and health consumers would not be equal. To ensure that any reporting differences between physicians and health consumers were indeed significant and not due to chance inference for proportions-sample size calculation were performed (Rosner, 2006). The following formula was used: $n_1 = \left[\sqrt{pq} (1 + 1/k) z_{1-\alpha/2} + \sqrt{p_1q_1 + p_2q_2/k} z_{1-\beta} \right]^2 / \Delta^2$, $n_2 = kn_1$ (Rosner, 2006). Assuming that 80% of serious ADRs would be reported by physicians and 70% of serious ADRs would be reported by health consumers, with $\alpha = 0.05$ (two tailed), and the required power level = 0.80, the estimated minimum sample size for each group was 294 with a total sample size of 588. The total sample size of 588 represents the minimum sample size needed for sufficient power.

A total of 198,781 ADR reports from the Data File for the Time Period: January 1st, 2000 to December 30th, 2014 was available for analysis. Only serious ADR reports were analyzed.

3.2.5. Data Source and Collection Procedures

Using secondary data for the purpose of research is cost-effective and time efficient (Singleton & Straits, 2005). Secondary data that was used in this research was obtained from Health Canada website. This data is coded and redacted by Health Canada.

The ADR reports were collected from the Canadian Vigilance Online Database website, MedEffect, a public database that resides within the Health Canada website. The raw data were collected via those reports. Health Canada utilizes these ADR reports for further investigation and analysis of drugs and devices, looking for potential medication safety signals. The ADRs are received by Health Canada from HCPs, health consumers, and market authorization holders. HCPs and health consumers report voluntarily to Health Canada. HCPs and health consumers are also able to report directly to manufacturer. Also, it is mandatory by law for market authorization holders to report these reactions to Health Canada (Health Canada, 2012). ADR reporting forms are available in two

languages (English and French) and can be filled online using the Canadian Vigilance Online Voluntary Report Form (see Appendices G and H), by phone (1-866-234-2345), or by submitting the form by mail or fax (1-866-678-6789).

According International Conference on Harmonization (ICH) guidelines the minimum reporting criteria for an ADR report is: an identifiable reporter, health consumer, an adverse reaction, and a suspect product (ICH, 2003). Reports were classified in the MedEffect based on the reporter type, seriousness, SOC and ATC. The ADRs in the ADR reports were coded using MedDRA codes and the drug types were coded using the WHO Drug Dictionary, as described in greater detail in Chapter 5. Criteria for seriousness were based on the Council for International Organizations of Medical Sciences (CIMOS) criteria.

The data extracted from the Health Canada website, MedEffect, contained the name of the suspect drug as reported. To group drugs into categories, the drug name (as reported) was first converted to a generic equivalent and then mapped to the most appropriate code within the Anatomical Therapeutic Chemical (ATC) drug classification system. The ATC system is used worldwide to classify drugs into groups according to their therapeutic use. The therapeutic products were classified based on ATC groups. Of the 14 ATC groups, there are five levels. ATC level 1 was the main group, ATC level 2 was the therapeutic subgroup, ATC level 3 was the pharmacological subgroup, ATC level 4 was the chemical subgroup, and ATC level 5 was the chemical substance or otherwise known as the active ingredient (WHO, 2011). Because the ADRs are reported using either the brand name (manufacturer name), it was necessary to use the ATC level 5 for coding purposes and then convert to ATC level 1 or the main group (Aagaard et al., 2009). For example, amlodipine (calcium channel blocker) belongs in the cardiovascular ATC or ATC Group C. The ATC level 5 groups were coded as follows:

- ATC group A: Alimentary tract and metabolism,
- ATC group J: Anti-infective for systemic use,
- ATC group L: Antineoplastic and immunomodulating agents,

- ATC group P: Antiparasitic products, insecticides and repellents,
- ATC group B: Blood and blood forming organs,
- ATC Group C: Cardiovascular system,
- ATC group D: Dermatologicals,
- ATC group G: Genito urinary system and sex hormones,
- ATC group M: Musculo-skeletal system,
- ATC: group N: Nervous system,
- ATC Group R: Respiratory System,
- ATC group S: Sensory organs,
- ATC Group H: Systemic hormonal preparation, sex hormones, and insulin
- ATC Group V: Various.

Serious ADRs as determined by the CIOMS seriousness criteria were included. The reporters were health consumers (patients, patients relatives or general public) and physician. Legal reports were not collected.

Data downloaded from Health Canada's database of the ADRs reported by physicians and health consumers was anonymous and in encrypted form. No personal identifiers were present. The data was received in a line-listing format. A unique number is assigned for identifying an ADR report. Health consumer information is not available to requestors of information. Secondary data analysis does not pose a privacy risk to participants the way primary data collection and analysis (Singleton & Straits, 2005).

After the raw data was extracted from the MedEffect database the drug names and ADRs were converted into the excel format for easier handling. ADRs and drug names were coded using MedDRA version 15.0 coding instrument. All ADR terms were already coded to the Preferred Term (PT) within MedEffect. The preferred term was used to obtain the correct system organ class. The coding of drugs was done using the WHO Drug Dictionary 5.5 to the anatomical therapeutic classification first level (WHO, 2011). Nonspecific drug terms were excluded. For instance, if the

drug terms were for stomach, anti-depression medication, drugs used for cholesterol, and so on, then such terms were excluded from the study. Only specific names of drugs were included in the study. Combination products were coded using the same strategy.

For this study ADR reports downloaded from Health Canada website were analyzed for Time Period: January 1, 2000 to December 30, 2014. The data were screened for duplicate reports. Therefore, full systematic search for duplicate reports was undertaken using SPSS and any duplicate reports identified were deleted.

The p-value of <0.001 was used to determine significance. The p-value from the chi-square test looks at 2x2 tables; therefore, the test looked at the differences between the two groups. Physicians and health consumers were the first group (rows), serious and non-serious ADRs were the second group (columns). The p-value represented the significant difference between physician and health consumers in reporting of seriousness of an event. The Odd Ratio (OR) represented how much more likely health consumers are to report a serious event versus physicians.

3.2.6. Data Analysis.

The goal of the statistical analysis was to investigate the differences in the number of ADRs reported by health consumers and physicians classified by seriousness, SOC, and ATC using the chi-squared test of independence as described later in this section.

The test for association or dependence between the reporter, the seriousness, SOC, and ATC of the ADR were done using the chi-square test for independence and/or using 2x2 tables. The chi-square test for independence is used to test for association between two categorical variables (Gerstman, 2008). The chi-square test for independence procedure is appropriate because the following conditions are met: (i) the sampling method is simple random sampling and (ii) the variables under study are each categorical. The statistical significance in association between reporter and seriousness, SOC and ATC were shown with a p-value of less than 0.01. The OR, which is another measure for dependence for categorical data (Gerstman, 2008), was used together with the chi-square test for independence (Aagaard et al., 2009). The rationale being that the chi-square only

illustrates that an association exists; the OR displays the strength of the association. The OR for each category was determined using a 2x2 table for reporter type and the SOC and ATC group using bivariate analysis. The confidence intervals were calculated at 95% for each OR. Statistical analysis was performed using SPSS version 22.

3.2.7. Medical Dictionary for Regulatory Activities (MedDRA) Overview

The Medical Dictionary for Regulatory Activities (MedDRA) was developed by the International Conference on Harmonization (MedDRA, 2009). MedDRA is required for electronic exchange of information on suspected adverse reactions between industry and regulatory authorities after drug registration in the European Union (Brown, 2004). It is clinically validated international medical terminology used by regulatory authorities and the regulated biopharmaceutical and pharmaceutical industries (Mozzicato, 2009). The same terminology is applied to premarketing clinical trials, postmarketing, data entry, retrieval, assessment, and representation of ADRs (Mozzicato, 2009). Medical information includes symptoms, signs, diseases, diagnoses, indications, investigations-procedures, and medical-social history (Mozzicato, 2009). The terms in MedDRA are numerically coded to support electronic means of data transmittal and retrieval. It has 26 broad groups called system organ classes (SOCs; see Appendix A). The SOCs consist of more specific subgroups that finally group single medical concepts and equal terms used for codifying clinical information linked to ADR (Mozzicato, 2009). As previously stated, MedDRA has a five-tier hierarchy (see Figure 3.1) of terms combined into 26 SOCs.

Currently, MedDRA has around 2,400 subscribers around the world. These subscribers are regulatory authorities, pharmaceutical companies, research organizations, academics, and institutions. MedDRA is available in English, Japanese, French, Spanish, German, Italian, Portuguese, Dutch, and Czech (Mozzicato, 2009).

MedDRA is essential in coding events, medical history, laboratory values, and procedures. It is helpful when one form of coding is used universally for consistency. MedDRA was used for coding ADR reported by HCPs and health consumers in this study.

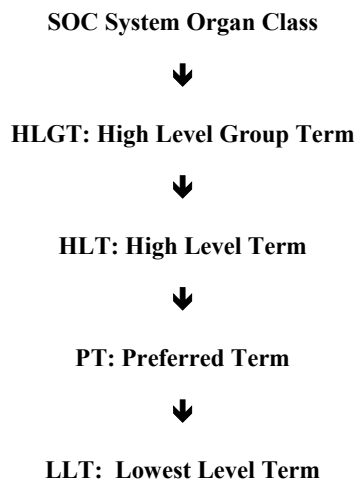


Figure 3.1. Five Tier Hierarchies of Terms Using MedDRA

3.2.8. Theoretical/ Conceptual Framework

To explore the differences between health consumer and physicians reporting of ADRs, risk perception theory was used. The risk perception theory works on the concept that ‘different classes of people (professionals and non-professionals, scientists or the public) will have a different view on the possible risks associated with some action or environment’ (Wahlberg, 2001).

There are three different approaches within the risk perception theory. These include heuristics and cognitive, cultural approach, and *social amplification of risk framework (SARF)* (Wahlberg, 2001). SARF asserts that the perception of risk is based on the individual’s psychological state, social state, and cultural perception (Kasperson et al., 1988). SARF was used to further explain the health consumer perception of risk during the data interpretation phase. SARF concept based on that ‘events related to hazards interact with psychological, social, institutional, and cultural process in way that can affect individual and social perceptions of risk and shape risk behavior’ (Kasperson et al., 1988). Health consumers often differ in their perception of risk with respect to drug therapy as compared to HCPs (Aronson, 2006). Blenkinsopp et al. (2007) reported that health consumer reports do not differ from HCP reports in terms of validity and content; they do differ in types of categories of events as compared with HCPs. Additionally, physicians generally underreport or report life-

threatening events only, and more often than not, they report on new drug therapies (Bongard et al., 2002). For example, in one of the studies, healthcare professionals ranked anticoagulants and non-steroidal anti-inflammatory drugs (NSAIDs) as the most dangerous drugs with respect to ADRs while health consumers did not rank NSAIDs as the most dangerous drugs and believed that aspirin posed the least threat (Bongard et al., 2002).

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Several factors influence the perception of risk, specifically three types: factors related to the individual, factors related to the presentation of the risk, and factors related to the characteristics of the risk (Association of Reproductive Health Professionals [ARHP], 2006). Although it would be beneficial to collect data regarding these factors, it is not possible in this study because secondary data will be used. If the results of this study are significant, it may indicate that future studies that include variables related to the risk perception theory may be warranted. An example given by ARHP is as follows: “A woman whose sister became pregnant while using a particular contraceptive method may be less likely to trust that method, even if it has a low rate of contraceptive failure in the population” (ARHP, 2006, p. 8).

Besides individual risk perception and risk presentation, factors related to the characteristics of the risk also influence perception of risk. The variables looked at in this study were ADR, reporter, seriousness, SOC, and ATC group. It is assumed that the consumer’s risk perception would differ with the HCPs perception of risk.

3.3. Qualitative Study

The systematic review allowed us to determine several key barriers and motives for health consumers reporting ADR from the literature. A qualitative study was conducted, in order to explore the factors influence health consumer ADR reporting in Canada and the usability of the Canadian

Vigilance Online System. Section 3.3 describes the objective, study design, study setting, sampling and data extraction, instrumentation and materials, and data analysis.

3.3.1. Objective.

The overall aim of the qualitative study was to explore health consumers' experiences reporting ADRs and the usability of the Canadian Vigilance Online System. The specific research questions that guided this study were:

- What factors influence health consumer reporting of ADRs in Canada?
- What are the health consumers' perceptions of the Canadian Vigilance Reporting System?
- Is the Canadian Vigilance Reporting Form easy to use by health consumers?

3.3.2 Study design.

A qualitative study was conducted using an interpretive description design (Thorne, 2008). Since little is known about what influences health consumers to report an ADR, the interpretive description design is suited to developing understanding about this subject. This design allows investigators to incorporate their personal views and values when interpreting participants' interviews and allowing investigator to better understand participants' realities(Thorne, 2008).

Merriam (2009) describes a basic interpretive qualitative study as one that demonstrates the four characteristics common to qualitative research. The four characteristics are: 1) the researcher strives to understand how people construct meaning in their lives; 2) the researcher is the means of collecting and analyzing data; 3) the process is inductive, so the data collected may result in hypotheses, themes, or concepts; and 4) the results are richly descriptive. The description is in words and pictures rather than numbers, and uses quotes and excerpts from documents as part of the description. This approach allows more flexibility, as it is a generic rather than specific approach (Lichtman, 2006). An interpretive descriptive design seeks to describe, understand, and interpret an experience by examining the multiple realities possible within a context.

The strengths of an interpretive descriptive approach are the flexibility, the researcher's role, and the rich description of an experience and its meaning (Merriam, 2009). The interpretation can emerge from the data during the data collection and analysis process; the researcher can be responsive to the data as it emerges. The interactions of the researcher with the participants provide a deeper understanding of the participants' perspective. The rich description that results is a valuable means of communicating experiences and its meanings (Merriam, 2009).

3.3.3. Study Setting.

ADRs are reported in at least 1% of the annual hospital admissions in Canada (Nichols et al., 2009). Health Canada is responsible for the handling of the spontaneous reporting system for ADRs. Health Canada accepts ADR reports from different reporters (physicians, pharmacists, nurses, manufacturers, and health consumers) through electronic reporting forms, paper forms, or by telephone. Health consumers' forms are similar to the forms used by HCPs in terms of content. Some mandatory fields in these forms ensure the completeness of the information before it can be sent to Health Canada. Health consumer ADR reports are first screened by evaluators for the four minimum criteria: an identifiable health consumer, a reporter, a suspect drug, and a reaction. All ADR reports are entered into the database of the Canadian Vigilance Online Database. Evaluators assess adverse reaction reports from the database, along with other relevant sources of information, as part of the overall safety assessment of a product to determine if there are post-surveillance problems requiring action. This database can be accessed by the public to see ADRs that have been reported for a specific health product (Health Canada, 2011).

3.3.4. Participants and Sampling.

We invited health consumers over 18 years old living in Canada and able to answer questions in English or French to participate in the study. Purposeful sampling was used to represent a range of ages (18-45, 45-64, 65-80) and sex (male, female). We aimed to have participants from different provinces in Canada and with a variety of educational backgrounds. Given slow recruitment, a

snowball-sampling approach was used to have participants identify other potential participants (Creswell, 2007).

Based on an interpretive descriptive study design, there are no specific rules for determining sample size (Thorne, 2008). Thus, data saturation was used for determining the sample size, defined as no new information is obtained from subsequent interviews and redundancy in findings occurs (Morse, 1995). According to Francis et al. (2010), data saturation is often achieved by 10 participants, and then an additional three participants should be interviewed to ensure no new findings are identified.

3.3.5. Procedure.

The primary investigator (RD) facilitated the recruitment of participants by sending an invitation recruitment letter, with brief information about the study, through social media (i.e., Kijiji, Facebook, Twitter) and through health associations such as Patient's Canada, Canadian Arthritis Society, Canadian Cancer Society, or Heart & Stroke Society (see Appendix D). Individuals expressing interest in the study were sent an email containing information about the study and a consent form (see Appendix E).

After confirming eligibility, participants were scheduled for an in-person, telephone, or Skype interview at a time and location convenient for them. The primary investigator (RD) conducted interviews using a structured interview guide (see Appendix F).

The interviews were planned for 30-45 minute sessions and audio-recorded, with notes documented. Prior to the interview, participants were asked to sign the written consent form, and were given a copy of the interview guide without prompts. During the interview, participants were asked the questions in the interview guide and, as necessary, prompted to share their ADR experiences. At the end of the interview, participants were asked demographic questions.

3.3.6. Data Collection Tools.

The interview guide was developed based on key sensitizing concepts from the literature on ADR reporting and reviewed by experts in pharmacovigilance, knowledge translation to health

consumers, and health policy. The interview guide consisted of open-ended questions with prompts intended to elicit further comments or clarifications during interviews (Creswell, 2007). The primary investigator (RD) pilot tested the interview guides with two health consumers before conducting further interviews, to assess and refine questions and procedures (Creswell, 2007). The first set of questions were meant to explore participant experiences with ADRs, severity, who they report side effects to, and expectations about reporting. The second set of questions were focused on the user-friendliness of the ADR reporting form that is available on the Canada Vigilance Online Database (see Appendix G&H).

3.3.7. Data Analysis.

Audio-taped interviews were transcribed verbatim, and transcripts were compared with recordings for accuracy, and read several times for immersion in the data (RD). Two interviews were in French and transcripts were translated into English for analysis. Demographic data were entered into an Excel database and analyzed descriptively. Inductive content analysis was used to build knowledge derived from participant responses since little is known about ADR reporting by health consumers (Thorne, 2008).

The inductive content analysis for the interview transcripts and field notes included the following steps:

1. Transcripts were read line-by-line with open coding conducted using notes and categories describing content written in transcripts' margins (RD).
2. Keynotes and categories were gathered into a coding scheme and used to create sub-categories (RD). Sub-categories were compared and contrasted with each other and merged into larger sub-categories with more general description of content. Then, these larger sub-categories with similar reports, understandings, trends, and incidences were grouped together to formulate main categories. Concurrently, a second team member (DS) independently analyzed three transcripts. Twelve other interviews were coded by two persons independently (RD, SM) using free codes.

3. The findings were audited by co-authors (RD, DS, SY, DK) and categories were further refined.

To enhance credibility and transferability of the findings, several strategies were used (Shenton, 2004). Credibility relates to the truth of the findings (Shenton, 2004) and in this study was enhanced by two team members independently analyzing transcripts and three team members auditing the analysis process. To ensure transferability of findings, a rich description of the study setting was provided (Lincoln & Guba, 1985; Shenton, 2004).

3.3.8. Ethical Considerations.

For the qualitative study, research ethics approval was obtained from the University of Ottawa Research Ethics Board in July 2014 (H05-14-18) (see Appendix J). To ensure confidentiality and to follow the Tri-Council Policy Statement, participants completed a study consent form prior to their interview. Participants were informed about the risks, confidentiality, anonymity, conservation of data, and voluntary participation via the consent form. All personal identifiers were removed from transcripts and numbers were used to identify participants (e.g., P1, P2...P15); participants were informed that no identifying personal or organizational data would be published and that they had the right to withdraw from the study at anytime. All collected data including the audio-tapes were kept securely in a locked file cabinet. Data will be stored for 5 years after data collection (until May, 2020) and then destroyed.

The systematic review, quantitative, and qualitative studies were designed to contribute to an increasing understanding of the involvement of reporting ADR by health consumers. The study proposal responded to the objective of the Canadian Institutes of Health Research (CIHR) to increase the evidence on drug safety and effectiveness available to regulators, policy-makers, health care providers and health consumers. Having evidence to support ADR reporting fits with one of the four strategic directions of the CIHR Three-Year Implementation Plan (2013-2015), namely to accelerate capturing the advantages of health research on health and on the economy (CIHR, 2013).

**Chapter Four. Factors Affecting Health Consumers Reporting of Adverse
Drug Reactions: A Systematic Review**

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British Clinical Journal of Pharmacology

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Factors Affecting Health Consumers Reporting of Adverse Drug Reactions: A Systematic**Review****Abstract**

AIM: To determine barriers and motives influencing health consumers reporting adverse drug reactions (ADRs).

METHODS: A systematic review guided by the Cochrane Handbook was conducted using electronic searches of MEDLINE, EMBASE, PSYCHINFO, CINAHL, PUBMED and the Cochrane Database of Systematic Reviews from 1964 to December 2014. Eligible studies addressed health consumers' perceptions of ADR reporting and factors influencing health consumer reporting. Studies about healthcare professionals (HCPs) reporting ADRs were excluded. Studies were quality appraised and results analyzed descriptively.

