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Pharmacovigilance: A Comparative Study About the Knowledge of Adverse Drug Reaction (ADR) Reporting that Private Practitioners and Government Doctors Gained in a Random Locality in India

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Pharmacovigilance: A Comparative Study About the Knowledge of Adverse Drug Reaction
(ADR) Reporting that Private Practitioners and Government Doctors Gained in a Random

Locality in India

by

Shanthan B Pingili

Thesis

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in

Clinical Research Administration

Thesis Committee:

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March 15, 2013

Ypsilanti, Michigan

DEDICATED

to

My Family

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Abstract

The present pilot study aims to compare the knowledge pertaining to ADR reporting systems that government doctors and private practitioners gained in a random, tier-II city in India, by conducting a questionnaire based survey. Their knowledge of ADR reporting, related guidelines and/or regulations, the frequency of ADRs they observe and diagnose, their opinion on mandatory reporting by doctors, type of ADRs they would generally report, and to whom ADRs should be reported are discussed besides evaluating the attributable reasons for underreporting, if any. A total of 47 (21.36%) responded to this random survey, of whom 27 (57.4%) were government doctors and 14 (29.7%) were private practitioners. Interestingly, 68.2% of doctors from either groups liked the idea of ADR reporting being made mandatory for doctors. The Chi-square test turned out to be significant with $\chi^2= 26.729, p < 0.05$, indicating there exists a difference between government doctors and private practitioners regarding the types of ADRs they would generally report. Lack of time, unavailability of ADR reporting forms, and system of reporting being too bureaucratic were cited as reasons for underreporting of ADRs. Creating awareness, among doctors of both groups, about ADR reporting via CME programs, offering incentives to reporters, and establishing ADR monitoring and reporting systems in hospitals and clinics under the supervision of pharmacists will help improve ADR reporting in this selected tier-II city of Warangal, in the state of Andhra Pradesh in India.

Key Words: Adverse Drug Reaction (ADRs), ADR reporting systems, Pharmacovigilance, Central Drug Standard Control Organization (CDSCO), National Pharmacovigilance Program (NPP).

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Chapter 1: Introduction

1.1 Introduction

Effectiveness and efficacy are two attributes of a drug that are sought for whenever clinicians choose a drug to cure or treat an underlying ailment. While effectiveness is the capacity of a drug to produce known pharmacological effect, efficacy is the ability of a drug to produce and reproduce, under ideal circumstances, a desired pharmacological effect. Drugs also produce side effects (besides desired pharmacological effects) which are defined as normally unavoidable secondary effects of a drug at therapeutic levels/concentrations. These side effects, at higher doses or of higher severity are often termed as Adverse Drug Reactions (ADRs). Depending upon the severity ADRs can cause even hospitalization or death. The International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice (GCP) defines ADRs as a response to a drug that is noxious and unintended and that occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function (World Health Organization [WHO] report 498, 1972).

In the recent years, deaths due to adverse drug reactions are increasing (Shepherd, Mohorn, Yacoub, & May, 2012; Kieve, 2012). To lower the incidence or prevent those deaths, spontaneous reporting of ADR is the best possible way, and Desai et al. (2011) opined spontaneous reporting of ADRs as an important tool in pharmacovigilance. They also observed that, in daily practice, medical practitioners report very few adverse effects which are caused by drugs. According to the authorities at Central Drug Standard Control

Organization (CDSCO), hospitalization, disability, and life-threatening reactions caused by the drugs need to be reported. But only a small portion of these are officially reported.

1.2 Background

A study conducted by Schneeweiss et al. (2002) shows that 5 to 10% of patients were admitted to hospitals as a consequence of ADRs. In several studies the frequency was estimated to be 20% of all cases admitted to the geriatric department as well as in the internal medicine departments.

A study conducted by Lazrou, Pomeranz, and Corey (1998) concludes that incidences of serious ADRs reported were 6.7% and fatal ADRs were 0.32% of hospitalized patients. They also estimated that in the year 1994, a total of 2,216,000 hospital consumers had serious ADRs and about 106,000 hospital consumers had experienced fatal ADRs, making them the fourth to sixth leading cause of death in the United States.

A study conducted by Routledge and co-worker (2004) concludes that the expenditure of ADRs has been anticipated to be as high as £ 0.5 billion each year in the United Kingdom (UK) due to the prolongation of hospital visits.

Ramesh, Pandit, and Parthasarathi (2003), in their study conducted in a south Indian hospital, reported that 0.7% of hospital admissions were because of ADRs and of the 3.7% in-patients who suffered an ADR, a total of 1.3% were fatal. Another study conducted by Arulmani et al.(2007) recorded a 3.4% of ADR related admissions into hospital and 3.7% of recorded ADRs during hospital stay in nine months. An observational study conducted by Singh et al. (2010) revealed that in a tertiary care facility (in Northern India) there were 154 ADRs reported over a period of 6 months, which reiterates the regular occurrence of ADRs. It

was also reported by Arulmani et al. (2007) that ADRs and related hospitalizations prove a financial burden on the hospitals and thus on the State. They calculated the average cost per ADR per patient to be ₹ 481 (£6) while Ramesh and co-workers calculated the average cost in managing reported ADR (per ADR) to be ₹ 690 (\$ 12.5).

It's possible that some or many other ADRs might have gone unreported during the course of the above referenced studies. There are various reasons, as cited by researchers, for ADRs being not reported to the extent they should. A few are as follows:

- Lack of knowledge with regard to the guidelines/regulations of ADR reporting
- Lack of clarity regarding the responsibility (is it up to the doctor or to other medical staff [pharmacists/nurse] to report ADRs?)
- Too busy to report ADR/ ignorance with respect to ADR reporting
- Malfunctioning of an established ADR reporting system (unavailability of required forms), and so on.

Desai et al. (2011) evaluated the KAP (Knowledge, Attitude and Practice) of prescribers with regard to ADR reporting and found that though the attitudes are positive, practice is lacking, citing some of the above reasons. Many studies were conducted to evaluate the practice of ADR reporting in various parts of India and to suggest methods to streamline the system. Sampling studies were conducted in many metropolitan and cosmopolitan cities like Mumbai, Mysore, Ahmedabad and so on, but a perfect figure would only be obtained when random studies are also taken up in tier-II and tier-III cities. In an effort to understand the general trend of the ADR reporting system in those tier-II and tier-III cities and to contribute to the general understanding of the knowledge of ADRs and its

reporting systems across India, this study was proposed. Methodology was similar to other studies. The survey questionnaire was administered randomly to prescribers and the statistical methods like Student T- test and Chi-square test were used. Prime motive of this research was to study and understand the general trend of this ADR reporting system in a randomly selected tier-II city, analyze restraints to this system (if any), and suggest ways to establish a perfectly functional system, if need be. This research study could serve as a foundation study in the randomly selected city in tracking the trend of ADR reporting system and in suggesting changes (if needed) from time to time.

1.3 Purpose

The present study was undertaken to investigate the knowledge that private practitioners and government appointed doctors gained about the ADR reporting system and/or the guidelines thereof, in a random locality (a tier-II city) in India.

1.4 Objectives

1.4.1 Primary Objective (Research Question)

Are the doctors (both private practitioners and government appointed) in a random locality in India familiar with ADR reporting system (and/or guidelines/regulations)? If yes, do they take responsibility in reporting ADRs or do they rely on their staff to do so?

1.4.2 Secondary objective:

- To determine the factors responsible for under-reporting of ADRs (if any)
- To suggest ways of increasing the ADR reporting

1.5 Hypothesis

1.5.1. Null Hypothesis (H_0): All doctors, both private and government-appointed doctors, have enough knowledge of the guidelines/regulations for ADR reporting and they do take responsibility in reporting ADRs to pharmacovigilance authorities or the pharmaceutical companies.

1.5.2. Alternate Hypothesis (H_1): There is a difference in the knowledge that private practitioners and government doctors have regarding the guidelines/regulations of ADR reporting and the clarity they have regarding the responsibility of ADR reporting.

Chapter 2: Literature Review

2.1 Definition of Adverse Drug Reaction

The WHO, in its technical report series (WHO report 498, 1972), defined an Adverse Drug Reaction as "noxious, unintended and which occurs at dosages normally used in human beings for prophylaxis, diagnosis or therapy for the disease or for the modification of the physiological function." Allergies, idiosyncrasies, pharmacological and toxicological mechanisms, and interactions between different drugs were also included in the definition with them being independent of the mechanism of ADR. The former was later adapted by the ICH- GCP as their definition of an ADR. Parker (1982) opined that ADR might involve immunological or non-immunological mechanisms as well.

2.2 Classification of ADRs

Until recently most of the researchers followed the conventional classification of ADRs by Rawlins and Thompson (1977). Some of the researchers, prescribers, and pharmacovigilance professionals extrapolated the classification of ADRs based on works of Rawlins and Thompson (1977) and Naranjo et al. (1981). The classification of ADRs is still being researched owing to the fact that new kinds of ADRs are being reported that do not fit into any other previous classifications.

The conventional and probably one of the first classifications of ADR by Rawlins and Thompson (1977) divide adverse reactions into Type A reactions (also termed as augmented reactions), which are the undesired pharmacological effects of drugs and are dosage-dependent, and which are predictable and thus preventable too. Some examples of this type are bradycardia-with the use of beta blockers, hemorrhage-with use of anticoagulants, and

drowsiness-with benzodiazepines. Though Type A reactions depict rather high incidence and morbidity, associated mortality is comparatively low. Inevitably, unpredictable reactions with an unknown pharmacological mechanism at normal dosages were grouped into Type B (Bizarre). One example is malignant hypothermia upon administration of general anesthesia. The associated mortality rate was said to be high with these Type B ADRs while the incidence rate and morbidity were comparatively low.