RESULTS: Of 1435 citations identified, 22 studies were eligible. Studies were primarily conducted in the UK, Netherlands, and Australia. The identified barriers to health consumers reporting ADRs (n =16 studies) were poor awareness, confusion about who should report the ADR and to whom, difficulties with reporting procedures and forms, lack of feedback on submitted reports, mailing cost, ADRs resolved, and prior negative reporting experience. The identified motives for health consumers reporting ADRs (n =11 studies) were: preventing others from having similar ADRs, wanting personal feedback, improving medication safety, informing regulatory bodies, improving HCP practices, responding to HCPs not reporting their ADR and having been asked to report ADRs by HCPs.

CONCLUSIONS: Most health consumers were not aware of reporting systems and others were confused about reporting. Health consumers were mainly motivated to make their ADRs known to prevent similar suffering in other health consumers. By increasing health consumer familiarity, reporting systems could better achieve health consumers' motives to help others avoid ADRs.

4.1. Introduction

Adverse drug reactions (ADRs) are a worldwide problem that affects diverse populations. ADRs cause significant disability and mortality, and are associated with an economic drain on the healthcare system [1]. ADRs are monitored in the majority of countries and by the World Health Organization (WHO) using spontaneous reporting systems. A common problem with these reporting systems is underreporting [2]. It is estimated that between 5% and 10% of ADR are reported [3]. Given that health consumers are often knowledgeable about health conditions and their treatments, they are well positioned to participate in reporting ADRs and improve drug safety [7].

In order to improve voluntary reporting of ADRs by health consumers and to increase rates of ADR reporting, it is important to identify factors influencing health consumer reporting of ADRs. Identifying these factors will help to develop strategies for encouraging the communication of risks associated with drug use and provide better safety for health consumers. In this context, the objective of this study was to identify the barriers and motives that influence reporting of ADRs by health consumers.

Although there is no estimation of health consumer reporting, a median of 95% health care professionals (HCPs) do not report ADRs (range 6% - 100%) [4]. In 1976, a British physician, Inman, was the first to publish reasons for underreporting by HCPs [5], including; 1) complacency (believing serious ADRs are well documented when the drug is released in the market); 2) fear of being involved in a lawsuit (legal process); 3) guilt for having been responsible for damage observed in health consumer; 4) ambition of group to publish case series or financial benefit; 5) ignorant of notification process (believing only serious and unexpected ADRs must be reported); 6) insecurity about reporting suspicions of ADR (believing there should be notification only if there is certainty that damage was caused by use of specific medication); 7) and indifference (lack of interest, time, or other excuses related to postponing report of ADR). These factors were confirmed in findings from two systematic reviews of barriers and motives of HCPs reporting ADRs [4,6]. One of these systematic reviews with

studies from 12 countries concluded that direct reporting from health consumers may be one means of reducing underreporting rates [4].

However, there is no systematic review reporting factors influencing health consumers reporting ADRs.

4.2. Methods

A systematic review guided by the Cochrane Handbook [8] was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses criteria (PRISMA) [9]. In accordance with PRISMA guidelines, our systematic review was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on December 4, 2014 and was last updated on January 19, 2015 (registration number CRD42014015310)[9].

4.2.1. Search Strategy

A Health Sciences Librarian (E.W.) was engaged to create search strategies. Literature search strategies relied on medical subject headings (MeSH) and text terminology related to health consumer reporting of ADRs. The following databases were searched without language restriction: MEDLINE, EMBASE, and PSYCHINFO (all Ovid interface; CINAHL; PUBMED; Cochrane Database Of Systematic Reviews; and Grey Literature. The PROSPERO registry was also searched for ongoing or recently completed pertinent systematic reviews.

Search terms designed for Medline (see Appendix A) and other databases included the following terms: health consumers, consumers, public, adverse drug reactions, report, reporting, spontaneous, pharmacovigilance, and surveillance. Reference lists of qualifying studies were also scanned. Citations published from inception of spontaneous ADR reporting in 1964 to December 5, 2014 were searched.

4.2.2. Selection Process

Studies were eligible for inclusion if: (1) they addressed health consumers' perceptions of ADR reporting and (2) focused on factors influencing health consumer reporting of ADRs. No language requirements were imposed, although due to resource limitations only non-English

publications amenable to Google Translate conversion were included (Table 4.1).

After identification of studies, duplicates were removed using standard software (ENDNOTE 7). Two independent reviewers conducted three levels of screening. Level one screening, using citation titles only, was to determine study relevance to the overall objective of the systematic review. Only citations judged as exclude by both reviewers were removed. Level two screening, using title and abstract, was to determine if citation met the inclusion criteria (see Table 4.1). Level three screening of full text was to determine if citation met inclusion criteria. The two reviewers independently extracted data with disagreement resolved through discussion.

Study findings were extracted using a data extraction form that was initially pilot tested on three randomly selected included studies before its actual use. The two reviewers used the form to extract data independently.

All included studies were appraised, by both reviewers, using the Critical Appraisal Skills Program (CASP) tool [10]. For the CASP tool, the two reviewers were tested each study independently for: 1. clear statement of aims; 2. methodology appropriate; 3. research design appropriate to address research aims; 4. recruitment strategy appropriate; 5. data collected appropriately; 6. relationship between researcher and participants considered; 7. ethical issues considered; 8. data analysis sufficiently rigorous; 9. clear statement of findings; 10. valuable research. Disagreements were resolved by consensus. Studies were considered high quality if they scored 80% or above of CASP criteria, medium quality if they scored 67–79.9% of CASP criteria, and low quality if they scored <60% of CASP criteria.

4.2.3. Data Analysis

The data was synthesized by classifying different study types. Due to heterogeneity across study outcomes, data were analyzed descriptively. Study comparisons were grouped to answer research questions and findings were synthesized based on outcomes. Characteristics of included studies were analyzed descriptively and results were presented in a narrative format recommended by PRISMA.

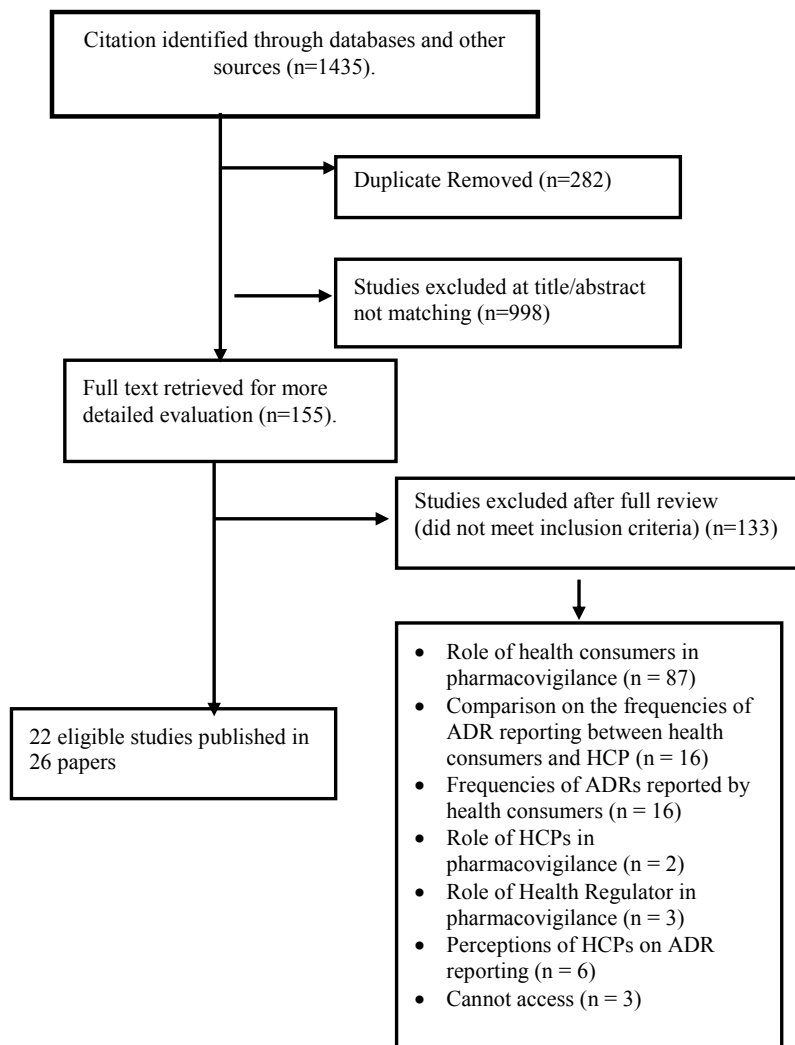
The Measurement Tool to Assess Review (AMSTAR) was used to assess the methodological quality of this systematic review [11]. AMSTAR characterizes the quality of systematic reviews at three levels: 8-11 is high quality, 4-7 is medium quality, and 0-3 is low quality [12].

Table 4.1 Systematic Review Inclusion and Exclusion Criteria

	Inclusion Criteria	Exclusion Criteria
Study Design	Regardless of methodology, qualifying studies that answered the question ‘what factors influence reporting of ADRs by the public?’ were included.	Letters, editorials, and narrative reviews were excluded.
Participants	All studies addressing health consumers’ perceptions of ADR reporting were included.	Studies addressing health consumer and HCP role in pharmacovigilance; perception of HCPs on ADR reporting; studies comparing frequencies of reported ADR by health consumers versus HCPs; frequencies of ADR reported by health consumers; and studies addressing role of regulators on pharmacovigilance
Language	Studies reported in all languages, if able to translate.	Studies unable to translate.

4.3. Results

Of 1435 citation reviewed, 22 studies published in 26 papers were eligible for inclusion (see **Figure 4.1**). 1413 excluded studies were duplicates (n = 282), title and abstract not matching (n = 998), and/or not meet inclusion criteria (n = 133) (see Appendix C).

Figure 4.1. Flow Diagram of Study Selection Process

The 22 studies were published between 2008 and 2014, with most published in 2013. Studies were conducted in: the UK (n=6), Netherlands (n=4) Australia (n=3) and one each in Italy, Portugal, Romania, Bulgaria, Malaysia, Nepal, Pakistan, Uganda and Saudi Arabia (see Table 4.2). Of these 22 studies, 12 were cross-sectional, 8 were qualitative, and 2 used mixed methods. Overall, quality ratings for 20 studies in this context were medium to high and 2 were low (Public Health, 2009).

Table 4.1. Characteristics of Included Studies

Author/Year	Location	Design	Participants	Data Collection	Quality Rating
Aljadhey, (2013) [13].	Saudi Arabia	Observational - cross-sectional study	204 adults	Self-administered structured questionnaire	Medium
Anderson, (2012)[23].	UK	Qualitative	5 adults	Focus group	High
Arnott, (2013)[22].	UK	Qualitative	17 parents without previous experience of submitting ADR report and 27 with previous experience of submitting ADR report	Semi-structured telephone and face to face interviews	High
Avery, (2011) [14].	UK	Observational - cross-sectional study	Health consumers reported ADR (30 for telephone interviews, 48 for focus group, and 62,018 for Omnibus survey)	Semi-structured telephone interviews, and focus group, Omnibus survey	High
Braun, (2010) [24].	Australia	Observational - cross-sectional study	620 health consumers at 60 community pharmacy and rural pharmacies in three Australian states	Self-administered structured questionnaire	Medium
Bukirwa, (2008) [25].	Uganda	Qualitative	16 adults	Focus group	High
Elkalmi, (2013) [15].	Malaysia	Qualitative	334 adults	Face-to-face interview using a structured questionnaire	High
Farcas, (2010) [31].	Romania	Qualitative	50 health consumers taking antidepressant	Self-administered structured questionnaire	Medium
Gujral,(2010) [35].	UK	Observational - cross-sectional study	154 adults	Self-administered structured questionnaire	Medium
Harmark, (2013)[27].	Netherland	Mixed model approach combining qualitative and quantitative research methods	21 adults	Face-to-face interview using a structured questionnaire	High
Jha, (2014)[26].	Nepal	Observational - cross-sectional study	23 adults	Face-to-face interview using a semi-structured questionnaire	High
Krska,(2011) [16].	UK	Qualitative	272 adults	Face-to-face interview using a semi-structured questionnaire	High
Lebanova, (2014) [17].	Bulgaria	Observational - cross-sectional study	211 adults	Self-administered questionnaire	High
Lorimer, (2012) [21].	UK	Qualitative	15 adults	Face-to-face interview using a semi-structured questionnaire	High

Matos, (2014) [18].	Portugal	A descriptive-correlational study	948 adults	Closed-answer questionnaire	Low
Parrella, (2014) [36].	South Australia	Observational - cross-sectional study	2002 adults	Face-to-face interview using a structured questionnaire	High
Qamar, (2014) [37].	Pakistan	Observational - cross-sectional study	1566 adult	Face-to-face interview using a structured questionnaire	Medium
Robertson,(2013) [19].	Australia	Observational - cross-sectional study	2484 adults	Structured telephone interview and online survey	High
Rolfes, (2014) [28].	Netherlands	Qualitative	3 adults	Face-to-face interview using a semi-structured questionnaire	Low
Salvo, (2013) [38].	Italy	Observational - cross-sectional study	744 adults	Structured questionnaire telephone interview	Medium
Van Hunsel, (2010) [29].	Netherland	Observational - cross-sectional study	1005 adults	Web-based questionnaire	High
Van Hunsel, (2010) [30].	Netherlands	Qualitative	21 adults	Face-to-face interview using a structured questionnaire	Medium

4.3.1. Barriers to health consumer ADR reporting

Of 22 studies, 16 described barriers to the ADR reporting process as: 1) poor awareness; 2) confusion as to who reports ADRs and to whom; 3) difficulties with ADR reporting procedures and forms; 4) ADR disappearance or resolution; 5) lack of feedback on ADRs submitted; 6) mailing costs; and 7) prior negative experience (see Table 4.3).

Poor awareness. Of the 16 studies, 14 qualitative and quantitative studies cited poor public awareness of ADR reporting systems. Many did not know they could report ADRs to a national regulatory authority. The seven quantitative studies had a median of 75% (range 44.1–93.8 %) of participants not aware about available ADR reporting systems [13-19].

Confusion as to who reports ADRs and to whom. In most studies, uncertainty was expressed as to the legitimacy of health consumer ADR reporting and to whom such reports would be issued. In eight out of 16 studies, health consumers were not sure who should report an ADR and to whom. For example, in the UK, some participants considered it their duty to report ADRs, whereas others held

HCPs responsible [20-22]. One included study indicated that individuals having little personal or informal contact with HCPs were unlikely to be cognizant of reporting systems [22].

Difficulties with ADR reporting procedures and forms. Lack of familiarity with procedures and reporting forms was common in reviewed studies. Five quantitative and qualitative studies identified difficulties with procedures and forms. Difficulties were reported as 15.9% in the UK and 80% in Saudi Arabia [13,14]. For example, in the three UK studies, participants noted that: a) paper forms were tedious, lengthy, awkwardly constructed, inconsistent with online forms, and available only in English; b) telephone reporting was limited to working hours, which was found to be inconvenient and time consuming; and c) technical problems encountered online often resulted in a loss of information [14,20,23].

ADR resolution. Five qualitative studies reported that health consumers believed ADRs would resolve after stopping or completing their treatment and did not think they would benefit by submitting an ADR report [14,19,21,24,25].

Lack of feedback on ADRs submitted. Two out of 16 studies reported health consumers' concerns over lack of feedback to submitted ADRs reports. For example, in a UK study, 32% of participants expected feedback from the ADR report, and 1.9% felt that lack of detailed feedback might discourage them from completing an ADR report in future [14, 22]. This problem was not reported in Netherlands, where the health authority provides customized feedback on each ADR report submitted to them [14].

Mailing costs. Only two out of 16 studies, conducted in Uganda and Nepal, identified that health consumers' poor economic status was a barrier to reporting ADRs, as they could not afford the cost of mailing their reports [25,26].

Prior negative experience. One study in Uganda described prior negative experience as a barrier. Health consumers reporting ADRs were associated with fear of reproach by their HCPs [25].

Table 4.3: Barriers to Report ADRs by Health Consumers

Included studies, Country	Poor Awareness	Confusion on who should Report ADRs and to Whom	Difficulties with Reporting Procedures and Forms	ADRs Resolved	Lack of Feedback	Mailing Cost	Prior Negative Experiences
Aljadhey, (2013) [13]. Saudi Arabia	87%		80%				
Anderson, (2012) [23]. UK			√				
Arnott, (2013)[22]. UK	√	√			√		
Avery, (2011) [14]. UK	74%	√	15.9%	√	√		
Braun, (2010) [24]. Australia	√	√		√			
Bukirwa, (2008) [25]. Uganda				√		√	√
Elkalmi, (2013) [15]. Malaysia	65.6%						
Gujral, (2010) [35]. UK	√	√					
Jha, (2014)[26]. Nepal	√	√	√			√	
Krska,(2011) [16]. UK	93.8%						
Lebanova, (2014) [18]. Bulgaria	78.7%	√					
Lorimer, (2012) [21]. UK	√	√	√	√			
Matos, (2014) [18]. Portugal	44%	√					
Parrella, (2014)[36]. Australia	√						
Robertson, (2013) [19]. Australia	89.7%			√			
Salvo, (2013) [38]. Italy	√						
Total	14	8	5	5	2	2	1

4.3.2. Motives for Health Consumers to Report ADRs

There were 11 qualitative and quantitative studies that addressed motives for health consumers to report ADRs (see Table 4.4). Motives were: 1) preventing similar ADRs in others; 2) improving drug safety; 3) serious ADR; 4) desire for personal feedback; 5) informing others; 6) improving HCP practices; 7) responding to HCPs not reporting their ADRs; and 8) having been asked to report ADRs by HCPs.

Table 4.4: Motives for Health Consumers to Report ADRs

	Preventing similar ADRs in others	Improving drug safety	Having a serious ADRs	Wanting personal feedback	Informing others	Improving HCPs practice	Responding to HCPs not reporting health consumer ADRs	Being asked to report ADR by HCPs
Anderson, (2011) UK [20]	26%	12.7%	√		7%	12.2%	7.8%	
Arnott, (2013). UK [22]	√	√		√				
Avery, (2011). UK [14]	13.3%	13.9%		60.8%	12.3%	13.4%	8%	
Farcas, (2010). Romania [31]	√							
Harmark,(2013) Netherland [27]	89%	√		√		84%		√
Krska, (2011). UK (Krska et al., 2011)[16]			86%					
Lorimer, (2012).UK [21]			62.4%					
Matos, (2014). Portugal [18]			81.1%	√				
Rolfes, (2014). Netherland [28]	√							
van Hunsel, (2010). Netherland [29]	√	√	√	√	√			
van Hunsel, (2010). Netherland [30]	√	√			√	√		
Total	8	6	5	5	4	4	3	2

Preventing similar ADRs in others. Eight of 11 studies reported that health consumers wanted to prevent others from suffering similar problems and perhaps help find better treatments [14,20,22,27-31].

Improving drug safety. Health consumers in six out of 11 studies believed that improved drug safety could be achieved by reporting ADRs [14, 20, 22, 27, 29, 30]. For example, in the Netherlands, health consumers were willing to invest time in ADR reporting to enhance drug safety [27].

Serious ADRs. Three quantitative studies and two qualitative studies indicated that having a serious ADR was the main personal motivation for health consumers to report [16, 18, 20, 21, 29]. For example, in two UK surveys, the majority of respondents (62–86%) declared that only serious ADRs requiring hospital admission or impacting daily life were worthy reporting [16,21,29]. Similar opinions emanated from Portugal, where participants agreed or strongly agreed that reaction severity was the primary reason to report ADRs [18].

Desire for personal feedback. One quantitative and four qualitative studies out of 11 studies discussed health consumers' desire for personal feedback on experienced ADR. Participants were anxious to learn and find others, who shared the same experience, to acquire more details of ADRs and to seek confirmation [14,18,22,27,29].

Informing others. In four out of 11 studies, health consumers felt that informing regulators, drug manufacturers, HCPs, and the public of ADRs were the only way to create awareness of such incidents [14,20,29,30].

Improving HCP practices. In three quantitative studies and one qualitative study, health consumers raised the view that HCPs need to be informed about ADRs and perhaps change their practice. They felt that reporting ADRs would inform HCPs about unknown ADRs and this would improve their knowledge and practices [14,20,27,29].