Edwards and Aronson (2000) further expanded the classification of ADRs into:

- Type C - reactions associated with prolonged therapies for chronic ailments/diseases. One example is analgesic nephropathy
- Type D - uncommon delayed reaction that become apparent only after an elapsed period of time and those which are dose dependent. Examples are carcinogenesis and teratogenesis
- Type E - reactions that are associated with the withdrawal of drugs. Examples include antidepressant discontinuation syndrome associated with the withdrawal of Serotonin Nor-epinephrine Re-uptake Inhibitors (SNRIs) or other class of Selective Serotonin Re-uptake Inhibitors (SSRIs)
- Type F- Failure of therapy owing to intrinsic properties of drugs, which are dose-related and supposed to be caused by drug interactions

Naranjo et al. (1981) devised a method to estimate the causality of ADRs and classified them based on the probability of causality as definite, probable, possible, and doubtful. This mode of classification helped clinicians and pharmacists reach consensus in assessing and reporting ADRs.

Hunziker et al. (2002), relying on the conventional classification of ADRs by Rawlins and Thompson (1977), classified ADRs based on the largely accepted, contemporary, pathomechanisms into Type A₁ - Type A₇ and Type B_a (allergic/immunological reactions) and Type B_{pa}. (pseudo allergic/anapylactoid reactions):

- Type A₁ : reactions not specified in Type A
- Type A₂ : dose related reactions
- Type A₃ : patient related reactions - Idiosyncrasies
- Type A₄ : drug related (intolerance to drugs example: patients allergic to penicillins)
- Type A₅ : drug-to-drug interactions
- Type A₆ : rebound or withdrawal effects
- Type A₇ : secondary reaction to drugs

This was one of the most comprehensive classifications of ADRs encompassing many mechanisms and types of reactions. This sort of classification would help manage the drug market with more efficacy by assisting clinicians and pharmacists in the detection of ADRs with accuracy. This in turn would encourage the healthcare professionals to indulge more in ADR reporting than before.

2.3 Concept of Pharmacovigilance: Origin

Pharmacovigilance, a science of activities relating to the detection, assessment, understanding, and prevention of adverse drug reactions or any other drug-related problems, evolved in the mid-1900s (WHO, 2002). Collecting numerous data related to a product's actions, that is, drugs' life cycles, both pre-market and post-market, is the most important part

with a concern to public safety. One of the important tools in this area of science is the spontaneous reporting of ADRs either by clinicians or the pharmacists. This aids in an exceptional management of various diseases using drugs. A brief review of unfortunate events in the past associated with drugs will help understand the importance of pharmacovigilance whilst giving a clear picture of the conception of this skill.

Elixir Sulfanilamide, effectively used in the treatment of streptococcal infections, in the year 1937 made it to the headlines in the radio and print media for it was responsible for the death of more than 100 patients (both adults and children) within a period of two months. Sulfanilamide tablets and powder were used safely in patients and had dramatic curative effects, which reiterated that Sulfanilamide was not to blame. The elixir mixture contained diethylene glycol, an anti-freeze agent used in automobiles, a potent toxic chemical. This chemical was used in the elixir mixture as Sulfanilamide dissolves in this chemical and that the mixture had good taste, flavor, and texture. Barely any toxicological studies were performed on this new preparation, perhaps owing to fact that sulfanilamide was already being effectively used. This episode warranted a swift action on the part of FDA which accelerated the final enactment of the Federal Food, Drug, and Cosmetics Act 1938 (Ballentine, 1981).

Supposedly, the first need and/ or act of ADR reporting followed the death of a 15-year-old girl due to ventricular fibrillation upon administration of general anesthetic chloroform in the year 1948. With the concerns of public health and profession about anesthetic safety, The Lancet set up a commission inviting doctors from within Britain and its colonies to report any anesthesia related deaths (Routledge, P., 1998). This event was marked as the origin of the concept of pharmacovigilance on a national scale.

Chloramphenicol (bacteriostatic antimicrobial) had a Type B, unpredictable ADR associated with its administration. Upon a series of aplastic anemias detected after the administration of chloramphenicol in 1950, the drug was subjected to further pharmacological studies after it was marketed. Kramer (1981) cited more examples like chloramphenicol, highlighting the importance of continuous studies on a drug's behavior in various populations in different situations that do not come under the purview of clinical trials. Clinical trials have always been in a conditioned and controlled environment where a drug undergoes rigorous testing only in select populations in limited numbers. On the other hand, they are not tested in those populations in which they are marketed and used. These contrasting environments in a drug's life cycle warrants a pharmacovigilance program in force for efficient management of diseases and, in turn, the life cycle of a drug.

Thalidomide is another example. Phocomelic babies were born when pregnant women were treated with thalidomide for their acute morning sickness during pregnancies. This was a Type-D ADR according to Edwards and Aronson's (2000) classification of ADRs. Thalidomide was later withdrawn from the market because of its teratogenic effects upon receiving numerous ADR reports from physicians. German physicians published thalidomide issue in various journals. McBride (1961) stated that this event associated with thalidomide drove many developed countries to establish an organized and systematic evaluation system of drugs and associated-ADRs. These systems, in totality, were dependent on physicians and pharmacists. Sweden, Canada, the Netherlands, New Zealand, and Australia were the first to implement a naïve pharmacovigilance program, and many other countries followed. Gay (1997) published astonishing facts about the uses of such pharmacovigilance programs in her article. Upon withdrawal from the market, thalidomide was subjected to various other studies;

long-term effects of this drug were also studied and by chance it was discovered that this drug could be used in treating Erythematous Nodular Leprosy (ENL). Upon satisfactory results in trials, thalidomide was re-introduced in the market for treating leprosy. It was learned that thalidomide is effective in treatment of HIV and some cancers; trials are underway and under the scrutiny of the FDA. These by-chance discoveries were attributed to the success of pharmacovigilance programs as new information regarding the drugs in question would be gathered with each and every ADR reported.

2.4 Established ADR systems across the world

2.4.1 United Kingdom

In the aftermath of the thalidomide event, the Committee on Safety of Drugs (CSD) was established in the United Kingdom in 1963, which was later transformed into the Committee on Safety of Medicines (CSM) in 1968, in the purview of the Medicines Act of 1968. Since 2005, CSM has become CHM- Commission on Human Medicines which provides independent expert advice to the MHRA (Medicines and Healthcare products Regulatory Agency) on safety of drugs. Any new chemical entity or vaccine is effectively put on a two-year probation by the MHRA with a black triangular caution symbol in the product labeling, warranting a strict follow-up on the effectiveness and safety of medicines, by the prescribers/doctors, during the probationary period. This will effectively give a chance to collect much more data than those collected during the clinical trials on potential and/or possible side effects upon longer exposure to the drug. The black triangle mark is not removed by the MHRA unless the drug shows satisfactory safety profile in larger populations. The black mark may also be placed on new formulations of marketed drugs. On the other hand, MHRA mandates pharmaceutical companies to closely monitor the side effects caused

by their marketed products. Besides doctors and manufacturers, MHRA also requests patients to report potential side effects to OTC (Over The Counter) products and prescription medications via the Yellow card scheme (retrieved from www.mhra.gov.uk). All information pertaining to the demographics of reporter, drug therapy treated upon, route of administration of the drug, dose specification, diagnostic report, and description of reactions, along with contact information, is sought while using the Yellow card system (Breckenridge et al., 1998; Jefferys et al., 1998; Moore et al., 1985).

2.4.2 United States of America

The Federal Food & Drug Administration (FDA), being the primary governing body to regulate the pharmaceutical and medical devices industry, has a dictum to investigate and publish information on adverse drug events associated with approved products on the market. In order to serve this purpose, FDA has established a service: Adverse Events Reporting Service (AERS/FAERS) called MedWatch. (Craigle, 2007). MedWatch is primarily a reporting tool focusing on medical devices and medicines with two main purposes: AERS tools for use by medical professionals and the public to report adverse events and medical injuries associated with products. They provide information to the public on the following: prescription drugs, OTC drugs, biologics, medical and radiation-emitting devices, and special nutritional products, such as infant formulas and dietary supplements.

MedWatch achieves FDA's purpose by encouraging medical professionals and the public to voluntarily report any adverse events and/or medical injuries, but for the industry (including drug and device manufacturers, importers, and medical facility users) it is mandatory to report these events as required by law. MedWatch has the reporting form hosted

on their website www.fda.gov/medwatch/getforms.htm, making it easily accessible and downloadable from the website. The forms may be downloaded, duly filled in, and sent via email, fax, or regular mail. Special dial-in numbers are available to verbally report any AEs (Kessler, 1993).

Upon receiving reports pertaining to a single drug or medical device, the FDA summons more studies into those events whilst temporarily pulling out those products from the market. The FDA also sends "Dear health care professionals" letters to medical practitioners warning them of the discovered adverse events and requesting them to refrain from prescribing "products in question" until more research is done. The FDA holds the authority to withdraw the market approval, permanently, in case the products cannot be altered to rectify the problem. MedWatch serves as an impeccable tool for the prescribers in learning more about the trend in prescription drugs, that is it serves as a CEP (Continuing Education Program) tool as well. More importantly, it is a nationwide single authority that pools information on AEs rather quickly and at one place, allowing for swift action in the interest of public safety. Craigle (2007) mentioned, after reading IOM's report, about the alarmingly high \$3.2 billion lost in maintaining AE-related injuries. This loss in economy in the form of Medicare/Medicaid budgets and lost wages could be addressed rather quickly with the aid of such an important reporting tool. The reporting tool, being available over the internet, helps PI's (Principal Investigators)/prescribers from across the globe, working on offshore trials (under the FDA's regulatory guidance) of drugs meant also to be marketed in the USA, to report AEs/associated problems, directly, which has become a huge advantage.