Responding to HCPs not reporting their ADRs. Three out of 11 studies cited that failure of HCPs to report health consumers' ADRs motivated health consumers to report their ADRs. Participants emphasized how health practitioners consulted had not taken their concerns about ADRs

seriously [22]. This motivated some health consumers in UK to self-report [20]. Given that HCPs have limited time to complete ADR reports and may be incapable of providing precise details, health consumers had less confidence that HCPs would report their ADRs accurately [14].

Asked to report ADRs by HCPs. Two qualitative studies described that health consumers were urged by HCPs to self-report ADRs. For example, in the Netherlands, participants were encouraged by pharmacy assistants to self-report ADRs [27], while in the UK pharmacists promoted participants to report [14].

4.4. Discussion

In order to improve voluntary health consumer reporting of ADRs and to increase rates of ADR reporting, it is important to identify factors influencing health consumer ADR reporting. Identifying these factors will help to develop strategies for encouraging the communication of risks associated with drug use and improve health consumer safety. The intent of this systematic review was to identify barriers and motivators that influence health consumer ADR reporting.

All of the 22 included studies were published since 2008, suggesting a growing interest in this area. Our finding showed that 16 studies focused on barriers to health consumer ADR reporting, while 11 studies reported factors that motivated reporting.

Common barriers to health consumer ADR reporting were similar to barriers to HCP reporting identified in two other systematic reviews [4,6]. Poor awareness about available reporting system, uncertainty of the responsibility to undertake such reports, and lack of feedback to submitted reports were the major barriers for both groups. Barriers to health consumers that were unique from HCPs were mailing cost, prior negative experiences, and disappearance or resolution of ADRs. Mailing costs for health consumers to report ADRs was reported in two developing countries, which may not be an issue in most countries with health consumer reporting or electronic reporting available.

Motives for health consumers to report ADRs were either altruistic or personal. Altruistic motives were: health consumers noted that ADR reporting might prevent harm to others [29]; health

consumers stated they felt responsible for reporting ADRs and disseminating them publically to improve medication safety [14]. Moreover, personal motives for health consumers to report ADRs primarily were related to the severity of reactions and a desire for personal feedback. This motive was similar for HCPs to report ADRs [6]. Another personal motive for health consumers to report ADRs was lack of interest and time limit for HCPs to report ADRs. Health consumers felt that HCPs failure to report their ADRs and that encouraged them to start self-reporting [6].

Strategies to enhance health consumer ADR reporting need to focus on increasing health consumers' awareness of reporting systems and HCPs' awareness that health consumers can directly report their ADRs. If health consumers are ignorant of available reporting systems, how they work, and how they are accessed, their contributions will continue to languish. Also, health consumers reporting ADRs for the first time were unsure of what happened to their submitted information, which discouraged return ADR reporting. National regulatory agencies could benefit from issuing letters of acknowledgment and including links to websites that provide quality drug information, thus motivating health consumers to make future efforts. By increasing awareness about the importance of health consumer ADR reporting, there will be an opportunity to promote educational interventions as well as drug safety.

Interestingly, most of the included studies were conducted in the UK, Netherlands, and Australia and none were conducted in North America. This may be related to the establishment of separate national ADR registration systems since 1968 in Ireland, Netherlands, Sweden, and the UK. These countries were invited to participate in the Program of International Drug Monitoring of the World Health Organization for the purpose of assessing the safety of commercially available medications [6]. However, most other countries including Canada and USA joined the program in the 1990s or later into 2000.

By identifying factors that influence health consumers' reporting, strategies can be developed to encourage feedback on drug-related risks and to better define the role that the health consumers can play in drug safety.

4.5. Limitations & Strengths

A number of limitations of our review exist. First, three full-text articles were not accessible to determine if they were eligible to be included [32-34]. The titles of those studies were related to the health consumer ADR reporting but the authors were not listed. Second, although each author had their own interpretation of factors influencing health consumer ADR reporting, measured using a variety of approaches, this systematic review appropriately synthesized the diverse forms of evidence identified. The methodological quality of this systematic review scored a high level using the AMSTAR instrument (9 out of 11). Items nine and ten of the AMSTAR instrument were excluded because they were not applicable (were the methods used to combine the findings of studies appropriate and was the likelihood of publication bias assessed).

4.6. Conclusion

Several barriers and motives influencing health consumer reporting of ADRs were identified in 22 studies. Poor health consumer awareness of available reporting systems was the main barrier to health consumer ADR reporting. Altruism was the main motive for health consumer ADR reporting; they wanted ADRs to be known to prevent others from suffering the same problems. Recognizing that health consumer reporting of ADRs must be actively elicited, there needs to be greater health consumer familiarity with availability of ADR reporting systems and clear guidance on using them. Furthermore, resources should be allocated to support and aim for more user-friendly reporting systems. Strategies informed by related factors may improve spontaneous health consumer ADR reporting.

4.7. Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years, no other relationships or activities that could appear to have influenced the submitted work.

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**Chapter Five. Adverse Drug Reaction Reporting in Canada: A
Retrospective Observational Analysis of Health Canada's Adverse Drug
Reaction Database from 2000 to 2014**

Formatted for submission to

the Drug Safety Journal

Authors: Al dweik, R., Kohen, D., Stacey, D., Yaya, S.

**A Retrospective Observational Analysis of Health Canada's Adverse Drug Reaction Database
from 2000 to 2014**

Abstract

Background: In Canada, adverse drug reaction (ADR) reporting was initiated in 1965. Since 2005, health consumers and others have been able to report ADRs directly to the Canadian Vigilance Online Database, MedEffect. The objective of this study was to compare ADRs reported by health consumers with ADRs reported from physicians in terms of seriousness, ADR type, and the suspected medicine class involved.

Design and Setting: Guided by risk perception theory, a retrospective observational cross-sectional study was conducted in Canada.

Methods: This study compared the number of ADR reports received by the Canadian Vigilance Online Database from January 2000 to December 2014. A total of 198,781 spontaneous ADR reports were analyzed in terms of reporter, seriousness, and category of ADRs classified by system organ class and anatomical therapeutic chemical group. Chi-square tests for independence and odd ratios (OR) were used to test for the relationship between reporters (health consumers and physicians) and the dependent variables of the type of ADR (system organ class), seriousness, and the anatomical therapeutic class (ATC) group.

Results: Of 198,781 ADR reports, 57,078 (28.7%) were from health consumers, 52,843 (27%) from physicians, 45,462(22.5%) from pharmacists, 42,446 (21%) from other healthcare professionals' (including drug manufacturers and distributors), and 952 (0.5%) from lawyers. Compared with physicians, health consumers tended to report two times more serious ADRs for the system organ classes: 'psychiatric disorders' (OR = 2.2; 95% CI 2.08 – 2.32); ' surgical and medical procedure' (OR = 2.24 ; 95% CI 1.99 – 2.53); and ' social circumstances' (OR = 2.41; 95% CI 1.79 – 3.24) than physicians. However, compared with health consumers, physicians reported more serious ADRs for the following system organ class: 'blood and lymphatic system disorder' (OR = 0.21; 95% CI 0.19- 0.25). Health consumers were more likely to report ADRs from the anatomical therapeutic classes:

group R ‘respiratory system’ (OR = 2.20; 95% CI 1.5 – 2.9); group H ‘systemic hormonal preparations’ (OR = 2.56; 95% CI 1.9 – 3.8); group D ‘dermatological’ (OR = 2.30; 95% CI 2.0 – 2.8); and group S ‘sensory organs’ (OR = 2.72; 95% CI 1.99 – 3.1) than physicians. Physicians reported more serious ADRs from the anatomical therapeutic class group B ‘blood and blood forming organs’ (OR = 0.30; 95% CI 0.28 – 0.34), than health consumers. ‘*General disorder and administration site conditions*’ was the most common category of system organ class reported by both health consumers and physicians.

Conclusions: The study showed that health consumers reported on different categories of system organ classes and anatomical therapeutic chemical groups than physicians. Health consumer reports should not be dismissed and should not automatically be assumed as messy or confusing to surveillance systems. These reports may provide useful input from different perspectives. Direct health consumer reporting should be encouraged and considered as a new source for medication safety in pharmacovigilance.

5.1. Introduction

Adverse drug reactions (ADRs) affect drug users worldwide. The market for a new drug, once it has been approved, most often includes health consumers and disease groups never assessed in pre-market clinical trials [1]. This means that ADRs are often not reported until years after a drug is on the market [2]. ADR reporting is one of the key elements of the medication safety process. Since 1960, the World Health Organization (WHO) has been monitoring ADRs via spontaneous reporting systems [2]. The main aim of these ‘pharmacovigilance’ systems is to gather new information about possible serious, rare and unknown ADRs at an early stage of post-marketing surveillance [2].

In 1965, when ADR reporting systems began, only physicians and dentists were allowed to report ADRs [3]. Then in 1995, WHO mandated drug manufacturers to report ADRs to health regulators. However, substantial under-reporting of ADRs by healthcare professionals (HCPs) was noticed in 2003 [4]. Thus pharmacists, nurses and health consumers were allowed to report ADRs, in the hopes that this would increase the volume and quality of the reports [4].

Only 46 countries recognize health consumer-submitted ADR reports in their pharmacovigilance systems. These countries include Canada (1965), the US (1969), Denmark (2003), the Netherlands (2003), the UK (2005), and Sweden (2008) [5]. Direct health consumer reporting may be important for continuous improvement and successful pharmacovigilance because it increases chances to identify new safety issues. However, the literature is sparse regarding the role of direct health consumer reporting and its effects on pharmacovigilance activities [6]. Much debate remains among experts concerning the utility and efficacy of incorporating health consumer ADR reports into pharmacovigilance systems [7,8]. Some researchers believe that health consumer ADR reporting is detrimental to pharmacovigilance activities because too many reports of non-serious and well-known ADRs can flood systems and cause too much noise and confusion [9]. Others fully support health consumer ADR reporting and argued that direct health consumer reporting provides additional information for good pharmacovigilance since health consumers, as users of medications, have first-hand knowledge of their experiences with ADRs [4,10,11].

In Canada, spontaneous ADR reporting systems are maintained by Health Canada with HCPs and health consumers were encouraged to voluntarily report any suspected ADRs [12]. Market Authorization Holders (manufacturers and distributors) were mandated by law to report ADRs [13]. ADR reporting is one of the tools that enables Health Canada to monitor the safety of health products and to determine if their benefits outweigh their risks.

Several studies have been conducted to explore differences in information reported by health consumers and HCPs [14]. The Netherland Pharmacovigilance Center, Lareb, compared three years of health consumer ADR reports with those from HCPs and found significantly more life threatening ADRs and disability reported by health consumers [15]. In Denmark, health consumers compared to HCPs were more likely to report ADRs from system organ class (SOCs): 'nervous system disorders', 'psychiatric disorders', and 'reproductive system and breast disorders' than other sources [5]. However, in the UK, while health consumers reported more ADRs than HCPs, HCPs reported more serious ADRs that resulted in hospitalization or death [16]. Finding similarities and differences between health consumer and HCP reports may help clarify the potential value of direct health consumer reporting to pharmacovigilance systems [17].

The objective of this study was to compare ADRs reported by health consumers with ADRs reported by physicians in terms of seriousness, type of ADR, and suspected medicinal class involved.

5.2. Methods

5.2.1. Study Design

A retrospective-observational cross-sectional study design was used to compare health consumers and physicians ADR reports submitted to Health Canada. The study included all ADR reports submitted to Health Canada from January 1st 2000 through December 30 2014, inclusive. Due to the public availability of electronic reports and the potential for improving the power level, all reports were analyzed based on seriousness. The identification of serious ADRs is the primary focus of spontaneous reporting systems and is of particular public health interest [9, 11].

In this study, the analysis based on system organ class and anatomical therapeutic class group only focused on ‘serious’ ADR reports because they are the most important goal of spontaneous reporting and . This study followed the design used by Aagaard et al. (2009) in their analysis of the Danish ADR database, the Danish Medicine Agency [5].

5.2.2. Study Setting

This research was conducted in Canada, using the Canadian Vigilance Program Online Database, MedEffect. Spontaneous ADR reports by HCPs, health consumers, lawyers, and market authorization holders are submitted to MedEffect by post, telephone, or via the Internet [11]. Health Canada’s website contains detailed information on reporting procedures and search criteria [18]. This database contains all spontaneous ADR reports in Canada.

The four main criteria that define any ADR report and must be included in all reports are: i) health consumer information; (ii) the suspected medicine(s); (iii) ADR outcome information; and (iv) reporter information. Two different ADR forms are available, one for health consumers and the other for HCPs. An important difference exists in the reporting form with respect to outcome(s) of the suspected ADR. The health consumer form does not ask directly whether the health consumer considers the reaction to be serious but the health consumer is asked to indicate how bad the ADR was and asked to select one option from:

- Uncomfortable, but did not affect everyday activities
- Bad enough to affect everyday activities
- Bad enough to be admitted to hospital
- Caused long-term serious disability
- Life-threatening
- Caused death
- Caused birth defect
- Other

Then an evaluator at Health Canada evaluates the report based on the Council for International Organizations of Medical Sciences (CIOMS) criteria [19].

However in the HCP ADR reporting form, the HCP is asked ‘Do you consider the reaction to be serious?’ and is given a ‘yes’/‘no’ response option. If ‘yes’ is ticked then the HCP is requested to specify one or more of six reasons for considering the reaction to be serious. These are based on CIOMS criteria as:

- Death
- Life threatening
- Hospitalization
- Hospitalization – prolonged
- Disability
- Congenital malformation
- Required intervention to prevent damage/impairment
- Other

MedEffect defines the following five categories of reporters to the database as: (i) Health consumers: health consumers, health consumers' relatives, other members of the public; (ii) Physicians: general practitioners, hospital doctors and dentists; (iii) Pharmacists; (iv) Other healthcare professionals: drug manufacturers and distributors; and (v) Lawyers and insurance companies.

5.2.3. Data Extraction

Data extraction of eligible files was comprehensive. Medeffect database contains the latest quarterly files, which were extracted and downloaded from the database for the specific period. ADR information was placed in anonymous form with encrypted identification. Once the data downloaded, information about the reporting date, type of reporters, seriousness criteria, system organ class, and drug type were extracted. ADRs were coded according to Medical Dictionary for Regulatory Activities (MedDRA) on system organ class (SOC). ADR reports were classified according to

seriousness using CIMOS criteria [20]. Data were screened for duplicate reports by conducting a full systematic search for duplicate reports and this was undertaken using SPSS; any duplicate reports identified were deleted.

5.2.4. Medical Dictionary for Regulatory Activities (MedDRA)

The ADR data contained within MedEffect database is coded using MedDRA terminology. MedDRA is composed of standardized terms for symptoms, signs, diseases, syndromes, and diagnoses [21]. The terminology is organized into hierarchy of five distinct levels from System Organ Class (SOC), High Level Group Term (HLGT), High Level Term (HLT), Preferred Term (PT), to Low Level Term (LLT). These groupings are used in post-marketing surveillance databases to aid in the retrieval, evaluation, and presentation of ADR data coded with MedDRA [21]. System Organ Class (SOC) is the highest level of the hierarchy, and provides the broadest concept for data retrieval. Each SOC contains several similar ADR terms that relate to one specific organ system of the body (i.e., cardiac disorders). SOCs are useful when searching for a set of similar adverse reaction terms (i.e., cardiac arrest and heart attack). There are 26 SOCs in MedDRA [22]. In this study, the ADRs were coded according to the MedDRA structure on 'SOC' (see Appendix A).

5.2.5. Anatomical Therapeutic Chemical System (ATC)

This is a system that classifies medicinal products based on their chief ingredient, the organ on which they exert their medicinal function, and their chemical, pharmacological and therapeutic properties using WHO Dictionary [10]. Medicinal products are classified into groups on five different levels. The medicines are divided into 14 main groups (first level), with one pharmacological/therapeutic subgroup (second level), chemical/pharmacological/therapeutic subgroups (third and fourth levels), and the chemical substance (fifth level). The second, third, and fourth levels are often used to identify pharmacological subgroups rather than the therapeutic or chemical subgroups [23]. In this study, the first ATC level were used to comprehensively categorize ADR data into one of 14 groups because the extraction from the ADR database (MedEffect) only provides information on the trade names of medicinal products that have been reported as causing ADRs.

5.2.6. Data Analysis

The main goal of the statistical analysis was to investigate the association of the ADR reporter and the reported ADR (classified by SOC and ATC group) using a chi-squared test for independence¹. Odd Ratio (OR) was calculated using a 2x2 table for each category of reporters (health consumers and physicians) and each ATC group or SOC. Confidence intervals were calculated for all ORs (95% level). Statistical analyses were performed using SPSS statistical software version 22 (SPSS, Chicago, IL). A sensitivity test was conducted to ensure that the significant differences between number of ADR report between health consumers and physicians were not due to the sensitivity of the chi-square test to the large sample size. We randomly selected smaller subsample and test for difference.

5.3. Results

A total of 198,781 spontaneous ADR reports were received by Health Canada from January 1, 2000 to December 30, 2014. Of these, 57,078 (29%) were health consumer reports, 52,843 (27%) were physician reports, 45,462 (22.9%) were pharmacist reports, 42,446 (21%) were other HCP reports, and 952 (0.5%) were lawyer reports (see Table 5.1).

The total number of spontaneous ADR reports received by Health Canada increased from 5,570 in 2000 to 23,663 in 2014. The health consumer reports contributed 13% of the total number of reported ADRs in 2000 and 31% reported in 2014.

5.3.1. ADR Distribution based on Seriousness

Of the total number of ADR reports submitted by health consumers and physicians (N = 109,921), approximately 66% of these reports were categorized as serious. Health consumers submitted significantly more serious ADR reports than physicians (OR: 1.08, CI: 1.05, 1.10, p<0.001) (see Table 5.1).

Table 5.1. Classifications of ADR Reports Based on Reporter and Seriousness

Reporters	Serious ADRs [n(%)]	Non-Serious ADRs [n(%)]	Total ADRs [n(%)]
Health consumers	38867 (29%)	18211 (27%)	57078(29%)
Physicians	35086 (26.7%)	17757 (26%)	52843 (27%)
OHCPs *	31005(23.6%)	11441 (17%)	42446 (21%)
Lawyers	945 (0.72%)	7 (0.01%)	952 (0.50%)
Pharmacist	25367 (19.3%)	20095 (30%)	45462 (22.9%)
Total	131270	67511	198781

*OHCP: Other healthcare professionals: pharmaceutical companies and distributors, nurses

The sensitivity test ensured that the significant differences between the number of ADR report between health consumers and physicians were not due to the sensitivity of the chi-square test to the large sample size. For the small samples (N = 588), the p-value (0.03) was less than alpha (0.05), and this confirmed that the difference was not solely driven by sample size and the results remained the same.

5.3.2. Distribution of ADRs by Type of Reporter and System Organ Class

There was a difference in the distribution of ADRs for various SOC categories and type of reporter ($p < 0.001$) (see Table 5.2).