2.4.3 Republic of India

Pharmacovigilance in India started in the year 1986 with the establishment of 12 regional centers that oversee areas with population sizes of approximately 50 million each (Kulkarni, 1986). These centers were vested with the authority to collect formal ADRs but failed to do so. In 1997, India Joined WHO's ADR reporting program based in Uppsala, Sweden, in order to participate healthily and to contribute to the effort. In 2005, the Ministry of Health and Family Welfare in India initiated the National Pharmacovigilance Program (NPP), coordinated by the Central Drugs Standard Control Organization (CDSCO) based in the national capital, New Delhi. This new program was established because of the failure of earlier attempts at pooling ADR reports on a national scale. The established NPP was again reviewed in July 2010 according to Biswas and Biswas (2007) and Gupta (2010). NPP was visualized to be rolled out in three phases:

- Phase I - to include 40 ADR Monitoring Centers (AMCs) in the program
- Phase II - to get 140 MCI (Medical Council of India) recognized medical colleges and teaching hospitals involved in the program by the end of 2011
- Phase III - to orchestrate and weave the program into the healthcare by the end of year 2013

ADRs collected at the AMCs will be relayed to the regional coordinating centers, which then would report the same to the Uppsala monitoring committee. The collected ADRs would be analyzed, and the data generated would be used to assess risk patterns, if any, like the population at risk. NPP will then circulate the data within the regulatory agencies,

allowing them to update warnings and drug labeling. So far, only 24 regional centers have been established in the country to serve NPP's purpose.

A close comparison of the US and UK pharmacovigilance programs with that of the Indian program reveal the fact that NPP in India is still at its infancy, and only in its first phase since its establishment in 2005. When compared with the rest of the world, ADR reporting percentage in India is only 1% (Prakash, 2007). One of the major reasons for this could be unawareness of ADR reporting guidelines/regulations on the part of the prescribers/medical practitioners. Another reason could be poor literacy rate of the population affecting their ability to read and understand drug labels and cautions written on the labels, and lack of support from the government at the county/district level to make it a success. Needless to say, incorporating pharmacovigilance concepts into the already extensive syllabi of Indian medical and pharmacy schools will be a difficult process for state governments. Nonetheless, doing so will equip medical/pharmacy professionals with tools to identify ADR signals during the first phase of clinical trials. Instituting a spontaneous ADR reporting system on par with those in the developed countries would be ideal for India as data of ADRs associated with marketed drugs can be pooled and analyzed rather easily and in short period of time with the help of spontaneous reporting tools, which in turn will help update the labeling on the drugs. This will help to lower the rate of morbidity and mortality besides reducing the budget spent on ADR management on the whole.

2.5 Past studies on ADR reporting systems (a review)

Numerous studies conducted in various parts of the world indicate that ADR reporting is not satisfactory, and has not reached the anticipated level in the nations with established pharmacovigilance programs. In the United States of America, Rogers et al.(1988) studied the knowledge, attitude and practice of 3000 physicians using a questionnaire. Out of the 1121 (37.3%) physicians that responded only 638 (57%) physicians knew about the FDA's established ADR reporting system. However, the study concluded that many of the physicians felt the reporting system was inconvenient. This inconvenience in the reporting system's functioning or the use of reporting system could lead to a prevalent underreporting of ADRs. While in another meta analysis conducted on a 32 year data on ADRs, Lazarou et al.(1998) concluded that 6.7% of ADRs reviewed were serious and 0.32% were fatal. They estimated that ADRs are one among the six leading causes of death in the United States of America. In a situation where ADRs contribute in a good proportion to mortality, poor practices of ADR reporting proves as a financial burden on the nation, besides being a threat to the lives of the public.

In the United Kingdom, Belton, Lewis, Payne and Rawlins (1995) studied 500 randomly selected doctors from the 1992 Medical Directory of UK to investigate their attitude towards CSM's ADR reporting scheme. They assessed the understanding of the doctors about the scheme and tried to identify the possible reasons behind underreporting of suspected ADRs. Out of the 284 (57%) respondents only 179 (63%) were stated to have previously reported ADRs to either the CSM or to pharmaceutical companies. They assessed that, though the number of reporting doctors was higher compared to other studies, a significant percentage of doctors lacked an understanding of the CSM's yellow card system, which they

thought was contributing to the underreporting of ADRs. They reported lack of time, lack of reporting forms and a misunderstanding on the part of doctors in maintaining confidentiality in the diagnosis of ADRs as the reasons for underreporting.

In India, Singh et al.(2010) observed the trend of ADR reporting with respect to a poly pharmacy at a tertiary care facility in Northern India and found that in a period of six months there were 154 ADRs recorded of which 23 (14.9%) were fatal. Gupta and Udupa (2011) cited only 2.9% of ADRs being reported in the city of Mumbai despite 90% resident doctors deemed it important to report ADRs to regional centers. They found that the resident doctors did not have adequate knowledge about the reporting responsibilities, type of events to be reported and mechanism of ADR reporting. They also cited the resident doctors' perception of the reporting process being time consuming, lack of knowledge and expertise as reasons for underreporting. Upadhyaya, Seth, Moghe, Sharma and Ahmed (2012) reported poor knowledge among postgraduate medical students regarding ADR reporting in India. They reported only 50% of the students were taught about ADRs and associated reporting system while only 50% were reported to have witnessed ADRs during their training. They suggested need to periodically check on the knowledge of ADR reporting of the medical students. Rehan, Vasudev and Tripathi (2002) in another study, suggested a need to improve the Knowledge, Attitude and Practice of medical students, despite the study revealed an adequate knowledge of ADR reporting among the students.