Table 5.2: Distribution of 'serious' ADRs between Health Consumers and Physicians based on System Organ Class (Jan 1 2000 to Dec 30 2014) in Canada. *The bold fields indicate the category of ADR reports (SOC) for which health consumers and physicians have reported significantly different ($p < 0.001$)

System Organ Class	Health consumers (n(%))	Physicians (n(%))	OR (95%CI)	p-value
General Disorders and Administration Site Conditions	6114(17.3)	5115 (15.6)	1.1(1.0-1.2)	<0.001
Psychiatric Disorders	4383(12.4)	1973 (6.02)	2.2(2.08-2.32)	<0.001
Nervous System Disorders	3568 (10.1)	3636 (11.11)	0.89(0.85-0.94)	<0.001
Gastrointestinal Disorders	2790 (7.88)	2899 (8.85)	0.88(0.83-0.93)	<0.001
Injury, Poisoning and Procedural Complications	2058(5.81)	1304 (3.98)	1.5(1.4-1.6)	<0.001
Infections and Infestations	1873(5.29)	1249 (3.81)	1.4(1.3-1.5)	<0.001
Immune System Disorders	361 (5.2)	390 (1.19)	0.86(0.74-0.99)	<0.032
Investigations	1839 (5.2)	2753 (8.40)	0.60(0.56-0.63)	<0.001
Musculoskeletal and Connective Tissue Disorders	1631 (4.60)	1495 (4.56)	1.0(0.93-1.08)	<0.79
Respiratory, Thoracic and Mediastinal Disorders	1548 (4.37)	1648 (5.03)	0.86(0.80-0.93)	<0.001
Skin and Subcutaneous Tissue Disorders	1369 (3.87)	1562 (4.77)	0.80(0.75-0.87)	<0.001
Cardiac Disorders	1283 (3.62)	1558 (4.76)	0.75(0.70-0.81)	<0.001
Eye Disorders	1004(2.85)	729 (2.22)	1.3(1.2-1.4)	<0.001
Surgical and Medical Procedure	927 (2.62)	387 (1.18)	2.24(1.99-2.53)	<0.001
Neoplasms Benign, Malignant and Unspecified	826 (2.33)	1344(4.10)	0.56(0.51-0.60)	<0.001
Vascular Disorders	815 (2.30)	1086 (3.30)	0.69(0.63-0.75)	<0.001
Metabolism and Nutrition Disorders	709 (2.00)	625 (1.90)	1.05(0.94-1.17)	<0.38
Reproductive System and Breast Disorders	642 (1.81)	381 (1.16)	1.57(1.38-1.78)	<0.001
Renal and Urinary Disorders	470 (1.32)	633 (1.93)	0.68(0.60-0.77)	<0.001
Pregnancy, Puerperium and Perinatal Conditions	272 (0.77)	293 (0.89)	0.86(0.72-1.01)	<0.069
Hepatobiliary Disorders	235 (0.66)	354 (1.08)	0.61(0.52-0.72)	<0.001
Blood and Lymphatic System Disorder	229 (0.65)	950 (2.90)	0.21 (0.19-0.25)	<0.001
Ear and Labyrinth Disorders	197 (0.55)	135 (0.41)	1.4(1.1-1.7)	<0.001
Social Circumstances	156 (0.44)	60 (0.81)	2.41(1.79-3.24)	<0.001
Endocrine Disorders	57 (0.16)	105 (0.32)	0.5(0.36-0.69)	<0.001
Congenital, Familial and Genetic Disorders	43 (0.12)	78 (0.24)	0.51(0.35-0.74)	<0.001

The bold fields in table 5.2 indicate the category of ADR reports (SOC) for which health consumers and physicians have reported differently $p < 0.001$. When health consumer reports were compared with reports from physicians, health consumers were more likely to report ADRs from the SOCs 'general disorders and administration site conditions' (OR = 1.1; 95% CI 1.0 – 1.3);

'psychiatric disorders' (OR = 2.2; 95% CI 2.08 – 2.32); 'injury, poisoning and procedural complications' (OR = 1.5; 95% CI 1.4 – 1.6); 'infections and infestations' (OR = 1.4; 95% CI 1.3 – 1.5); 'eye disorders' (OR = 1.3; 95% CI 1.2 – 1.4); 'surgical and medical procedure' (OR = 2.24 ; 95% CI 1.99 – 2.53); 'reproductive system and breast disorders' (OR = 1.57; 95% CI 1.38 – 1.78); 'ear and labyrinth disorders'(OR = 1.4; 95% CI 1.1 – 1.7); and 'social circumstances' (OR = 2.41; 95% CI 1.79 – 3.24). Compared with physicians, health consumers reported fewer ADR reports from the SOCs 'blood and lymphatic system disorder' (OR = 0.21; 95% CI 0.19-0.25); 'endocrine disorders' (OR = 0.5; 95% CI 0.36 – 0.69); 'congenital, familial and genetic disorders' (OR = 0.51; 95% CI 0.35 – 0.74); 'neoplasms benign, malignant and unspecified' (OR = 0.56; 95% CI 0.51 – 0.60); 'investigations' (OR = 0.60; 95% CI 0.52 – 0.72); 'hepatobiliary disorders' (OR = 0.61; 95% CI 0.52 – 0.72); 'renal and urinary disorders' (OR = 0.68; 95% CI 0.6 – 0.77); 'cardiac disorders' (OR = 0.75 ; 95% CI 0.70 – 0.81); 'skin and subcutaneous tissue disorders' (OR = 0.8 ; 95% CI 0.75 – 0.87); 'respiratory, thoracic and mediastinal disorders' (OR = 0.86; 95% CI 0.80 – 0.93); 'gastrointestinal disorders' (OR = 0.88; 95% CI 0.83- 0.93); and 'nervous system disorders' (OR = 0.89; 95% CI 0.85 – 0.94).

5.3.3. Distribution of Serious ADR Reports based on the Type of Medicine (ATC Group) and Reporters

There was a significant difference in the number of ADR reports for both reporters (health consumers and physicians) based on the type of medicines (ATC group). The bold field in table 5.3 shows the type of medicines (ATC groups) for which health consumer reports were significantly different when compared with reports from physicians. Health consumers were more likely to reports ADRs from the ATC group L, 'antineoplastic and immunomodulating agents' (OR = 1.23; 95% CI 0.98 – 1.9); group M, 'musculoskeletal system' (OR = 1.3; 95% CI 1.1 – 1.9); group A, 'alimentary tract and metabolism' (OR = 1.3; 95% CI 1.2 – 1.5); group R, 'respiratory system' (OR = 2.20; 95% CI 1.5 – 2.9); group H, 'systemic hormonal preparations' (OR = 2.56; 95% CI 1.9 – 3.8); group D, 'dermatological' (OR = 2.30; 95% CI 2.0 – 2.8); and group S, 'sensory organs' (OR = 2.72; 95% CI

1.99 – 3.1). Physicians reported more serious ADRs from the anatomical therapeutic class group B, ‘blood and blood forming organs’ (OR = 0.30; 95% CI 0.28 – 0.34); group C, ‘cardiovascular system’ (OR = 0.73; 95% CI 0.68 – 0.77); and group J, ‘anti-infective for systematic use’ (OR = 0.77; 95% CI 0.71 – 0.84), than health consumers.

Table 5.3 Distribution of 'serious' ADRs reports based on type of medicine (ATC) group, and type of reporters

ATC	Health consumers	Physicians	OR (95%CI)	P-value
L (Antineoplastic and Immunomodulating Agents)	4089 (12.44)	3142 (9.56)	1.23 (0.98-1.9)	<0.001
N (Nervous system)	3840 (11.68)	3196 (9.72)	1.14(1.08-1.20)	<0.093
M (Musculoskeletal System)	2491 (7.58)	1819 (5.53)	1.30(1.1-1.9)	<0.001
G (Genito-urinary system and sex hormones)	1675 (5.11)	1516 (4.61)	1.04(1.0-1.09)	<0.153
A (Alimentary Tract and Metabolism)	1148 (3.49)	831 (2.53)	1.3(1.2- 1.5)	<0.001
R (Respiratory System)	863 (2.63)	379 (1.15)	2.20 (1.5 - 2.9)	<0.001
C (Cardiovascular system)	831 (2.53)	1051 (3.19)	0.73(0.68-0.0.77)	<0.001
B (Blood and blood forming organs)	706 (2.15)	1909 (5.80)	0.30 (0.28-0.34)	<0.001
J (Anti-infective for systemic use)	600 (1.83)	728 (2.21)	0.77(0.71-0.84)	<0.001
H (Systemic Hormonal Preparations)	475 (1.44)	181 (0.55)	2.56(1.9-3.8)	<0.001
D (Dermatological)	433 (1.32)	184 (0.56)	2.30(2.0-2.8)	<0.001
S (Sensory Organs)	316 (0.96)	113 (0.34)	2.72 (1.99 - 3.1)	<0.001
V (Various)	136 (0.41)	130 (0.40)	0.99(0.91-1.08)	<0.400
P (Anti-parasitic products)	46 (0.14)	44 (0.13)	0.98 (0.92-1.05)	<0.623

5.4. Discussion

This study described health consumers compared with physicians in order to ascertain differences in reporting serious ADRs. The study was based upon the most recently available electronic data collected by Health Canada over the last 14 years. The study indicated that in the Canadian Vigilance Reporting system, ADR reporting from health consumers and physicians differed with regard to seriousness of ADRs, reported ADRs (SOC) and therapeutic categories. The use of

health consumers' data in systematic ADR monitoring in the Canadian Vigilance System had not previously been studied.

In Canada, the total number of ADR reports increased from 5,570 in 2000 to 23,663 in 2014. This may be because in 2005 Health Canada launched "MedEffect", a new website dedicated to collecting ADR reports from Canadian physicians and health consumers, as well as posting the drug-safety information gained as a result of these reports [27]. In this study, health consumer ADR reports contributed 29% of the total number of reported ADRs. This finding is inline with studies from other countries that have shown that health consumers contributed 7 – 23% of the total reported ADRs [11, 15].

5.4.1. Seriousness of ADR

In Canada, the proportion of health consumer ADR reports classified as serious were statistically significantly higher than the proportion from physicians. Basch (2010) noted that physicians generally tend to downgrade the severity of symptoms and that health consumer reports commonly capture ADRs that physicians ignore [25]. In the Denmark and the Netherlands studies, no significant differences in the number of serious ADR reports were detected between health consumers and HCPs [10, 15].

Health consumers primarily reported ADRs for the SOCs 'psychiatric disorders' and 'nervous system disorders' and the medicine in ATC group N (Nervous System), which is in keeping with previous analyses of health consumer reports in Denmark, the Netherlands, Sweden and the UK [27-29].

5.4.2. Theoretical Interpretation

This study was guided by risk perception theory, which was used to explain differences between health consumer and physician reporting of ADRs. Risk perception theory explains that different classes of people (professionals and non-professionals, scientists and the public, or in this case, health consumers and physicians) will have different views on the possible risks associated with ADRs. The main hypothesis of risk perception theory affirms that risk events influence the public's

psychological, social, and cultural interpretations in ways that will impact their perception of risk [30].

SARF is one of the risk perception theory approaches (Wahlberg, 2001). This approach developed to explain why an unimportant or mild risk event can result in a widespread reaction by the public (Kasperson et al., 1988). These wide spread reactions usually have a large influence on the social and economic aspects of society (Heberlein & Stedman, 2009).

SARF was used to further explain the consumer perception of risk. The chief hypothesis of SARF affirms that the risk events influence the public's psychological, social, and cultural interpretations in ways that will impact the public's perceptions of risk (Kasperson et al., 1988). These changes in risk perception then affect the behavior of the public that in turn impacts social and/or economic aspects and thereby increases or decreases the physical risk (Kasperson et al., 1988).

Risk perception and public behaviors greatly affected by mass media (Kasperson et al., 1988). The media can communicate the risk event such a detrimental way as to amplify the risk even though the perceived risk may not be based on scientific evidence. In this example, consumers may receive their cue from television commercials of mass litigation trials, radio announcements, newspaper articles that may single out a drug class unfairly, portraying the statistical evidence incorrectly, or even discussions amongst each other with incomplete information.

Public and health professionals have differing risk perceptions of ADRs [26]. This is due in part to education. Health consumers may perceive any ADR, whether serious or non-serious, as a risk, based on information in advertisements or the Internet. This may explain the difference in the number of ADRs reported by health consumers and physicians, as seen in this study.

Health consumers and physicians perceive the dangers of one drug class over another drug class differently, as was shown by Bongard et al. (2002). This may help to explain why when drugs were grouped into their ATC anatomical classifications, physicians reported more on ATC group B (blood and lymphatic system disorder agents), while health consumers reported more on ATC group L (antineoplastic and immunoglobulating agents). Also, differences may be explained due to the

interests of physicians to report ADRs for new medicines compared with older ones and the interest of health consumers to report on ADRs that have a larger impact on their quality of life and daily activities [26].

5.4.3. Health Consumer Reporting and Pharmacovigilance

The aim of including health consumer reporting in a spontaneous ADR reporting system is to add values to the reporting system and to try to detect signals earlier or find new signals not detected by HCPs [4]. Different patterns of ADRs in terms of the number of serious reports, the suspected drugs, and the SOC were found in health consumers' reports. This suggests that health consumers have important contribution to ADR reporting. These results are noteworthy as there are no other studies conducted using the Canadian MedEffect database for comparison and the findings can be considered as a starting point for future research.

5.5. Strength and Limitations of the Study

To our knowledge, this is the first Canadian study to compare all ADR reports from health consumers and physicians. In this study, we did not investigate the validity of health consumers and physicians reports because we only had access to the data from MedEffect and not to the original reports. Also, we focused only on the 'serious' ADR reports because these reports are of particular public health interest. An analysis of the remaining 'non-serious' reports could be interesting with regard to health consumer versus physician perspectives on ADRs. One of the limitations in the study was a potential for bias in ADR reports from health consumers. Health consumers were not asked directly whether they consider the reaction to be serious. Evaluators from Health Canada classified the seriousness of reported ADR. From the available data, it was difficult to obtain information on the clinical relevance of the reported ADRs for both health consumers and physicians. Further research should investigate why physicians in Canada report significantly fewer ADRs than health consumers: Are these ADRs downgraded by physician as inconsequential? If so, should they be? These kinds of questions might best be answered by additionally research including qualitative studies on how valuable are health consumers reports.

5.6. Conclusion

In Canada between 2000 and 2014, health consumers contributed 25% of all ADR reports. This study showed that health consumers and physicians reported on different SOC and ATC categories. Hence ignoring or not considering consumers' reports in pharmacovigilance may result in missing early identification of safety alerts or missing important safety data. Health consumer reports could positively affect pharmacovigilance systems by supplementing databases and adding additional information not reported by physicians. The findings of this study may prompt regulators from other countries to incorporate health consumer reports into their pharmacovigilance activities, as is the case in Canada. Reports from health consumers should be included in post-marketing surveillance and physicians, pharmacists, and other healthcare professionals should encourage health consumer reporting.

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Chapter Six. Health Consumers' Experiences Reporting Adverse Drug Reactions and Usability Of The Canadian Vigilance System: A Qualitative Study

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Health Consumers' Experiences Reporting Adverse Drug Reactions and Usability Of The Canadian Vigilance System: A Qualitative Study

Abstract

Background: Spontaneous reporting of adverse drug reactions (ADRs) is an important source of information for post-marketing drug safety evaluation. Most countries have public access to reporting systems but health consumers' report only 3% of all ADRs worldwide. Little is know about factors affecting health consumer reporting.

Objectives: To explore health consumers' experiences reporting ADRs and the usability of the Canadian Vigilance reporting system, MedEffect.

Methods: An interpretive description qualitative study was used. Adults in Canada, who experienced an ADR, were invited to participate through social media (Kijiji, Facebook, Twitter) and by associations (e.g., Patients Canada or Canadian Arthritis Society). Participants were interviewed in English or French using structured interview guides. Inductive content analysis was used.

Results: Fifteen interviews were conducted from October 2014 to May 2015. Two participants reported ADRs to MedEffect and others to physicians and/or pharmacists. Motives for reporting were: intolerable side effect impacting on daily activities and encouragement from others to report (e.g., family, colleagues). Factors that interfered with reporting were: physicians normalized or minimized the side effect, confusion on what to report, no feedback after report submission to MedEffect, and previous experience with side effects. MedEffect forms were described as comprehensive and important but usability was affected by the number of questions and the complexity of some questions.

Conclusions: Most participants were unaware of MedEffect and reported ADRs to physicians and pharmacists. Several barriers and motives affected health consumers' reporting of ADRs. The MedEffect form could be simplified for use by health consumers.

6.1. Introduction

Adverse drug reactions (ADRs) affect users worldwide. They can cause significant disability and mortality, and are expected to be associated with an economic drain on the healthcare system [1,2]. In 1964, following the thalidomide tragedy, an ADR reporting system was initiated by the World Health Organization (WHO) as a voluntary spontaneous process for collecting and analyzing ADRs [3]. Subsequently, most countries established a process for spontaneous ADR reporting by physicians, pharmacists, nurses, midwives, manufacturers, and health consumers. The process typically involves completing a form (hard copy or electronic) for submission to designated governmental health authorities through pharmacovigilance centers (e.g., Health Canada, US Food and Drug Administration, or Medicines and Healthcare Products Regulatory Agency of UK). Reports of possible ADRs are used to detect ADRs in the post-marketing phase. Currently, 46 countries allow health consumers to report ADRs directly and health consumer reporting is seen as an increasingly important for pharmacovigilance [3,4].

There is controversy among experts on the utility and efficacy of incorporating health consumer ADR reports into pharmacovigilance activities [5,6]. Some believe that health consumer ADR reporting is detrimental to pharmacovigilance activities, while others believe that health consumers, as users of medications, have first-hand knowledge of their experiences with ADRs that can add an extra layer for good pharmacovigilance [3,7,8]. However, the literature is deficient on direct health consumer reporting and its effects on pharmacovigilance activities [9]. Allowing direct health consumer spontaneous reporting also supports health consumers to be actively involved in their treatments [11].

Under-reporting is a known issue as evidenced by only 3% of all ADRs being reported to regulatory authorities [10]. By adding health consumer reports along with health care professionals' (HCPs) reports, a spontaneous surveillance database has the potential to acquire data rich with additional information about ADRs [11] and hence speed up the drug alert detection process. Although factors influencing HCP reporting of ADRs have been studied thoroughly [12-24], limited

studies have explored factors influencing health consumer reporting of ADRs. Factors that influence ADR reporting by health consumers have included: awareness of direct health consumer reporting [25], altruism, and a desire to find out if others had experienced similar problems [4], feedback to reporters [4], and the severity of the ADR [26]. Understanding how health consumers are involved in ADR reporting can provide new insights into the importance and limitations of integrating health consumer ADR reports into pharmacovigilance and might help improve medication safety in Canada. This study explored health consumers' experiences reporting ADRs and their views on the usability of the Canadian Vigilance reporting system, MedEffect.

6.2. Method

6.2.1. Design

A qualitative study was conducted using an interpretive description design (Thorne, 2008). This design was used due to the exploratory nature of the study. Since little is known about what influences health consumers to report ADRs, the interpretive description design is suited to develop an understanding about this subject. This design was useful for exploring health consumers' reactions and experiences [27].

6.2.2. Setting.

In Canada, ADRs are reported in at least 1% of annual hospital admissions and approximately 0.3% of admissions may be caused by an ADR [10]. Health Canada is responsible for handling the spontaneous reporting system for ADRs with reporting guidelines on the MedEffect website. Health consumers are able to report ADRs directly to Health Canada through an electronic reporting form, telephone, or paper form. These forms are similar to those used by HCPs in terms of content. Some mandatory fields in the form ensure information is complete before it can be sent to Health Canada via MedEffect. Health consumer ADR reports are first screened for the four minimum criteria: an identifiable health consumer, a reporter, a suspect drug, and a reaction. These reports are entered into the MedEffect. Evaluators assess ADR reports from the database, along with other relevant sources of information, as part of the overall safety assessment of a product to determine if there are post-

surveillance problems requiring action. The MedEffect database can be accessed by the public to see ADRs that have been reported for a specific health product [28].

6.2.3. Participants and Sampling.

Eligible participants were adult health consumers, over 18 years old, living in Canada and able to answer questions in either English or French. Purposeful sampling was used to represent a range of ages (18-45, 45-64, 65-80) and sexes (male, female). A snowball technique was also used to have participants identify other potential participants [29]. Recruitment was continued until data saturation was reached [30].

6.2.4. Procedure.

Participants were informed about study details and invited to participate through social media (e.g., Kijiji, Facebook, Twitter) and health associations (e.g., Patients Canada, Canadian Arthritis Society, Canadian Cancer Society, Heart & Stroke Foundation). Individuals expressing interest were sent an email introducing the study.

After confirming eligibility, participants were scheduled for an in-person, telephone, or skype interview at a time and location convenient to them. Interviews were conducted using a semi-structured interview guide. The semi-structured interview guide was developed based on key sensitizing concepts from the literature on ADR reporting and reviewed by experts in pharmacy, knowledge translation to health consumers, and health policy. The first set of interview questions explored participant experiences with medication-related side effects, severity, who they reported side effects to, and expectations about reporting. The second set of interview questions focused on the user-friendliness of the ADR reporting form that is available on the MedEffect website. The interviewer (RD) led each participant through the ADR form step-by-step and then asked questions to explore the clarity of the questions, ease of use, readability, and font size. Respondents were encouraged to express their own views openly [31]. Interview guides were pilot tested and few modifications were required (e.g., combined two questions and rearranged the flow of questions). Field notes were documented after each interview.

6.3. Ethical Considerations

The study was approved by the University of Ottawa Research Ethics Board in July 2014 (file no. H05-14-18). To ensure confidentiality, all personal identifiers were removed from transcripts and numbers were used to identify participants (e.g., P1, P2...P15). Written informed consent was obtained from all participants prior to their interview.

6.4. Analysis

Audio-taped interviews were transcribed verbatim, and transcripts were compared with the recordings for accuracy and read several times for immersion in the data (RD). Two interviews were in French and transcripts were translated to English for analysis. Demographic data were entered into an Excel database and analyzed descriptively.