However, numerous studies conducted all through India have consistently shown poor practice or attitude among medical practitioners regarding ADR reporting despite their adequate knowledge about the system. Commonality among all the cited studies was that they were performed in metro or cosmopolitan cities. Very few, if any, were performed in tier-II

and tier-3 cities which only would give us a complete picture of the current National Pharmacovigilance Program's success so far.

Chapter 3: Methods

3.1 Study design

The study was designed as a cross sectional, observational, questionnaire based survey. A questionnaire was drafted based on earlier studies and in a way that best suites the Indian setting and the locality in question. All subjects could answer the questionnaire with ease. The questionnaire was administered to over 200 subjects, selected at random, so as to represent the sample (tier-II city selected) under study, and to have statistical validity.

3.2 Setting

The study was conducted in Warangal, a tier-II city in the southern-Indian State of Andhra Pradesh, inhabited by a population of 865,527 (Census of India, 2004). A total of over 820 medical practitioners, distributed throughout the city, provide medical care (through various specialties) to the population (IMA - Warangal branch). The study was conducted over a period of three months from October, 2012 to December, 2012. Entire area of the city of Warangal was covered which included East, West, Southwest and the Central zones.

3.3 Questionnaire Development

A questionnaire consisting of 33 questions framed under six sections was prepared, adapted from previous studies on ADR reporting systems in India. However, the final questionnaire for the present study was unique in many regards to suit the purpose of the study and Indian setting. The questionnaire was structured to collect the demographics of the respondents (subjects of study) limited to their gender, field of study, specialty, type of practice and their experience, to start with. The rest of the questions were framed under

sections-A through section-E that were designed to test the knowledge, attitude and current practice of doctors with regards to ADR reporting in the locality. A total of twelve questions were designed to evaluate the knowledge, three questions to test the experience they gained, three questions to assess their attitudes towards ADR reporting and ADR systems, six questions to evaluate their practice of ADR reporting and six questions to understand the factors, in their perspective, posed as a hindrance in an efficient pharmacovigilance program. (Appendix A).

Questions on knowledge would help in gaining information with regards to understanding the concept of pharmacovigilance, ADRs and guidelines and/or regulations pertaining to the ADR reporting system by the prescribers in the locality. Questions oriented on the practice of ADR reporting system and its establishment in a hospital/clinic gave an insight into current practices of pharmacovigilance by the practitioners as well as governance, with respect to ADRs, by the Health Administration in the locality. Two questions were structured specifically to understand how willing are the prescribers to take upon the responsibility of screening, diagnosing and reporting ADRs. A series of six questions were framed into a section that covered various factors, as possible reasons, in the prescribers' perspective.

In order to maintain confidentiality about the participants, the entire questionnaire was designed to maintain anonymity. Design of the questionnaire includes consideration of question format that is, open-ended or closed ended. Provision was also made for suggestions on ADR reporting system and its establishment within hospitals and clinics besides specifying the reason for not having the system established in the first place.

3.4 Approval of the study

An approval for this study was obtained from the Human Subjects Research Review Committee (HSRC), College of Health and Human Services at Eastern Michigan University on October 11, 2012 with respect to the initial submission made on August 27, 2012 (file # MS 1083) to comply with the guidelines of human subjects research established by the Eastern Michigan University (Appendix B).

3.5 Subjects

A total of 220 doctors were chosen randomly, from among 820 registered medical practitioners serving the locality. A list of contacts of all those registered practitioners was requested from the secretary of IMA (Indian Medical Association- Andhra region, Warangal Chapter). The contact list was edited (de-identified) to only include contact e-mail id's of the doctors and sorted for common id's, if any. Later 220 doctors were selected randomly using their contact email id's. The selected doctors included both government appointed and private practitioners.

3.6 Inclusion and Exclusion Criteria

An email was sent to each of these selected doctors with HTML link to the online survey. A letter accompanied each of these emails with a note for their informed consent. It was the doctors decision either to participate or withdraw from the study. Those who were not willing to participate in the study were suggested not to respond to the email sent. Those who had registered their response were deemed to have voluntarily participated in the study.

Subjects were also informed that in case they wished to participate but have lost the HTML link previously sent, they could request the HTML link via email and the same was furnished in the letter document that accompanied the emails. (Appendix C).

No specific inclusion and exclusion criteria were followed in the enrollment of subjects into this study except that subjects who did not answer the questionnaire were automatically deemed as excluded from the study.

3.7 Data collection and Statistical analysis

The questionnaire was validated by reviews from research guide, Dr. Irwin Martin and practicing doctors. Questionnaire was distributed to ten doctors and were given a period of four days to answer. They were requested to note the time taken to answer the questionnaire in full and were requested to express their perspective on the suitability of the questionnaire to local setting. Upon satisfactory feedback, the questionnaire was distributed without any major changes. Those ten recorded responses were added to the original data collected.