Analysis of the open interview questions was guided by inductive content analysis [31]. Analysis of participant interviews focused on *factors influencing health consumer reporting and views and experiences of the health consumers with the reporting form on MedEffect*. The inductive content analysis for the interview transcripts and field notes included the following steps: First, each interview transcript was read line-by-line with open coding conducted using notes and categories describing content were written in transcripts' margins (RD). Second, notes and categories were grouped into a coding scheme and used to create sub- categories (RD). Sub-categories were compared and contrasted, with some merged into larger sub-categories with more general description of content. Then, these larger sub-categories with similar events, understandings, trends, and incidences were grouped together to formulate main categories. Concurrently, a second team member (DS) independently analyzed three transcripts and twelve other interviews were coded by two persons independently (RD, SM) using free codes. Third, two team members (RD, DS) conducted constant comparative analysis to systematically compare emerging categories for all 15 interviews. Finally, data analysis findings were audited by co-authors and categories were further refined (RD, DS, SY, DK). Specific closed-ended questions about usability of the ADR form were described.

Several strategies were used to enhance credibility and transferability of the findings [33]. To enhance credibility, two team members independently analyzed transcripts and the analysis process was audited by three team members. To ensure transferability of findings, a rich description of the study setting was provided [32,33].

6.5. Results

In total, 15 interviews were conducted from October 2014 to May 2015 (see Table 6.1). Interviews were conducted in person (n = 5), via telephone (n = 6) or via Skype (n=4). Interviews were a median of 35 minutes (range: 25 to 45 minutes). Of the 15 participants interviewed, 13 were women and 2 were men (see Table 1). Two participants reported ADRs to Health Canada and one participant knew about the reporting system because of her profession. Participants had a range of education from high school to post-secondary.

The interviews revealed that most of the participants *were not aware* about the ADR reporting system. Twelve participants interviewed indicated that they knew nothing about the reporting system and had found out about it through the invitation letter submitted to them to participate in the study: “I just read about it from the consent form and invitation” (P3); “I honestly didn’t know that this form existed” (P1). Only three participants had heard of the reporting system before being interviewed them: “Actually, I was aware about it before and that’s due to my profession” (P7).

Table 6.1 Characteristics of the Interviewed Participants

Participants	Age range	Sex	Education Level	Occupation	Use of ADR Reporting System
P 1	<30	F	Community college	Assistant Teacher	Unaware
P 2	49	F	Community college	Unemployed	Unaware
P 3	<30	F	Undergraduate	Full-time student	Unaware
P 4	<30	F	High school	Full-time student	Unaware
P 5	<30	F	Undergraduate	Nurse Assistant	Unaware
P 6	<30	F	University	Full-time student	Unaware
P 7	30-40	F	University	Pharmacist	Know about it
P 8	41-50	M	University	IT Engineer	Unaware
P 9	<30	F	Undergraduate	Assistant Teacher	Unaware
P 10	<30	F	Undergraduate	Cashier/Tutor	Unaware
P 11	<30	F	Undergraduate	Full-time student	Used it once
P 12	>60	F	University	Unemployed	Used it twice
P 13	<30	F	Undergraduate	Full-time student	Unaware
P 14	<30	M	Undergraduate	Full-time student	Unaware
P 15	40-50	F	University	Sales	Unaware

6.5.1. ADR Characteristics

Participants described an ADR that they reported for themselves (n=13) or a family member (n=2). Two of the participants (P7, P12) suffered severe ADRs requiring hospital admission (see Table 6.2). Participant reports covered 14 different medications with ADRs ranging from change in mental health (e.g., memory loss, hallucinations), GI symptoms (nausea, diarrhea), rash, and impact upon activities of daily living. Seven participants reported their ADR to physicians, four reported to pharmacists, two reported to Health Canada, and two were not reported.

Table 6.2: Suspected ADR Reported by Interviewed Participants

Drug Involved	Suspected ADRs	Reported to
Oseltamivir	Drowsiness, faint, nausea	Boss at work and Family Doctor
Atomoxetine	Memory loss	Family Doctor
Methylphenidate	Memory loss	Family Doctor
Erythromycin	Rash	Family and Family Doctor
Desogestrel - ethinyl estradiol	Loss in sexual ability	ADR Not Reported
Escitalopram	Loss in sexual ability, memory loss	ADR Not Reported
Drospirenone and ethinyl estradiol	Weight gain, Enlarge breast tissue	Family Doctor
Ciprofloxacin	Hallucination, Idiopathic autoimmune haemolytic anemia	Consultant
Sertraline	Heartburn	Family Doctor
Clindamycin	Severe diarrhoea	Nurse, then Doctor
Citirazine	Drowsiness	Pharmacist
Lisinopril	Headache	Pharmacist
Ibuprofen	Abdominal pain	Pharmacist
Diclofenac	Hallucinating, Idiopathic autoimmune haemolytic anemia	ICU Doctor

6.5.2 Factors Influencing Health Consumers Reporting

Participants described factors that motivated them to report (e.g., intolerable side effect impacting on daily activities such as attending work, school), interfered with reporting (e.g., physicians normalized or minimized the side effect) and barriers to reporting (e.g., health consumers confusion on what to report, previous experience with side effects, no feedback after report submission and poor awareness).

Motives to Report an ADR

Participants described the factors that motivated them to report ADRs. One motive was ‘*an intolerable side effect*’ that had an impact on daily activities, quality of life, and willingness to continue treatment. These impacts were either physiological or psychological, such as unable to eat, or sleep: “I couldn't eat and I missed classes” (P1); another participant stated, “not really be able to fall asleep” (P2). While discussing their ADR experiences, participants expressed real fear at the uncertainty of what was happening. For example, one participant described her daughter as having a

side effect that “affected [my daughter's] self esteem and she pulled away from all of her spring activities” (P11).

Another motive was ‘*encouragement from others to report the ADR*’. These others included family members, colleagues or a supervisor at work. Participant said, “my supervisor advised me to report the side effect” (P3), and “I was talking to my parents and [they] asked me to tell my doctor about it” (P14).

Factor Interfering with Reporting an ADR

Eight out of the 15 participants emphasized that their ‘*physicians minimized or normalized their side effects*’. When they informed their physicians, the response was either “it’s an expected side effect with the medication you have used” (P3); or “these kind of side effects are tolerable and can happen” (P12). Participants were uncertain whether their physician cared about the side effect or submitted an ADR report: “he was just like yes there are side effects to different medicines because your body will sort of react in different ways” (P1). Physicians minimizing the side effect influenced the participants to report their ADR directly to health regulators: “[My daughter’s] physician did not think it had anything to do with the ‘Yasmin’, so we continued on with the prescription... and I reported to Health Canada” (P11). Some participants who linked their symptoms to the medication they used were unhappy at the lack of response from their physicians and had been unable to convince them that a drug might be the cause. Participants were unhappy when their concerns were not taken seriously. For example, an elderly woman was admitted to the ICU after using the antibiotic Ciprofloxacin and an anti-inflammatory, Diclofenac, for 14 days; her physicians had attributed her symptoms to the medications she was taking, but she felt her medical doctors ignored that: “there was really no interest in following that up or reporting it to determine or maybe prevent something from happening in the future.... I was concerned, surprised that they would not take it further ...it was just sort of dropped and that’s it” (P12).

Barriers to Reporting ADRs

Two of the interviewed participants failed to link the symptoms they experienced with the medications they used or their illness. They were '*confused on what to report*', meaning that sometimes participants associated experienced ADR symptoms with a disease and failed to consider a possible drug cause: "I was not sure what to really tell my doctor, I thought maybe I was getting sick from food I was eating... I didn't know at first that was the medicine I'm taking" (P1). Another participant stated, "I wasn't really sure what to tell my doctor because it was a side-effect on the form" (P3).

A participants stated that one of the reasons she did not report the side effect was her '*previous experience with side effect*' and also she did not expect to be hospitalized because of that side effect: "I was aware about it before and it just happens to some people and not everyone ... but I didn't know that I would be hospitalized from the side effect" (P7).

Participants were confused on who had a '*responsibility to report ADR*'. Some participants see information about medication side effects and reporting as the responsibility of HCPs. They felt that HCPs must explain all expected side effects to health consumers, no matter how rare or minor they are: "It is necessary to understand what is wrong and why the pill may not be good" (P3).

Participants expected to receive '*feedback or acknowledgement after ADR submission*'. Ambition for feedback including further information about the prevalence with which similar side effects had been reported, whether it was a well-known side effect and how common it was, and what action was taken. They demanded to know how reports were used and if their reports counted. One participant stated that he/she would prefer not to report again because the time taken to report, the lack of personal feedback, and the perception that their report may not have any impact: "Because I'm not quite sure what would be the consequences of that? What will happen with that form after I filled it? Is it worth it or like nothing will happen?" (P11); "I would like to know when you go through the process of reporting and then it feels like it goes into the black hole right now there no response back from Health Canada" (P12).

6.5.3. Usability of the ADR Reporting System in Canada

First, reporting forms were explained to participants. Then responses about the usability of reporting form were classified into “yes” and “no” (see Table 6.3).

Table 7.3. The Usability of ADR Reporting Form

Statement	N	Yes Frequency (%)	No Frequency (%)
Clear font and icons	15	13 (86.7)	2 (13.3%)
Space for data entry	15	6 (40%)	9 (60%)
Readability	15	13 (86.7%)	2 (13.3%)
Use the form in future	15	14 (93.3%)	1 (6.7%)

Nine participants [60%] found it was difficult to fit all the required information about the number of drugs being taken in to *the space* on the reporting form. Although the form suggests that further information be provide on a separate sheet, participants were generally not eager to do this: “if you look at someone older than me, maybe they have a lot of medications...there would not be enough space ” (P5).

Seven participants’ were positive about the form and they thought the form was *very detailed, easy to understand and was fairly to complete*: “Precise and detailed and professional” (P1); “I like the colors” (P11). However, another five participants perceived difficulty filling the form. These difficulties included: *long form, too many sections to fill out, sentence/words too difficult to understand, took quite some time to complete, and trouble recalling the time of ADR occurrence*: “I find it a little complicated, there are too many questions that I probably would not be able to answer” (P9). Some participants had trouble finding the DIN number of the medication package and were not aware about the purpose of the DIN question: “I’m a nurse and familiar with a lot number, manufacture number, suppose all of those things are very important but for another person, I’m not sure that they will easily understand this information” (P11); “Brand name and generic name, and I don't know how to fill in DIN & NPN, some of the stuff I have no idea how I would fill it” (P8).

Four participants stated that they would need the help of HCP to complete the reporting form. They felt that some of the required information might be hard to find: “Elderly need a physician to fill

everything else for them” (P5); “I probably have to fill it out with my doctor...because he would be able to tell me what does this mean” (P1).

One participant identified dissimilarity between the English and French ADR reporting forms: “The English version of the ADR form has more details than the French version, the number of sections are less on the French form” (P5). It is important to consider whether this additional information is required, and if so, whether it should also be collected on the French form.

All except two said they would consider using the reporting form in the future: “I definitely would use it in future” (P4). While many participants were positive about the reporting form and said they would consider using it in the future, none expressed that they would like to complete the form for the particular ADR that we had discussed during the interview.

6.6. Discussion

Our study explored health consumers’ experiences reporting ADRs and the usability of the Canadian Vigilance ADR Reporting form. Although participants were eligible to have used the Canadian ADR reporting system, only two had used it, and twelve were not aware of it.

Most of the participants suspected they had experienced an ADR, but few were aware of the process to report these via Canadian Vigilance Online System. Having been informed about the reporting system, respondents showed a high possibility that they would report an ADR to Health Canada in the future. Participants who had submitted an ADR form or knew about the reporting system either worked as HCPs or had personal contacts with them. This indicates that further work is needed to promote awareness of the Canadian Vigilance Online System. These findings are consistent with previous studies on health consumer reporting in the UK, which indicated that poor awareness of the ADR reporting system [34, 35].

The majority of participants were highly educated and more females were involved in our study than males. Higher incidence of women reporting is consistent with other studies showing similar patterns [36, 37]. As well, the participants had high school education or higher. Although we reached saturation in findings, it would be interesting to learn more about ADR reporting in

individuals of lower education status.

Based on the findings, health consumers reported ADRs for various reasons, of which the most important were: a severe ADR, worry about the ADR in a personal context, or the ADR not mentioned in health consumer information leaflet. Some participants cited emotional and psychological motives for reporting. Frustration associated with participants experiencing an ADR and physicians' failure to take health consumer reports seriously was one of the motives for participants to report an ADR. Van Hunsel's study of health consumer reporters also found health consumers who felt their concerns had been ignored [26]. These dismissive attitudes among HCPs were reported as being important among reporters to the Netherlands' ADR reporting system [38]. This is similar to findings reported in similar studies in the UK and Denmark [39, 40].

Experiences regarding the reporting form were generally positive. Participants saw value in direct reporting and there was widespread satisfaction with the reporting form. Almost all health consumers were generally supportive of the aims of reporting an ADR after it had been explained, and they were positive about using the form in the future.

The adaptation of a system designed for HCPs rather than designing a system that is tailored to health consumers has led to some problems including the issue of the DIN number. Some participants experienced trouble filling in the DIN number and remembering dates, or they felt that the form was too long. Those participants viewed ADR reporting as a job for healthcare professionals and viewed more serious ADRs as a medical responsibility. Also, participants commented that, if they were to complete the form in the future they would need help of healthcare professionals.

6.7. Limitation and Strength

There were some limitations and strengths in our study. Participants' education level was considered as a strength and a limitation. All the participants interviewed had high school or higher levels of education. The views of such participants were crucial in identifying how public participation in pharmacovigilance may be promoted. However, lower education participants might have had other barriers or motives to report an ADR that did not come to light in this study. Another

study strength included the rigor of analysis. Several strategies were used to enhance credibility and transferability. Credibility was enhanced through co-authors auditing the results and two team members independently analyzing transcripts. Transferability of findings was enhanced by detailed description of the ADR setting [32].

6.8. Conclusion

Several motives and barriers influenced Canadians reporting ADRs. Some participants who had experienced ADRs were unclear about their role in reporting ADRs to the Canadian Vigilance Online System and others presumed that submitting an ADR report was the responsibility of HCPs. While awareness of reporting schemes is important to broaden participation in ADR reporting, our findings indicated that raising awareness would not be enough to improve public participation by itself. Health Canada should go beyond raising awareness to presenting their plans in ways that empower and support health consumer reporting. Based on our findings, Health Canada could raise awareness about the ADR reporting system among the public and discuss its important role in promoting drug safety. The public needs to know that reports can be submitted even when there is uncertainty about whether a medicine caused a reaction. Improvements to the system, including the provision of feedback to reporters, increased public awareness about the Canadian ADR Reporting System and how to report unified English and French versions of the reporting form could be made.

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Chapter Seven. Integrated Discussion

In chapter 7, a summary is provided as well as an integrated discussion of the dissertation findings related to factors influencing health consumer adverse drug reaction (ADR) reporting and the usability of Health Canada's online ADR reporting system, MedEffect. The chapter considers the importance of health consumer ADR reporting for improving population health as well as future research opportunities. Table 7.1, at the end of the chapter, summarizes the implications for pharmacovigilance practice, education, organizational policies, and research.

7.1. Summary of Dissertation Findings

Systematic Review. In the systematic review, we identified 22 studies that focused on barriers to and motives for health consumer reporting of ADRs (Chapter 4). The 16 studies reporting barriers identified: poor awareness about the Canadian Vigilance Program, uncertainty regarding the responsibility to undertake such reports and lack of feedback for submitted reports. The six studies that focused on motives for health consumer ADR reporting identified altruistic or personal motives to protect other members of the public. Moreover, personal motives were related to the seriousness of ADRs and the failure of healthcare professionals (HCPs) to report ADRs was perceived by consumers to be due to time limitations and/or lack of interest in reporting (van Hunsel, et al. , 2010). Most of the included studies were conducted in the UK, Netherlands, Denmark and Australia and to our knowledge none were conducted in North America.

Quantitative Study. We subsequently conducted a retrospective observational descriptive cross-sectional study to compare the number of ADRs reported by consumers with the number of ADRs reported by physicians in the Canadian Adverse Drug Reaction Reporting System over the last 14 years (Chapter 5). In Canada, the total number of spontaneous ADR reports increased from 5,570 in 2000 to 23,663 in 2014. This study showed that the total number of serious ADRs reported by consumers (29%) was significantly higher than that of the total number of serious ADRs reported by physicians (27%). Also, consumers reported more on the system organ class 'psychiatric disorders' and the anatomical therapeutic chemical group L 'antineoplastic and immunomodulating agents'. Additionally, our results showed that physicians reported more on the system organ class 'blood and

lymphatic system disorder' and the anatomical therapeutic chemical group B, 'blood and blood forming organs'.

Qualitative Study. We also conducted an interpretive description qualitative study to explore health consumers' experiences of reporting ADRs and using Health Canada's online ADR system, MedEffect (see Chapter 6). Fifteen interviews were conducted with 13 in English and 2 in French. Most of the participants were not aware of MedEffect, ADRs were reported to their physicians. Two participants who had submitted an ADR form or who knew about the reporting system either worked as HCPs or had personal contact with HCPs. Participants' main motives to report ADRs were: serious ADRs, worried about ADRs in a personal context, ADRs not mentioned in patient information leaflets, and physicians being dismissive towards reporting an ADR. Lack of individual feedback from Health Canada after two health consumers' submitted ADR reports was the main barrier for not reporting again. In the ADR reporting form usability testing, nine participants found it was difficult to fit all the required information about the number of drugs being taken into *the space* on the reporting form. Although the form suggests that further information be provide on a separate sheet, participants were generally not eager to do this. One-third of the participants stated that they would need the help of HCP to complete the reporting form, and one participant identified dissimilarity between the English and French ADR reporting form.

7.2. Adverse Drug Reaction Reporting System

The Canadian ADR Reporting System has accepted health consumer reports since 1965. The baseline assessment of the Canadian Vigilance Reporting System revealed that, although health consumers who reported to the Canadian Vigilance Program had a positive attitude about future reporting, lack of awareness about the reporting system, lack of personalized feedback for submitted ADR reports, and difficulties with using the reporting forms were the common barriers for health consumers to report their ADRs.

The systematic review identified difficulty with the ADR reporting procedure and forms as one of the barriers to ADR reporting by health consumers. Lack of familiarity with procedures and

reporting forms was commonly reported in reviewed studies. The qualitative study tested the usability of the Canadian ADR Reporting Form and identified a number of challenges perceived by participants. These findings were consistent with findings from the UK, where participants noted that: paper forms were tedious, lengthy, awkwardly constructed, inconsistent with online forms and available only in English; telephone reporting was limited to working hours which was found to be inconvenient and time consuming; technical problems encountered online often resulted in a loss of information (Avery et al., 2011; Hazell et al., 2013). In Canada, the ADR reporting form asked health consumers to fill the DIN/ NPN numbers which were terms not commonly understood by health consumers. Another challenge in the form was the amount of space included on the form to report multiple medications. Participants involved in the usability testing were not keen to add additional sheets of information if there was not enough space.

The adaptation of a form designed for HCPs rather than designing a form specifically tailored to health consumers has led to the difficulties with using the reporting form. These forms must be assessed for health literacy; the public should have the capacity to obtain, process and understand the basic health information and services needed to make appropriate decisions (Baker, 2006; Speros, 2005).

Results from the systematic review and qualitative study help to identify a number of enhancements that could be made in order to improve the usability of the ADR reporting form. These enhancements include: redesigning the form to be specifically tailored to health consumer use and take health consumers opinions into account while redesigning the forms; test the forms for health literacy and ensure the public has the capacity to obtain, process, and understand basic health information and services needed to make appropriate decisions (Pignone, DeWalt, Sheridan, Berkman, & Lohr, 2005).

7.3. Health Consumer as Reporter

The other important component of good pharmacovigilance practice is the reporter. Reporters can be health consumers, physicians, other healthcare professionals, manufacturers and distributors, or

lawyers. In this dissertation we focused on health consumers as reporters and looked at the factors affecting health consumers in reporting ADRs.

The systematic review identified lack of awareness about the reporting system, uncertainty of the responsibility to undertake such reports and lack of feedback for submitted reports as barriers for consumers to report ADRs. These findings were consistent with our findings from the qualitative study where most participants suspected that they had experienced an ADR but few were aware of the Canadian Vigilance System. Participants who had submitted ADR reports were discouraged by the absence of individual feedback. Currently in Canada, reporters do not receive individual feedback about reported ADRs.

New Zealand, on the other hand, has the highest rate of ADR reporting in the world due to a variety of approaches used by the regulatory authority including: individual feedback provided to reporters, outreach strategies to encourage the reporters and the importance of reporting was emphasized (van Hunsel et al., 2012). Also, in the Netherlands, doctors and/or pharmacists assess ADR reports submitted to the pharmacovigilance center and then reporters are contacted with customized feedback on the ADR reported (Avery et al., 2011). Health Canada may need to consider providing individual feedback to reporters.

Another barrier for health consumer ADR reporting identified in the systematic review was HCP attitudes toward ADR reporting as some refused to make reports on health consumers' behalf. This finding was further supported by our qualitative study, which indicated ignorance from some HCPs toward participants reporting ADRs to them. Similar attitudes were noted in an American study, which questioned health consumers about their experiences reporting ADRs associated with statins to their physicians; the physicians dismissed the possibility that the suspected ADR might be linked to the statin (van Hunsel et al., 2009). Our study gives health consumer perspectives on HCP attitudes toward consumer ADRs and finds that HCPs need to be more aware of the availability of direct ADR reporting by health consumers. It would also help to explore why some HCPs have

dismissive attitudes toward health consumer reporting of suspected ADRs and whether these attitudes can be altered by exposure to study findings that indicate the benefits of health consumer reporting.

The findings from the quantitative study indicate that health consumers and physicians reported on different ADR classes and different drug types. Health and non-health professionals have differing risk perceptions of ADRs (Bongard et al., 2002). This is due in part to education. Health consumers may perceive any ADR, whether serious or non-serious, as a risk based on information in advertisements or on the Internet. Differences may also be explained due to HCP interest in reporting ADRs for new medicines compared with older ones and consumer interest in reporting on ADRs that have a larger impact on their quality of life and daily activities (Bongard et al., 2002). This means ignoring or not considering health consumer reports in pharmacovigilance may result in missing early identification of safety alert or missing important safety data. Health consumer reports would positively affect the pharmacovigilance systems by supplementing databases and adding additional information not reported by HCPs (Blenkinsopp et al., 2007).

Therefore, in order to facilitate ADR reporting by health consumers and overcome barriers, targeted interventions are required to make appropriate changes in health regulatory policies and procedures. These interventions may include:

- a. Educate and encourage health consumer direct reporting;
- b. Tailor ADR reporting forms to serve health consumers' needs and assess the forms for health literacy;
- c. Educate HCPs about the importance of ADR reporting by health consumers;
- d. Monitor the quality of health consumer ADR reports;
- e. Public awareness campaigns displaying posters in healthcare settings and patient association about the importance of ADR reporting;
- f. Distribute ADR reporting forms at healthcare facilities like hospitals, clinics and pharmacies.

The findings from this comprehensive study indicate that the health consumer reporting could become a valuable pharmacovigilance tool and it has been proved that their reports contributed to the safety signal generation (Härmark & Van Grootheest, 2008; van Hunsel et al., 2012).

7.4. Importance of Pharmacovigilance in Population Health

The provision of ADR reporting by health consumers in pharmacovigilance systems has the potential to ensure safer and a more effective use of medicines that in turn advance public health. Population health interventions are designed to improve the health and well-being of people by focusing on the interrelated factors that influence health over one's life course (Health Canada, 2001). In addition to addressing the determinants of health, other key elements in designing strategies to improve population health involve the use of multiple interventions, an upstream focus, collaboration across sectors, public involvement and accountability for health outcomes (Health Canada, 2001; Smedley & Syme, 2001).

The main objectives for pharmacovigilance are preventing harm from ADRs in humans arising from ADRs and promoting the safe and effective use of medicinal products. Therefore, pharmacovigilance contributes to health consumer protection and public health.

Currently, the Canadian ADR reporting system accepts reports from health consumers as well as HCPs. However, the Canadian Vigilance System still suffers poor public awareness. This study has contributed to the science of population health by:

- (1) Identifying factors that influence the public to report ADRs;
- (2) Introducing a public involvement approach to improve the Canadian Vigilance System which may result in promoting the safe and effective use of medicinal products;
- (3) Creating knowledge needed on how to improve the quality of ADR reporting by health consumers.

Evaluating the effectiveness of interventions is another important element of population health (Health Canada, 2001). Although involving health consumer reporting in signal detection was not evaluated in this study, previous studies have found that consumer reporting of suspected ADRs

has the potential to add value to pharmacovigilance practice by reporting types of drugs and reactions different from those reported by HCPs ultimately generating new potential signals and describing suspected ADRs in enough detail to provide useful information on likely causalities and impacts on health consumers' lives (Avery et al., 2011).

7.5. Future Research

Our study provides a solid foundation of knowledge evidence regarding factors influencing health consumer reporting of ADRs and highlights several areas requiring further research (see Table 7.1).

The following proposes several outcomes that could be monitored to improve pharmacovigilance practice for future research studies. First evaluate the usability of an ADR reporting system tailored for health consumers and public use; the system should be tested for health literacy. Second, valid and reliable tools to measure the usability of the ADR reporting system. Additional tools are required to measure the impact of health consumer reporting on safety outcomes.

Future research to determine the impact of health consumers ADR reporting on signal detection in Canada is another important area. Evaluating previously generated signals and identifying the effect of health consumer ADR reporting on drug information leaflets or the addition of a new warning box will show how health consumer reporting influences pharmacovigilance as well as medication safety. More research is required to evaluate the impact of increased publicity of ADR reporting on the number and types of consumer ADR reports. To our knowledge, no post-campaign studies have been conducted to evaluate the effect of reporting publicity on the number and quality of consumer reports. Conducting qualitative and quantitative analysis will help to identify the importance of these outreach programs and identify strategies that help to overcome barriers for consumer ADR reporting. Further research should investigate why physicians in Canada report significantly less serious ADRs than health consumers: Are these ADRs downgraded by physicians as inconsequential? If so, should they be? These kinds of questions might best be answered by qualitative studies.

Another research opportunity would be to develop an intervention study to address barriers to consumer ADR reporting. For example testing the barriers 'minimize the ADR by HCP'.

7.6. Conclusion

There is a greater need to monitor and promote the safety and effectiveness of health products in Canada. The pharmacovigilance system serves the purpose of developing a national system for tracking and monitoring ADRs of health products once they are launched in the market (WHO, 2002).

Substantial underreporting of ADRs by HCPs resulted in growing the interest in the involvement of health consumers as reporters to pharmacovigilance systems (Golomb et al., 2007; Inch et al., 2012). The potential benefits of health consumer ADR reporting include the promotion of health consumer rights and equity, acknowledging that health consumers have unique perspectives and experiences and those health regulators would benefit generally from health consumer involvement (Anderson et al., 2011).

Reports from health consumers may provide different information on suspected ADRs and drug types, as well as provide a broader picture of ADRs and their impact on individual daily activities, as compared with reports from HCPs. Consumer ADR reporting may increase the overall number of ADRs reported and may assist in earlier detection of important ADRs.

It is important to help develop monitoring systems, educate HCPs and health consumers, and encourage direct reporting. Pharmacovigilance databases that involve both types of reporters have a substantially better chance of early signal detection of ADRs not previously monitored.

The Canadian pharmacovigilance system is strong but efforts to increase public awareness of the reporting system and of the importance of ADR reporting are needed. The dissertation shows that Canada can develop a more rigorous pharmacovigilance system that would lead to safer and more effective use of medicines, which in turn would advance public health.

This dissertation's findings indicate areas where improvements to the Canadian pharmacovigilance system would improve health consumer safety. The publication of these results is both important and necessary for knowledge transfer.

Table 7.1 Implications for Practice, Education, Organizational Policies, and Research

Category	Implications
Pharmacovigilance Practice	<ul style="list-style-type: none"> ▪ Provide general and individual feedback to health consumers on what is done with their submitted reports and in relation to medication and suspected ADRs. ▪ Redesign the reporting form in line with suggestions made in this study for consumer use.
Education	<ul style="list-style-type: none"> ▪ Integrate the importance of pharmacovigilance into university curricula for healthcare teams. ▪ Educate public about the importance of reporting ADRs and how reporting affects their health.
Organizational Policies	<ul style="list-style-type: none"> ▪ Create policies to motivate the public and reduce barriers to consumer reporting of ADRs. ▪ Organize campaigns to target the public about health consumer reporting and provide further guidance to reporters on what information to report; evaluate the outcomes of campaigns. ▪ Encourage proactive efforts by HCPs to publicize and promote consumer reporting. ▪ Incorporate information about ADR reporting within health consumer information leaflets and provide this information at medication dispensing point. ▪ Increase health consumer awareness of medicines where Health Canada is undertaking intensive monitoring. For example, provide health consumers with reporting form at dispensing. ▪ HCPs need to be aware that health consumers can submit their own ADR reports and should not be dismissive to health consumers who have submitted ADR reports.
Research	<ul style="list-style-type: none"> ▪ Identify the impact of health consumer reporting on identified signal detection such as addition of new ADR to PILs or addition of warning box. ▪ Evaluate the use of health consumer reports in helping others who are seeking information on health consumer experiences with similar ADRs. ▪ Evaluate the impact of increasing publicity and enhancing reporting systems on the number and types of health consumer ADR reports.

Chapter Eight. Contribution of Collaborators

Contribution of Collaborators

The chapter introduces and identifies the contributions of collaborators and was written in accordance with the guidelines of the Faculty of Graduate and Postdoctoral Studies at the University of Ottawa (2012). Contributions are discussed as they relate to those who were involved as part of the research team and other collaborators on the manuscripts. Chapter 8 concludes by acknowledging stakeholders and research assistants who supported some aspects of the manuscripts and/or dissertation.

The Faculty of Graduate and Postdoctoral Studies at the University of Ottawa (2012) guidelines require that students writing manuscript-based dissertations describe their contribution to any of the manuscripts in depth and differentiate between their contributions and various co- authors contributions.

8.1. Research Team Collaborators

The primary researcher, RD conceived of, participated in, and led all aspects of the research study as part of the fulfillment of the requirements of the degree of Doctorate of Population Health (PhD) at the University of Ottawa. The collaborators were RD's dissertation supervisor, Dr. Sanni Yaya PhD, and two committee members, Dr. Dawn Stacey RN, PhD (DS), and Dr. Dafna Kohen MD, PhD (DK).

All committee members participated in different phases of the dissertation (see Table 8.1). They provided content expertise and approved the research proposal. For the manuscripts, they provided consultation and feedback, participated in the validation of data, contributed intellectual content to the manuscripts, and approved the final versions.

RD is a Registered Pharmacist with Jordan and United Arab Emirates Government. RD worked as a pharmacist in Jordan then worked as a medication safety officer and drug regulatory officer for more than ten years in the Health Authority of Abu Dhabi, United Arab Emirates, where she was involved in drug regulation and polices. She has over 17 years of insightful experience across researching, medication safety, pharmacovigilance, drug information, drug-risk management,

post marketing surveillance, strategic planning & implementation, operations management and quality assurance. RD's received a four years Admission Scholarship for doctoral studies from University of Ottawa.

SY is an Associate Professor of Economics and Global Health at the School of International Development and Global Studies where he teaches courses on International Development Issues, International Development Programming and International Project Management. He is the Editor of the Innovation Journal, and currently leads a series on Society and Health at the University of Ottawa Press. Professor Yaya was a Postdoctoral Research Fellow at Yale University, and a Senior Visiting Scholar at New York University (NYU). He has experience in the design and implementation of randomized controlled trials and observational epidemiologic studies of maternal and child health, infectious diseases and chronic diseases. Dr Yaya has published 18 books and numerous book chapters and technical reports. His research articles have appeared in leading peer-reviewed journals, including The Lancet, Health Policy and The International Journal of Medicine (Oxford University Press). As well, Professor Yaya has been a senior advisor to several health intervention programs and international developments projects funded by World Health Organization, United Nations International Children's Emergency Fund, United Nation Development Program, The World Bank, private foundations, and many governments.

DS is a Full Professor in the School of Nursing and Scientist at the Ottawa Hospital Research Institute. In 2012, her outstanding and continuous accomplishments in research were recognized when she received a University Research Chair in Knowledge Translation to Patients. Dr. Stacey is Director of the Patient Decision Aids Research Group at the Ottawa Hospital Research Institute as well as, a member of the Faculty of Graduate and Post-doctoral Studies at the University of Ottawa, academic appointee at The Ottawa Hospital, and a member of the Nursing Best Practice Research Centre. She won the 2009 Young Researcher Award for the Faculty of Health Sciences and the 2012 Canadian Association of Nurses in Oncology/Pfizer award of excellence in nursing research.

Dr. Stacey's research program is focused on advancing the science of knowledge translation to patients. The overall goal is to understand, measure, and evaluate the effectiveness of knowledge translation interventions for patients and evaluate strategies to enhance patient engagement in shared decision making.

Dr. Stacey lectures extensively both nationally and internationally on various aspects of patient decision support, knowledge translation, oncology nursing, and telephone consultation. She is teaching and supervising students in graduate programs in nursing, population health, and clinical epidemiology. Dr. Stacey leads the Cochrane Review of Patient Decision Aids, is a co-investigator on the Cochrane Review of Interventions to Improve the Adoption of Shared Decision Making, and co-chairs the International Patient Decision Aid Standards Collaboration (IPDAS). Her research is conducted in Canada, the United States, Australia, the United Kingdom, and Chile.

DK is a Senior Research Analyst and Chief in the Health Analysis Division at Statistics Canada and adjunct professor at the School of Epidemiology, Public Health and Community Medicine at the University of Ottawa. Trained as a developmental psychologist she has degrees from McGill University, McMaster University, and Columbia University. Areas of research expertise include the use of population-based data to examine policy relevant research in the area of healthy child development and examinations of social determinants of health for vulnerable populations. Research funding from government as well as non-government departments include CIHR grant funded projects examining the health of caregivers of children with disabilities as well as work on community and family influences on Aboriginal child and youth health and well-being.

8.2. Other Collaborators

There were two other collaborators who met the International Committee of Medical Journal Editors guideline to be a co-author on one manuscript in the dissertation. Dr. Rana Shash (RS), and Erica Wright (EW) made important contributions to different stages of developing the systematic review (Chapter 4) (see Table 7.1). RS, pharmacist Cleveland Clinic Hospital in Abu Dhabi, participated in screening, extracting and validating data. EW, a Health Science Research Liaison

Librarian at the University of Ottawa collaborated on developing the search strategy for the systematic review.

8.3. Stakeholders and Research Assistants Acknowledgements

For the qualitative study, Shelley MacKenzie transcribed the interviews and Elina Hill provided English-language editing assistance with the dissertation. For the quantitative study, Dr. Hossein Sajjadi, Ph.D, Senior Statistical Data Analyst and Research Methodology Specialist in Sigma3s- Statistical Societal Services provided help in statistical analysis and using the SPSS software.

Table 8.1 Summary of Collaborators Contributions

Elements	Chapter 4	Chapter 5	Chapter 6
Conceptualize & Design	RD	RD	RD
Collect data	RD EW RS	RD	RD
Analysis and Data Interpretation	RD DS SY DK	RD DK DS SY	RD DS DK SY
Draft Content	RD	RD	RD
Revise Manuscript for important intellectual	RD DS SY DK	RD DS SY DK	RD DS SY DK
Approval Final Version	RD DS SY DK	RD DS SY DK	RD DS SY DK
Responsible for overall content	RD	RD	RD

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Appendices

Appendix A. 26 MedDRA SOCs

The 26 MedDRA SOCs include:

Blood and Lymphatic System Disorders	Metabolism and Nutrition Disorders
Cardiac Disorders, Congenital Familial and Genetic Disorders	Musculoskeletal and Connective Tissue Disorders
Ear and Labyrinth Disorders	Neoplasm Benign, Malignant and Unspecified (Including Cysts and Polyps)
Endocrine Disorders	Nervous System Disorders
Eye Disorders	Pregnancy, Puerperium and Perinatal Conditions
Gastrointestinal Disorders	Psychiatric Disorders
General Disorders and Administration Site Conditions	Renal and Urinary Disorders
Hepatobiliary Disorders	Reproductive System and Breast Disorders
Infections and Infestations	Respiratory, Thoracic and Mediastinal Disorders
Immune System Disorders	Skin and Subcutaneous Tissue Disorders
Injury, Poisoning and Procedural Complications	Social Circumstances, Surgical and Medical Procedures
Investigations	Vascular Disorders

Appendix B. Ovid MEDLINE database <1963 - December 2014> Search Strategy Keywords

- 1 exp "Drug-Related Side Effects and Adverse Reactions"/ (91869)
- 2 (adverse adj2 (event* or effect* or reaction*) adj2 (drug* or medication*)).tw. (18310)
- 3 or/1-2 (105036)
- 4 Self Report/ (10502)
- 5 (underreport* or over report* or report*).tw. (2716324)
- 6 Product Surveillance, Post marketing/ (5926)
- 7 databases, factual/ or databases, pharmaceutical/ (47311)
- 8 (regulatory adj1 (agenc* or authorit*)).tw. (6439)
- 9 or/4-8 (2766445)
- 10 3 and 9 (20774)
- 11 adverse drug reaction reporting systems/ or pharmacovigilance/ (6281)
- 12 pharmacovigilan*.tw. (2370)
- 13 or/10-12 (25934)
- 14 Health consumers/ (16871)
- 15 attitude/ or attitude to health/ or health knowledge, attitudes, practice/ (186227)
- 16 Behavior/ (27521)
- 17 or/15-16 (211128)
- 18 14 and 17 (2422)
- 19 ((health consumer* or consumer*) adj2 (awareness or attitude* or perception* or perspective* or belief* or behavior* or participation).tw. (34287)
- 20 consumer participation/ or health consumer participation/ (33633)
- 21 report* behavior*.tw. (1831)
- 22 or/18-21 (69254)
- 23 13 and 22 (225)

Appendix C. Excluded Studies

First Author, Year	Title	Reason for Exclusion
		Role of Health Consumers in Pharmacovigilance
Ahmed, S., et al. (2012).	"The use of patient-reported outcomes (PRO) within comparative effectiveness research: Implications for clinical practice and health care policy."	
Bahri, P. (2011).	"Patient, medicines and perceptions - "Bridging continents" for improving risk assessment and communication."	
Bains, R. K. (2012).	"Pressing timelines for pharmacovigilance!"	
Banerjee, A. K., et al. (2013).	"Patient-reported outcome measures in safety event reporting: PROSPER consortium guidance."	
Basch, E. (2013).	"Systematic collection of patient-reported adverse drug reactions: a path to health consumer-centred pharmacovigilance."	
Blenkinsopp, A., et al. (2007).	"Patient reporting of suspected adverse drug reactions: A review of published literature and international experience."	
Campbell, J. P. and J. G. Howie (1988).	"Involving the patient in reporting adverse drug reactions."	
Chaikoolvatana, A., et al.	"The evaluation of a recurrent Adverse Drug Reaction Prevention Program in the north-east region of Thailand."	
Choonara, I. (2004).	"Direct reporting of suspected adverse drug reactions by patients."	
Cox, A. (2009).	"Involving patients in reporting adverse drug reactions should be welcomed."	
De Abajo, F. J., et al. (2000).	"Pharmacovigilance: Goals and strategies."	
Edwards, I. R. (2012).	"Pharmacovigilance."	
Esther Salgueiro, M., et al. (2013).	"Direct reporting by patients of adverse drug reactions in Spain. [Spanish]."	
Fernandopulle, R. B. M. and K. Weerasuriya (2003).	"What can patient adverse drug reaction reporting add to existing health professional-based systems? Focus on the developing world."	
Fincke, B. G., et al. (1998).	"The interaction of patient perception of overmedication with drug compliance and side effects"	
Fisher, S., et al. (1994).	"Patient drug attributions and postmarketing surveillance."	
Fleuranceau-Morel, P. (2002).	"How do pharmaceutical companies handle patient adverse drug reaction reports? An overview based on a survey of French drug safety managers and officers"	
Foster, J. M., et al. (2008).	"The use of questionnaires for measuring patient-reported side effects of drug: Its importance and methodological challenges."	
Fouretier, A., et al. (2013).	"Adverse drug reaction reporting by patient: A new European challenge?"	
Fuller, C. (2003).	"Women and adverse drug reactions: reporting in the Canadian context."	
Gribelin, N., et al.	"About consumers and patients direct access to national	

(2011).	pharmacovigilance database: Example of four countries."
Haas, J. S., et al. (2010).	"Participation in an ambulatory e-pharmacovigilance system."
Hakkarainen, K. M., et al. (2013).	"Prevalence and perceived preventability of self-reported adverse drug events-A population-based survey of 7099 adults."
Hammond, I. W., et al. (2007).	"Effect of patient reporting on signal detection: using disproportionality analysis."
He, J., et al. (2014).	"Adverse drug reactions of spontaneous reports in shanghai pediatric population."
Herxheimer, A. (2012).	"Pharmacovigilance on the turn? Adverse reactions methods in 2012."
Herxheimer, A., et al. (2011).	"[Health consumers reported adverse drug reactions: what's happening in Europe]."
Ines Cuyegkeng, E. (1986).	"Adverse drug reaction reporting. Philippine experience."
Isacson, D., et al. (2008).	"Nationwide survey of subjectively reported adverse drug reactions in Sweden."
Jarernsiripornkul, N., et al. (2002).	"Health consumer reporting of potential adverse drug reactions: a methodological study."
Jha, N., et al. (2014).	"Need for involving consumers in Nepal's pharmacovigilance system."
Kieve, M. (2007).	"Adverse drug reactions (ADRs): A health consumer perspective on assessment and prevention in primary care."
Kitazawa, K. (2011).	"[Drug safety--from health consumers' perspective]."
Krska, J., et al. (2011).	"How Health consumer Reporters Identify Adverse Drug Reactions."
Kubota, K., et al. (2013).	"Temporal relationship between multiple drugs and multiple events in health consumer reports on adverse drug reactions: findings in a pilot study in Japan."
Kurz, X., et al. (2010).	"The PROTECT project: An innovative public-private partnership for new methodologies in pharmacovigilance and pharmacoepidemiology."
Kuzel, A. J., et al. (2004).	"Health consumer reports of preventable problems and harms in primary health care."
Leguay, D. (2006).	"[Report of the working group "families and health consumers"]."
Lopez-Gonzalez, E., et al. (2009).	"Determinants of under-reporting of adverse drug reactions."
Lula, N. Y., et al. (2013).	"Contribution of health consumer reporting by phone call to spontaneous reporting and signal detection: Case of antimalarial drugs."
Lynn, R. M., et al. (2010).	"The use of electronic reporting to aid surveillance of ADRs in children: a proof of concept study."
Margraff, F. and D. Bertram (2014).	"Adverse drug reaction reporting by health consumers: An overview of fifty countries."
Marlin, R. L. (1981).	"Reliability factors in adverse drug reaction reporting."
Menezes de Padua, C. A., et al. (2007).	"Self-reported adverse reactions among health consumers initiating antiretroviral therapy in Brazil."
Micoulaud-Franchi,	"One step more toward pharmacovigilance 2.0."