The questionnaire was distributed to all the subjects via email and were asked to register their responses in their free time. Considering the busy schedules of practicing doctors, all responses recorded in a 60 day time period were considered for the study, this was to give ample time for the subjects to participate in the study and to encourage non-respondents to participate in the study. Reminder emails were sent to non-respondents once in every two weeks. Responses recorded later than December 15, 2012 were not considered for the current study.

Data collected were analyzed using a software -Statistical Package for Social Sciences (SPSS) version 21.0. Results of the study were presented with descriptive measures such as

mean \pm standard deviation (for quantitative variables), median (for time related variables) and numbers with percentages and/or graphical presentations for categorical variables. All statistical analyses were performed at the Power of test at 80% and P value-0.05. Student T-test was used to compare means of two continuous variables. Chi-square test was performed to find the significant difference between the knowledge in ADR reporting system of private practitioners and government appointed doctors. Chi-square test was also used to find out the association between two attributes for yes or no questions at $P < 0.05$ significant level. Item scores were awarded and were added together to create a composite score to find out the significant difference between those two groups.

Chapter 4: Results

4.1 Demographic data

4.1.1 Response Rate

The survey was distributed to 220 doctors out of which 47 responses were registered, giving a 21.3% response rate. 30 respondents were male (64.8%) and 17 were female (36.2%). See Table 1.

Table 1: Frequency distribution of gender of participants

Gender	Frequency	Percentage
Female	17	36.2
Male	30	63.8
Total	47	100.0

This response rate was achieved only after reminders were sent at regular intervals (once in every two weeks) during the study period. More responses were recorded, comparatively, immediately after the reminders were emailed.

4.1.2 Type of Practice and Experience

A total of 27 subjects who responded to the study were doctors working in the government sector, that is in government run hospitals and/or clinics, which is an healthy 57.4%. On the other hand, a total of 14 (29.7%) respondents were private medical practitioners. See Table 2.

Table 2: Experience of study subjects in their respective specialties in medicine.

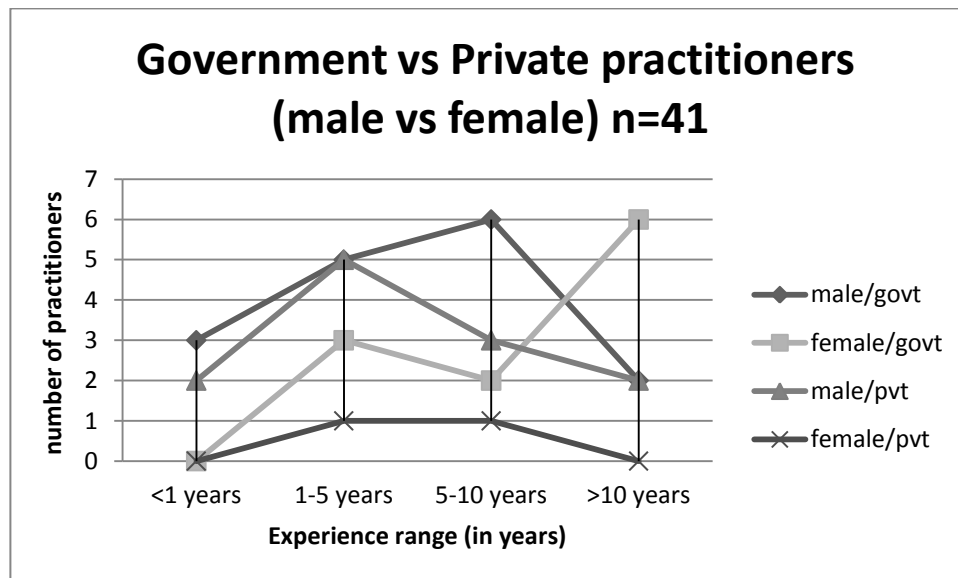
S.No	Experience (in Years)	Government practitioners		Private practitioners		Total	Percentage (%)	
		Male	Female	Male	Female			
1	<1	3	0	2	0	5	12.2	
2	1 - 5	5	3	5	1	14	34.2	
3	5 - 10	6	2	3	1	12	29.3	
4	> 10	2	6	2	0	10	24.3	
Total		16	11	12	2	41	100.00	

The rest of the six (6) responses recorded were by the staff of doctors. Five (5) of them were pharmacists and one (1) was a staff nurse. All the pharmacists worked in the private sector, of whom two (2) were male pharmacists and three (3) were female pharmacists. All pharmacists who responded to this survey on their doctors' behalf had 1 - 5 years of experience. The staff nurse who answered the questionnaire had greater than 10 years experience. The percentage response of non doctors was calculated to be 12.7% .