J. A. (2011).	Integration of web data community for a pharmacovigilance more alert."
Mitchell, A. S., et al. (1988).	"Health consumers as a direct source of information on adverse drug reactions."
Munro Raine, J. (2012).	"Drug safety: reporting systems for the general public."
Nwokike, J., et al. (2014).	"Comparative analysis of pharmacovigilance systems in five Asian countries."
Olsen, A. K. and M. D. Whalen (2009).	"Public perceptions of the pharmaceutical industry and drug safety: Implications for the pharmacovigilance professional and the culture of safety."
Opri, S., et al. (2011).	"Health consumer reporting of adverse drug reactions: First Italian experience."
Palaian, S., et al. (2010).	"Developing a consumer reporting program in Malaysia: a novel initiative to improve pharmacovigilance."
Plummer, R. C. and E. F. Cascade (2009).	"Quality of consumer generated adverse event reports."
Raine, J. M. (2012).	"Drug safety: reporting systems for the general public."
Roughead, E. E. and J. Lexchin (2006).	"Adverse drug events: Counting is not enough action is needed."
Sánchez I., et al. (2014).	"Assessment of an active pharmacovigilance system carried out by a pharmacist. "
Scurti, V., et al. (2012).	"A plea for a more epidemiological and health consumer-oriented pharmacovigilance."
Scurti, V. and G. Tognoni (2010).	"From a drug-centered practice of surveillance to an epidemiology where health consumers and population are subjects-protagonists. (Baiardini et al.)."
Shin, H. K., et al. (2013).	"Usage patterns and adverse experiences in traditional Korean medicine: Results of a survey in South Korea."
Srba, J., et al. (2012).	"Adverse drug reactions: analysis of spontaneous reporting system in Europe in 2007-2009."
Steinman, M. A. (2013).	"Reaching out to health consumers to identify adverse drug reactions and nonadherence: Necessary but not sufficient."
Toussi, M., et al. (2014).	"Tracking of adverse drug reactions in social media: Current status of requirements, best practices, methods and tools."
Van Grootheest, K., et al. (2003).	"Consumer adverse drug reaction reporting: A new step in pharmacovigilance?"
van Grootheest, K. and L. de Jong-van den Berg (2004).	"Health consumers' role in reporting adverse drug reactions."
Van Hunsel, F. (2012).	"Health consumer helps pharmacovigilance further: Altruism motivates health consumer to Lareb notifications. [Dutch]."
van Hunsel, F., et al. (2012).	"Experiences with Adverse Drug Reaction Reporting by Health consumers."
Varughese, S. S. (2012).	"Reporting adverse drug reactions: Health consumers to be involved or not?"
Vastag, B. (2005).	"Consumer groups look to improve adverse event reporting systems."
Vaughan, W.	"Adverse drug event reporting."
Weingart, S. N., et al.	"Lessons from a health consumer partnership"

(2004).	intervention to prevent adverse drug events."
Wilbur, K., et al. (2012).	"A survey of pharmacovigilance in Qatar and the middle east."
Williams, K. (2004).	"Health consumers will be able to report drugs' side effects."
World Health Organization – Drug Information (2000)	"Consumer reporting of adverse drug reactions."
Young D. (2002).	"FDA reporting program is key to safety information."
Health Action International (2003).	"Should health consumers be enabled to directly report adverse drug reactions?. [Dutch]."
Egberts TC. et, al. (1996).	"Can adverse drug reactions be detected earlier? A comparison of reports by health consumers and professionals."
WHO Drug Information (2008).	"Canada Vigilance: A new name and database."
Aagaard, L. and E. H. Hansen (2010).	"Consumers' reports of suspected adverse drug reactions volunteered to a consumer magazine."
Adams, S. A. (2013).	"Using health consumer-reported experiences for pharmacovigilance?"
Arlet, P. (2009).	"[Risk perception of adverse drug reactions-effects]."
Basch, E. (2010).	"The missing voice of health consumers in drug-safety reporting."
Bateman, E. and D. Keefe (2011).	"Health consumer-reported outcomes in supportive care."
Choonara, I. (2004).	"Direct reporting of suspected adverse drug reactions by health consumers."
Comparison on the Frequencies of ADR Reporting between Health consumers and HCPs	
Aagaard, L. and E. H. Hansen (2013).	"Adverse drug reactions reported by consumers for nervous system medications in Europe 2007 to 2011."
Abdul Razack, H. I. and V. Sree (2012).	"Evaluation and comparison of pharmacovigilance systems in 70 different countries for consumer reporting of adverse drug reactions."
Adams, S. A. (2013).	"Using health consumer-reported experiences for pharmacovigilance?"
Arda, E., et al. (2011).	"Our 6 years of local experience in pharmacovigilance."
Van Grootheest, A. C. and M. L. Bouvy (2000).	"Drug surveillance. [Dutch]."
van Hunsel, F., et al. (2011).	"The proportion of health consumer reports of suspected ADRs to signal detection in the Netherlands: case-control study."
Walji, R. (2008).	Reporting adverse drug reactions associated with herbal products: Consumer, health food store personnel and pharmacist perspectives. Ann Arbor, University of Toronto (Canada).
Brown, P. and L.	"The incidence and reporting of adverse drug reactions

Faloon (2001).	in the Division of Psychiatry."
Gawert, L., et al. (2010).	"The importance of health consumer perspective in drug surveillance systems."
Hazell, L., et al. (2013).	"How do health consumers contribute to signal detection? : A retrospective analysis of spontaneous reporting of adverse drug reactions in the UK's Yellow Card Scheme."
Hershman, D., et al. (2008).	"Health consumers' perceptions of physician-health consumer discussions and adverse events with cancer therapy."
Inch, J., et al. (2012).	"Health consumer versus healthcare professional spontaneous adverse drug reaction reporting: A systematic review."
McAuley, J. W., et al. (2009).	"An assessment of health consumer and pharmacist knowledge of and attitudes toward reporting adverse drug events due to formulation switching in health consumers with epilepsy."
McLernon, D. J., et al. (2009).	"Do adverse drug reaction reports differ between consumers and healthcare professionals?"
McLernon, D. J., et al. (2009).	"Adverse drug reaction reports: How do they differ between consumers and healthcare professionals?"
mith, B. J., et al. (2009).	"Concerns with AED conversion: Comparison of health consumer and physician perspectives."
Shin, H. K., et al. (2013).	"Adverse events attributed to traditional Korean medical practices: 1999-2010."
Frequencies of ADRs Reported by Health consumers	
Mira, J. J., et al. (2012).	"Health consumers informing of adverse events. Results in diabetes and kidney disease."
Arkell, P., et al. (2012).	"Health consumer experiences, attitudes and expectations towards receiving information about anti-TNF: A qualitative study."
Burgess, C., et al. (2012).	"Health consumers' perceptions of error in long-term illness care: Qualitative study."
De Smedt, R. H., et al. (2011).	"Self-reported adverse drug events and the role of illness perception and medication beliefs in ambulatory heart failure health consumers: A cross-sectional survey."
De Smedt, R. H. E., et al. (2011).	"Perceived adverse drug events in heart failure: health consumers' perceptions and related factors."
Chao, J., et al. (2007).	"Health consumer-reported perceptions of side effects of antihyperglycemic medication and adherence to medication regimens in persons with diabetes mellitus."
Durrieu, G., et al. (2011).	"Health consumer reporting of adverse drug reactions: First french experience after mass immunization campaign with (H1N1)v pandemic vaccines."
Durrieu, G., et al. (2012).	"First french experience of ADR reporting by health consumers after a mass immunization campaign with influenza a (H1N1) pandemic vaccines: A comparison of reports submitted by health consumers and healthcare professionals."

Goodman, M. J., et al. (2011).	"Generating adverse drug event hypotheses using consumer internet forums."
Jarensiripornkul, N., et al. (2009).	"Health consumer self-reporting of potential adverse drug reactions to non-steroidal anti-inflammatory drugs in Thailand."
Jarensiripornkul, N., et al. (2003).	"Health consumer reporting of adverse drug reactions: Useful information for pain management?"
Krska, J., et al. (2013).	"Health consumer participation in the reporting of adverse reactions to statins."
Lopes, L. C., et al. (2014).	"Health consumer reports of the frequency and severity of adverse reactions associated with biological agents prescribed for psoriasis in Brazil."
Martin, M. T., et al. (2007).	"Adverse side effects of antiretroviral therapy: Relationship between health consumers perception and adherence."
Finer, D., et al. (2000).	"Consumer reports on medicines - CRM: Policy and practice."
Role of HCPs in Pharmacovigilance	
Leone, R., et al. (2013).	"Effect of pharmacist involvement on health consumer reporting of adverse drug reactions: first Italian study."
Mardby, A. C., et al. clients."	"Beliefs about medicines and self-reported adherence among pharmacy."
Role of Health Regulator in Pharmacovigilance	
Du, D., et al. (2012).	"Despite 2007 law requiring FDA hotline to be included in print drug ads, reporting of adverse events by consumers still low."
Edwards, I. R. and T. Graedon (2010).	"What do stakeholders think about pharmacovigilance?"
Menniti-Ippolito, F., et al. (2013).	"A shared surveillance of suspected adverse reactions to natural products: The Italian system."
Perceptions of HCPs on ADR reporting	
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Santosh KC, et al. (2013).	"Attitudes among healthcare professionals to the reporting of adverse drug reactions in Nepal"
Marian Sorin PAVELIU, et al. (2013).	"Perception on Adverse Drug Reaction Reporting by Physicians Working in Southern Romania"
Oshikoya KA, et. Al. (2009)	"Perceptions of doctors to adverse drug reaction reporting in a teaching hospital in Lagos, Nigeria."
Cannot Access	

(2003). [No authors listed]	"Should health consumers be enabled to directly report adverse drug reactions?[Dutch]."
(2007). [No authors listed]	Direct reporting by health consumers: positive results."
(1984). [No authors listed]	"[Drug surveillance in health consumers of advanced-age]."

Appendix D. Recruitment Email for Participant

You are invited to participate in a study aimed to discuss reporting of medication side effects

Who: We are seeking adult (> 18 years) participants living in Canada.

WHAT: To participate in a 30-45 minutes interview about experiences reporting medication side effects.

WHERE: The interview will be at a mutually convenient time and place (in person, telephone, or Skype).

Participation is completely voluntary. Selection of participants will be based on first come, first serve. Any personal information discussed will be confidential.

Participants will receive \$10 gift certificate .

For more information , please contact:

Rania Al dweik
Doctoral Candidate
Institute of Population Health, University of Ottawa
Doctoral Supervisor: Dr. Sanni Yaya

Appendix E. Information Letter and Consent Form

Université d'Ottawa | University of Ottawa
École interdisciplinaire des sciences de la santé
Interdisciplinary School of Health Sciences

Consent form**Project title: Adverse Drug Reactions Reporting by Patients in Canada**

Rania Al dweik, Researcher
PhD Candidate
Institute of Population Health
University of Ottawa

Dr. Sanni Yaya, Thesis Supervisor
Associate Professor
Faculty of Health Sciences
University of Ottawa

Invitation to Participate: I am invited to participate in the above mentioned research study conducted by Rania Al dweik as part of a doctoral thesis project.

Purpose of the Study: The purpose of the study is to explore patients' views and experiences on reporting drug side effects.

Participation: My participation will consist of attending an interview session. During the interview, I will be asked to describe my experience with adverse drug reaction reporting. The interview will last between 45 minutes to 60 minutes, depending on how much information I would like to share. The interview will be conducted at a mutually convenient time as soon as possible after consent is given.

Risks: My participation in this study will entail that I volunteer very personal information, and this may cause me to feel some emotional discomfort when I do recalling a life-changing moment. I have received assurance from the researcher that every effort will be made to minimize these risks, so if I feels uncomfortable answering a particular question; I do not have to answer. Furthermore, I may withdraw from the interview or study at any time. Researcher also provides me with the following list of resources that I can contact if need be:

Ottawa Distress Centre: 613-238-3311
Good2Talk: 1-866-925-5454

Benefits: This study will allow an understanding of reporting behaviours and barriers to the current system to be explored. The study will contribute to research in a largely unexplored field. The project will provide practical information about the views and experiences about adverse drug reaction reporting system. These results may help Health Canada, responsible for administering the regulations, understand patient needs and perspectives.

Confidentiality and anonymity: I have received assurance from the researcher that the information I will share will remain strictly confidential. I understand that the contents will be used only for exploring patients' views and experiences in reporting side effects and that my confidentiality will be protected. My name will not be used for any stage of the research. An identification code will be used in place of my name that will only be known to the research team (listed below). Personal information will not be released to anyone else without a court order. Quotations from the interviews may be used in the final research report. However, my name and identifying information will not be included with these notes. The final report may be submitted for publication in a peer-reviewed journal.

Conservation of data: All documentation with personal information about me will be kept in a locked cabinet for five years. If I participate in the study and decided to withdraw at any time, my data will be kept in a locked cabinet for five years and will not be used in the study results. Data from the interview that is stored on a computer will require a password only known to the researchers.

Compensation: Participant will receive a voucher of \$5 from Tim Horton as appreciation for their time.

Voluntary Participation: I am under no obligation to participate and if I choose to participate, I can withdraw from the study at any time and/or refuse to answer any questions, without suffering any negative consequences.

Acceptance: I,,agree to participate in the above research study conducted by **Rania Al dweik** (*Population Health, Faculty of Graduate and Postdoctoral*), which research is under the supervision of **Dr .Sanni Yaya**.

If I have any questions about the study, I may contact the researcher or her supervisor.
 If I have any questions regarding the ethical conduct of this study, I may contact the Protocol Officer for Ethics in Research, University of Ottawa, Tabaret Hall, 550 Cumberland Street, Room 154, Ottawa, ON K1N 6N5
 Tel.: (613) 562-5387 Email: ethics@uottawa.ca
 There are two copies of the consent form, one of which is mine to keep.

Participant's signature: _____ **Date: (Date)** _____

Researcher's signature: _____ **Date: (Date)** _____

Appendix F. Structured Interview Guide for Canadian Experience with ADR Reporting**System**

1. Tell me about your experiences with side effects from taking medications? (Prompt: who do you tell, when, what was the response, who reports it?)
2. Do you describe the side effect as “bad” or “serious”? (Tell me what do you mean by bad or serious?)
3. Are you aware of the Canadian Vigilance System for reporting side effects from medications?
Yes / No
(If yes: please tell me what you know about this system?)
(In case of non-face to face interview, the Canadian adverse drug reaction report form will be sent to the participant). Introduce the form by walking the participants through the six sections of the form (Personal Information about the Reporter, Health information about the Reporter, the medication involved in side effect, Other health products used at the same time, Information about the outcome after side effect, and Information about the outcome after side effects) in two minutes.
4. What were your first impressions about the ADR reporting form?
5. Is there questions missing that you would like to see added or removed from the side effect reporting form?
6. Did you find that the questions included in the side effect reporting form were:
 - Much less than I expected
 - Little less than I expected
 - About right
 - Little more than I expected
 - Much more than I expected
7. Are the font and icons readable (i.e. font type and size)? Yes /No
8. Is there enough space for data entry? Yes / No

9. For the next questions, I will like to ask you to rate each section of the side effect report by choosing 'poor', 'fair', 'good', or 'very good' to show what you think about the clarity of the questions:

- | | | | | |
|---|------|------|------|-----------|
| 9.1 Personal Information about the Reporter | poor | fair | good | very good |
| 9.2 Health information about the Reporter | poor | fair | good | very good |
| 9.3 The medication involved in side effect | poor | fair | good | very good |
| 9.4 Other health products used at the same time | poor | fair | good | very good |
| 9.5 Information about the side effect | poor | fair | good | very good |
| 9.6 Information about the outcome after side effect | poor | fair | good | very good |

10. Would you use the form or tell someone about the side effect reporting form?

Yes / No / Not sure

11. Do you have any further comments on the side effect reporting form? Or your experience with reporting side effects?

Demographic Questionnaire

Please tell us about yourself

1. What is your age?

Under 30

30 – 40

41 – 50

51 – 60

61 – 70

71 and older

2. What sex are you?

Male

Female

3. What is the highest level of education you completed?

- Less than high school
- High School
- Community College
- University undergraduate degree
- University graduate degree

4. What is your current position?

Thank you very much for your time.

Appendix G. Adverse Drug Reaction Reporting Form for Consumers (English Version)



Health Canada Santé Canada

Consumer Side Effect Reporting Form

Canada Vigilance Program

Aussi disponible en français : www.sante.gc.ca/medeffet

PROTECTED WHEN COMPLETED – B**

Complete all mandatory items, marked by a *, and provide as much information as possible for the remaining items.

1. About you – the person reporting the side effect

Last name*		First name*	
Address			
Number – Street		City/Town	Province – Postal Code
Telephone*		Email	

2. About the person who had the side effect

Personal Information			
Sex*	<input type="checkbox"/> Male <input type="checkbox"/> Female	Age	<input type="checkbox"/> years <input type="checkbox"/> months
Weight	<input type="checkbox"/> kg <input type="checkbox"/> lbs	Height	<input type="checkbox"/> cm <input type="checkbox"/> feet, inches
Health Information			
Known medical conditions			
Allergies			
Other relevant information (smoking, pregnancy, alcohol use, etc.)			

3. About the health product that may have caused the side effect

Health products include prescription and non-prescription medications, biologics (including fractionated blood products and vaccines), natural health products and radiopharmaceuticals.

If you suspect that more than one health product caused the side effect, attach additional forms/sheets.

Name of product* (For natural health products, list ingredients or attach a copy of the label.)		Manufacturer	
DIN/NPN #		Lot #	
Expiry date yyyy-mm-dd	Start date yyyy-mm-dd	End date yyyy-mm-dd	
Dosage			
Strength (250mg, 1g, etc.)		Quantity (2 tablets, 3 puffs, etc.)	Frequency (twice daily, at bedtime, etc.)
What was the product taken for?		How was the product taken (by mouth, by injection, etc.)?	
Is the product still being taken? <input type="checkbox"/> Yes <input type="checkbox"/> No			
If the product was restarted, did the side effect return? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Does not apply			

** As per the Treasury Board of Canada Secretariat Government Security Policy.

A program of MedEffect™ Canada

HC Pub.: 8140 (January 2011)

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Canada

4. About other health products used at the same time				
List all products taken around the time of the side effect. Attach additional forms/sheets if necessary.				
Name of product	Strength (250mg, 1g, etc.)	Quantity (2 tablets, 3 puffs, etc.)	Frequency (twice daily, at bedtime, etc.)	Reason for taking the product
5. About the side effect				
When did the side effect start?	yyyy-mm-dd			
When did it stop?	yyyy-mm-dd			
How bad was the side effect? (Select all the boxes that apply)				
<input type="checkbox"/> Uncomfortable, but did not affect everyday activities	<input type="checkbox"/> Life threatening			
<input type="checkbox"/> Bad enough to affect everyday activities	<input type="checkbox"/> Caused death		yyyy-mm-dd	
<input type="checkbox"/> Bad enough to be admitted to hospital	<input type="checkbox"/> Caused birth defect			
<input type="checkbox"/> Caused long term serious disability	<input type="checkbox"/> Other			
Describe the side effect* (Also provide available details of lab tests or treatment taken for the side effect, attach additional forms/sheets if necessary.)				
How is the person feeling now?				
<input type="checkbox"/> Recovered <input type="checkbox"/> Partially recovered <input type="checkbox"/> No change <input type="checkbox"/> Getting worse <input type="checkbox"/> Other				
Have you reported this side effect to the manufacturer of the health product? <input type="checkbox"/> Yes <input type="checkbox"/> No				
6. Send your report by mail OR fax				
Canada Vigilance Program Marketed Health Products Directorate Health Canada Postal Locator 0701E Ottawa, Ontario K1A 0K9		Fax: 1-866-678-6789 (toll-free) Prepaid mailing labels are available at www.health.gc.ca/medeffect For more information visit us at www.health.gc.ca/medeffect or call us at 1-866-234-2345 (toll-free)		

Instructions to Complete the Consumer Side Effect Reporting Form**How do I complete the Consumer Side Effect Reporting Form?**

- Complete sections 1 to 5 with as many details as you know. You may use additional forms/sheets if there is not enough space.
- Your pharmacist, doctor or other health professional can provide information that will help you complete your report.

What information do I need to know when filling out the form?**Section 1 – About you - the person reporting the side effect.**

- Include the name and contact details of the person completing the form.
- Contact information is necessary in case we need more information to assess the report.
- Identity of the person reporting a side effect remains confidential and is protected under the *Privacy Act*.

Section 2 – About the person who had the side effect.

- Do not provide information that will identify the person who had the side effect (name, identifying numbers, etc.).
- Include any medical history and other information that you believe may help in the assessment of the side effect.

Section 3 – About the health product that may have caused the side effect.

- Include all details about the product(s) you suspect may have been the cause of the side effect.
- Provide exact name of the health product, including abbreviations such as SR, XR, etc.
- The DIN/NPN refers to the Drug Identification Number/Natural Product Number and is generally found on the product label or packaging. This number makes it easy to identify the exact product.
- If you suspect more than one product has caused the side effect, provide the additional information on a separate sheet.
- A person who has experienced a side effect should consult a health care practitioner about whether to continue using/restart the product.

Section 4 – About other health products used at the same time.

- Include details about all health products being taken when the side effect occurred (includes prescription and non-prescription as well as natural health products). The side effect experienced may have been caused by other health products than the one suspected or by the combination of products.

Section 5 – About the side effect.

- Provide as much information as possible to describe the side effect experienced, including dates involved, symptoms experienced and their severity.
- A serious or life threatening disability may include loss of physical strength or mobility, vision, speech or hearing impairment, etc.
- Include, if available, results of laboratory tests (e.g. blood and urine tests or bone density scans).
- Describe available details of treatment taken for the side effect (allergy medication, pain relievers, etc.).

Section 6 – Send us your report by mail or fax.

- Before sending, review the form to ensure you have not missed any important information.
- Be sure to include both pages of the form, all additional forms/sheets and other relevant documents when sending your report.
- A postage paid mailing label is available on MedEffect™ Canada Web site at: www.health.gc.ca/medeffect or by calling 1-866-234-2345 (toll-free).
- Reports can be faxed to: 1-866-678-6789 (toll-free) or mailed to:
Canada Vigilance Program
Marketed Health Products Directorate
Health Canada
Postal Locator 0701E
Ottawa, Ontario K1A 0K9

Additional Information About Reporting Side Effects

What is a side effect?

Side effects, also known as adverse reactions, are troublesome symptoms or feelings that occur when taking a health product. They can range from minor irritations, such as a skin rash, to serious and life-threatening reactions, such as a heart attack or liver damage. A side effect can also be when a product has no effect or has not performed the intended treatment. They can occur within minutes after taking a medicine, or can take years to develop.

What to report?

Suspected side effects to any health product, whether it was prescribed by your health professional or bought without a prescription, should be reported. Health products include prescription and non-prescription medications, biologics (including fractionated blood products and vaccines), natural health products and radiopharmaceuticals. Fractionated blood products, such as albumin, plasma derived clotting factors and immune globulins, are blood products that have undergone a manufacturing process and have a Drug Identification Number (DIN). Radiopharmaceuticals are drugs either of chemical or biological origin which are intentionally made radioactive for the purpose of diagnosing illness and are always prepared and given by a health professional.

You can report side effects that have happened:

- to you personally;
- to your child or other people you're responsible for; or
- someone who asks you to make a report on their behalf.

When to report?

Side effects should be reported as soon as possible, especially if they interfere with everyday activities or if they are not mentioned in the information supplied with the health product.

Why report a side effect?

All health products have benefits and risks. Although health products are carefully tested before they are licensed for sale in Canada, some side effects may become evident only after a product is in use by the general population.

When you report a side effect to the Canada Vigilance Program, the information from your report, along with other information, is used to check for new safety concerns about a product. As a consumer, your report contributes to improving the safety and safe use of health products for everyone.

Can I report a side effect without filling out the form?

You can also report side effects to health products to the Canada Vigilance Program:

- Online: www.health.gc.ca/medeffect
- By calling 1-866-234-2345 (toll-free)

NOTE: *If you are currently suffering from a side effect to a drug or health product, contact your health professional or local health authorities. The Canada Vigilance Program does not provide medical advice.*

Protecting your personal information

On the form, we ask for the name and contact details of the person reporting the adverse reaction. This is so we can get in touch if we need more information. When providing information about the person who had the suspected adverse reaction, do not include the patient's name. Personal information collected, used or disclosed under the Canada Vigilance Program is confidential and protected. For the purposes of the Canada Vigilance Program, information related to the identity of a patient and/or reporter of the adverse reaction will be protected as personal information under the *Privacy Act*, and under the *Access to Information Act* in the case of an access to information request. For details about personal information collected under this program, visit the Government of Canada web site on Institution-Specific Personal Information Banks under Health Canada, Health Products and Food Branch, Branch Incident Reporting System, PIB # ppu 088 at: <http://infosource.gc.ca/inst/shc/fed07-eng.asp> (Health Products and Food Branch, Branch Incident Reporting System).

Appendix H. Adverse Drug Reaction Reporting Form for Consumers (French Version)



Formulaire de déclaration des effets indésirables de Canada Vigilance

Déclaration d'effets indésirables présumés dus à des produits de santé commercialisés au Canada

Compléter tous les items obligatoires, indiqués par un *, et fournir autant d'information que possible pour les autres items. PROTÈGE LORSQUE COMPLETE - B**

A. Information reliée au patient		C. Produit(s) de santé soupçonné(s)	
2. Age <input type="checkbox"/> Ans <input type="checkbox"/> Mois	3. Sexe* <input type="checkbox"/> Homme <input type="checkbox"/> Femme	4. Taille cm pi	5. Poids kg lb
B. Effet indésirable		1. Nom*, teneur et fabricant (si connu) N°1 N°2	
1. Suite de l'effet indésirable (sélectionner ceux qui s'appliquent) <input type="checkbox"/> Décès : (aaaa-mm-jj) <input type="checkbox"/> Met la vie en danger <input type="checkbox"/> Hospitalisation <input type="checkbox"/> Hospitalisation – prolongée <input type="checkbox"/> Autre :		2. Dose, fréquence et voie d'administration N°1 N°2	
2. Date de l'effet (aaaa-mm-jj)		3. Date du traitement (ou durée) N°1 Du (aaaa-mm-jj) - au (aaaa-mm-jj) N°2 Du (aaaa-mm-jj) - au (aaaa-mm-jj)	
3. Date de déclaration (aaaa-mm-jj)		4. Indication pour l'utilisation N°1 N°2	
4. Décrire l'effet ou le problème*		5. Effet disparu après arrêt d'utilisation ou réduction de dose N°1 <input type="checkbox"/> Oui <input type="checkbox"/> Non <input type="checkbox"/> Ne s'applique pas N°2 <input type="checkbox"/> Oui <input type="checkbox"/> Non <input type="checkbox"/> Ne s'applique pas	
5. Tests/données de laboratoire pertinents (incluant les dates (aaaa-mm-jj))		6. N° de lot N°1 N°2	
6. Historique pertinente et conditions médicales préexistantes (p. ex. allergies, grossesse, consommation de tabac/d'alcool, dysfonctionnement hépatique/rénal)		7. Expiration N°1 (aaaa-mm-jj) N°2 (aaaa-mm-jj)	
		8. Effet réapparu après réadministration N°1 <input type="checkbox"/> Oui <input type="checkbox"/> Non <input type="checkbox"/> Ne s'applique pas N°2 <input type="checkbox"/> Oui <input type="checkbox"/> Non <input type="checkbox"/> Ne s'applique pas	
		9. Produits de santé concomitants, excluant le traitement de l'effet (nom, dose, fréquence, voie d'administration et date du traitement (aaaa-mm-jj))	
		10. Traitement de l'effet, incluant les dates (aaaa-mm-jj)	
		D. Information reliée au déclarant	
		1. Nom*, profession, adresse, numéro de téléphone*	
		2. Professionnel(le) de la santé? <input type="checkbox"/> Oui <input type="checkbox"/> Non	
		3. Déclaré au fabricant? <input type="checkbox"/> Oui <input type="checkbox"/> Non	

** Selon la Politique du gouvernement du Canada émise par le Secrétariat du Conseil du Trésor du Canada.



Directives pour compléter le Formulaire de déclaration des effets indésirables Canada Vigilance

- Utilisez ce formulaire seulement pour déclarer les effets indésirables dus aux médicaments d'ordonnance ou en vente libre; les produits de santé naturels; les produits d'origine biologique, comme les produits sanguins et les vaccins; les cellules, les tissus et les organes; les produits radiopharmaceutiques; les désinfectants et les produits d'hygiène comportant des allégations de propriétés de désinfection.
- Complétez le présent formulaire en fournissant autant de détails que possible et en utilisant un formulaire distinct pour chaque patient. On peut déclarer jusqu'à deux produits de santé soupçonnés sur un même formulaire. S'il y a plus de deux produits soupçonnés d'être responsables de l'effet indésirable, il faut joindre un autre formulaire. Des pages supplémentaires peuvent être jointes au formulaire au besoin.
- Pour la case « Identification », indiquez un code d'identification quelconque qui vous permettra, à vous le déclarant, de trouver le cas facilement si l'on communique avec vous pour davantage de renseignements, n'employez pas le nom du patient. Voir l'énoncé de confidentialité au bas de cette page.
- Tout renseignement concernant le suivi d'un effet indésirable qui a déjà été déclaré peut être communiqué sur un autre formulaire, signalant qu'il s'agit d'un suivi, incluant, si connus, la date de la déclaration initiale et le numéro d'effet indésirable fournis dans l'accusé de réception.
- Les déclarations peuvent être envoyées par télécopieur au 1-866-678-6789 (sans frais) ou par courrier à : Santé Canada, Direction des produits de santé commercialisés, Programme Canada Vigilance, Indice postal 0701E, Ottawa (Ontario) K1A 0K9. Des étiquettes d'adresse préaffranchies sont offertes à www.sante.gc.ca/medeffet ou en appelant au 1-866-234-2345 (sans frais). Ne pas soumettre une déclaration par courriel.

Information au sujet de la déclaration d'effets indésirables

Qu'est-ce qu'un effet indésirable?

Un effet indésirable est une réponse nuisible et non voulu à un produit de santé. Ceci inclut tout effet indésirable présumé d'être associé au produit de santé utilisé. L'abus de médicament, la surdose de médicament, les interactions médicamenteuses et les interactions entre les médicaments et les aliments et l'absence inhabituelle d'efficacité sont considérés comme étant des effets indésirables pouvant être déclarés.

Un effet indésirable grave est une réaction qui nécessite/prolonge l'hospitalisation, une malformation congénitale ou une invalidité/incapacité persistante ou importante, met la vie en danger ou entraîne la mort. Les effets indésirables qui nécessitent une intervention médicale importante pour éviter l'un des autres effets énumérés plus haut sont aussi jugés graves.

Quels effets indésirables devrait-on déclarer?

Tous les effets indésirables présumés doivent être déclarés, surtout s'ils sont :

- *imprévus*, peu importe leur gravité (compte tenu des renseignements sur le produit ou de l'étiquetage);
- *graves*, qu'ils soient prévus ou non;
- *liés à des produits récemment mis sur le marché* (commercialisés depuis moins de 5 ans), peu importe leur nature ou leur gravité.

Autres façons de déclarer

Vous pouvez déclarer les effets secondaires des produits de santé au Programme Canada Vigilance :

- par téléphone : 1-866-234-2345 (sans frais)
- en ligne : www.sante.gc.ca/medeffet

Le Formulaire de déclaration des effets indésirables de Canada Vigilance est également disponible en ligne à www.sante.gc.ca/medeffet ou à la fin du *Compendium des produits et spécialités pharmaceutiques* (CPS).

Renseignements supplémentaires

- Une déclaration n'équivaut pas à reconnaître que le personnel médical ou le produit a causé ou contribué à causer l'effet indésirable.
- Les déclarations sont, dans la plupart des cas, des associations soupçonnées. Une association temporelle ou possible peut justifier une déclaration, laquelle n'implique pas un lien causal définitif.
- Les professionnels de la santé et les consommateurs peuvent déclarer les effets indésirables au détenteur d'une autorisation de mise en marché. Indiquez, dans votre déclaration faite à Santé Canada, si le cas a été déclaré au détenteur d'une autorisation de mise en marché pour le produit.

Pour plus d'information, contactez un bureau régional de Canada Vigilance par téléphone au 1-866-234-2345 (sans frais) ou :

Bureau régional de Canada Vigilance – Colombie-Britannique et Yukon 400-4595, Canada Way, Burnaby (BC) V5G 1J9 CanadaVigilance_BC@hc-sc.gc.ca	Bureau régional de Canada Vigilance – Ontario et Nunavut 2301, avenue Midland, Toronto (ON) M1P 4R7 CanadaVigilance_ON@hc-sc.gc.ca
Bureau régional de Canada Vigilance – Alberta et Territoires du Nord-Ouest 730-9700, avenue Jasper, Edmonton (AB) T5J 4C3 CanadaVigilance_AB@hc-sc.gc.ca	Bureau régional de Canada Vigilance – Québec Bureau 202-40, Tour Est 200, boulevard René-Lévesque Ouest, Montréal (QC) H2Z 1X4 CanadaVigilance_QC@hc-sc.gc.ca
Bureau régional de Canada Vigilance – Saskatchewan 101, 22 rue E., Saskatoon (SK) S7K 0E1 CanadaVigilance_SK@hc-sc.gc.ca	Pour Nouveau-Brunswick, Nouvelle-Écosse, Île-du-Prince-Édouard, Terre-Neuve et Labrador :
Bureau régional de Canada Vigilance – Manitoba 510, boul. Lagimodière, Winnipeg (MB) R2J 3Y1 CanadaVigilance_MB@hc-sc.gc.ca	Bureau régional de Canada Vigilance – Atlantique 1625-1505, rue Barrington, Halifax (NS) B3J 3Y6 CanadaVigilance_ATL@hc-sc.gc.ca

Confidentialité

Les renseignements personnels recueillis, utilisés ou diffusés dans le cadre du Programme Canada Vigilance sont confidentiels et protégés. De la même manière, les renseignements sur l'identité des patients ou des personnes ayant déclaré les effets secondaires, recueillis par l'entremise du Programme Canada Vigilance, sont protégés comme renseignements personnels en vertu de la *Loi sur la protection des renseignements personnels* et, dans les cas de demande d'accès à l'information, en vertu de la *Loi sur l'accès à l'information*. La présentation des renseignements demandés sur ce formulaire est facultative. Les renseignements tirés des déclarations d'effets indésirables sont maintenus dans une base de données informatisée et sont utilisées dans le cadre de l'évaluation des produits de santé commercialisés, ce qui peut contribuer à la détection de problèmes potentiels en matière de sécurité ainsi qu'à l'évaluation de leurs bienfaits et de leurs risques. Pour en connaître davantage sur les renseignements recueillis dans le cadre de ce programme, veuillez consulter la section « Système de déclaration des incidents » (Direction générale des produits de santé et des aliments) (numéro du fichier : Scan PPU 088) de la page « Fichiers de renseignements personnels spécifiques aux institutions » (<http://infosource.gc.ca/inst/shc/fed07-fra.asp>).

Appendix I. University of Ottawa Ethics Approval

File Number: H05-14-18

Date (mm/dd/yyyy): 07/10/2014



Université d'Ottawa
Bureau d'éthique et d'intégrité de la recherche

University of Ottawa
Office of Research Ethics and Integrity

Ethics Approval Notice
Health Sciences and Science REB

Principal Investigator / Supervisor / Co-investigator(s) / Student(s)

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Glossary of Terms

The glossary contains a list of the terminology used in the dissertation

Adverse drug reaction (ADR): “Response to a drug which is harmful and unintended, and which takes place at doses normally used in humans for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function” (WHO, 2002, p.42). “According to Health Canada, an adverse event is any unwanted incidence associated with the use of a drug”.

Anatomical Therapeutic Chemical (ATC): This is a system that classifies medicinal products based on their chief ingredient, the organ on which they exert their medicinal function (Aagaard et al., 2009).

Canada Vigilance Reporting Online Database ‘MedEffect’: “Computerized information database intended to maintain Health Canada’s post-marketing safety surveillance program for all approved drug and biological”.

Health consumers: Can be patient, patients' relatives, and/or other members of the public.

Council for International Organizations of Medical Sciences (CIOMS): Provides ethical guidelines for biomedical research involving human subjects (Macrae, 2007).

Medical Dictionary for Regulatory Activities (MedDRA): It is clinically validated international medical terminology used by regulatory authorities and the regulated biopharmaceutical and pharmaceutical industries (Mozzicato, 2009). MedDRA is required for electronic exchange of information on suspected adverse reactions between industry and regulatory authorities (Brown, 2004). Medical information includes symptoms, signs, diseases, diagnoses, indications, investigations-procedures, and medical-social history (Mozzicato, 2009). It has 26 broad groups called system organ classes

Post-marketing Passive Surveillance: Systems that rely on reporters (healthcare professionals, health consumers, manufacturers) to report occurrences of ADRs. The advantages of passive surveillance are simplicity and the use of few resources. The disadvantages include underreporting

Pharmacovigilance: defined as “the science dedicated to the safety of drugs as used in the clinical practice” (van Grootheest & de Jong-van den Berg, 2004).

Seriousness criteria: “A criteria formulated by CIOMS, specifically death, life- threatening, hospitalization or prolongation of hospitalization, disability/incapacity, congenital anomaly/birth defect and other ADRs considered serious by the reporter” (de Langen et al., 2008).

Signal: “Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously” (WHO, 2002).

System Organ Class (SOC): MedDRA consists of 26 broad groups called system organ classes (SOCs). The SOCs consist of more specific sub groups that finally group single medical concepts and equal terms used for codifying clinical information linked to adverse events and ADR (Mozzicato, 2009).

Spontaneous reporting: “System in which case reports of adverse drug events are voluntarily submitted from health professionals and pharmaceutical companies to national regulatory authority agencies” (WHO, 2002).