Average experience of both government doctors and private practitioners were calculated to be 6.75 years and 3.5 years respectively and the median of experience was 5.12 years. Combined average experience of male doctors was 7 years and that of female doctors

was calculated to be 3.25 years. However, there were a total of 6 (14.6%) female doctors with greater than 10 years of experience when compared to 4 (9.7%) male doctors with the same years of experience. Out of them, only 2 doctors had a private practice, the rest were working in the government run hospitals. A graph was plotted with number of practitioners against their years of experience in both private and the Government hospitals/clinics to observe a pattern, if any. Results are shown graphically in Figure 1.

Figure 1: Line graph showing differences in the range of experiences gained by doctors (male and female) in the government sector and private sector.



It is clearly evident from the graph that, comparatively, government doctors had more experience than the private practitioners. It was found that there were only two female doctors who have a private practice while there were 11 working on government run hospitals/clinics.

4.1.3 Specializations of respondents

It has been observed that 6 (12.7%) non-doctors have registered their responses on behalf of doctors whom they worked for. Assuming the fact that surveys were administered only to doctors, it hints that the doctors were too busy to answer the questionnaire and instead had their support staff answer the same which was anticipated. The other 40 (85%) of the responses were by doctors who specialize in different areas of medicine (Figure 2). A trend has been observed though. Doctors belonging to super specialties like Cardiology, Neurology and Endocrinology made up only 8% of the registered responses. Most of the responses were registered by people practicing internal medicine /OBGY/pediatrics/orthopedics.

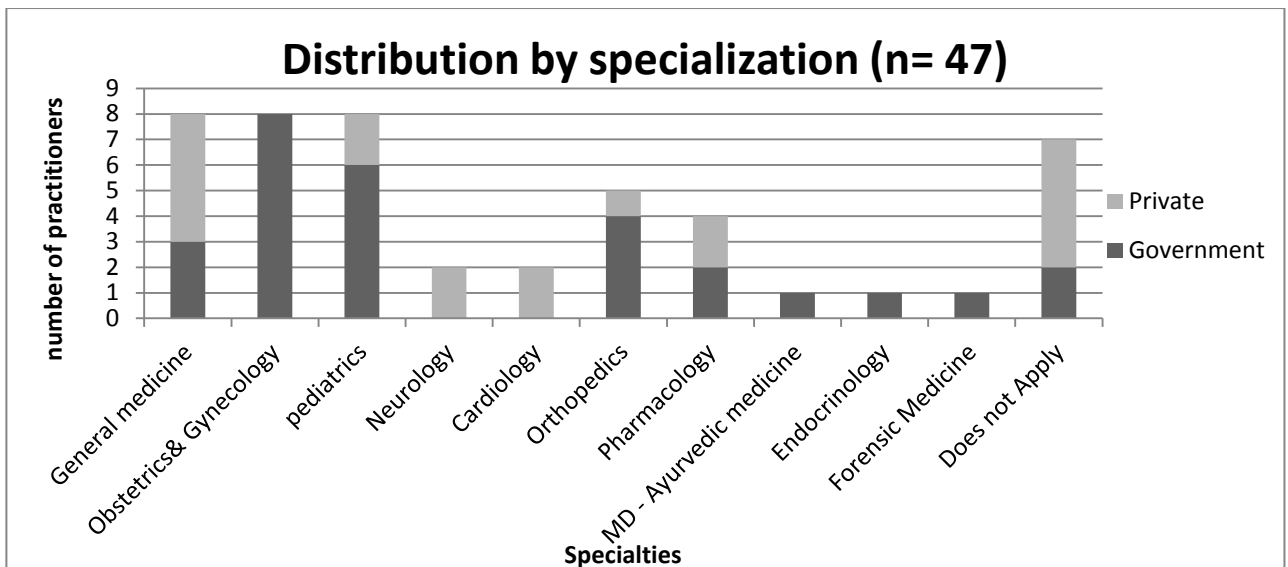


Figure 2: Distribution of number of respondents to survey by their specialization and type of practice

The graph validates random distribution of the survey with respect to the specialty of respondents with the fact that doctors specializing in Medical pharmacology, forensic medicine and Ayurvedic medicine were also surveyed.

4.2 Adverse Drug Reaction reporting - Knowledge

There were mixed responses from subjects to questions in this section. The responses are distinctive: 33 subjects (70%) reported they have observed ADRs in the past twelve months of which only 27 (57%, n= 47) diagnosed ADRs. More importantly, only 23 (48.9%) subjects have reported ADRs to either pharmacovigilance centers/pharmaceutical companies. The survey indicated that majority of the subjects observed less than 25 ADRs in a six month period. On the other hand, only 13% reported ADRs to pharmacovigilance centers and 28% reported to the companies.

A total of 34% respondents revealed that they neither had any information on current ADR reporting systems established in the area, nor had they any past knowledge in regards to ADR reporting systems. However, they all exercised knowledge of the country's guidelines and/or regulations pertaining to ADR reporting. Most of the respondents gathered information on ADR systems either verbally from colleagues (30%) or through Continuing Medical Education (CME) programs (23%). A total of 28% respondents were willing to update their knowledge with respect to the guidelines and/or regulations on ADR reporting. (See Table 3).

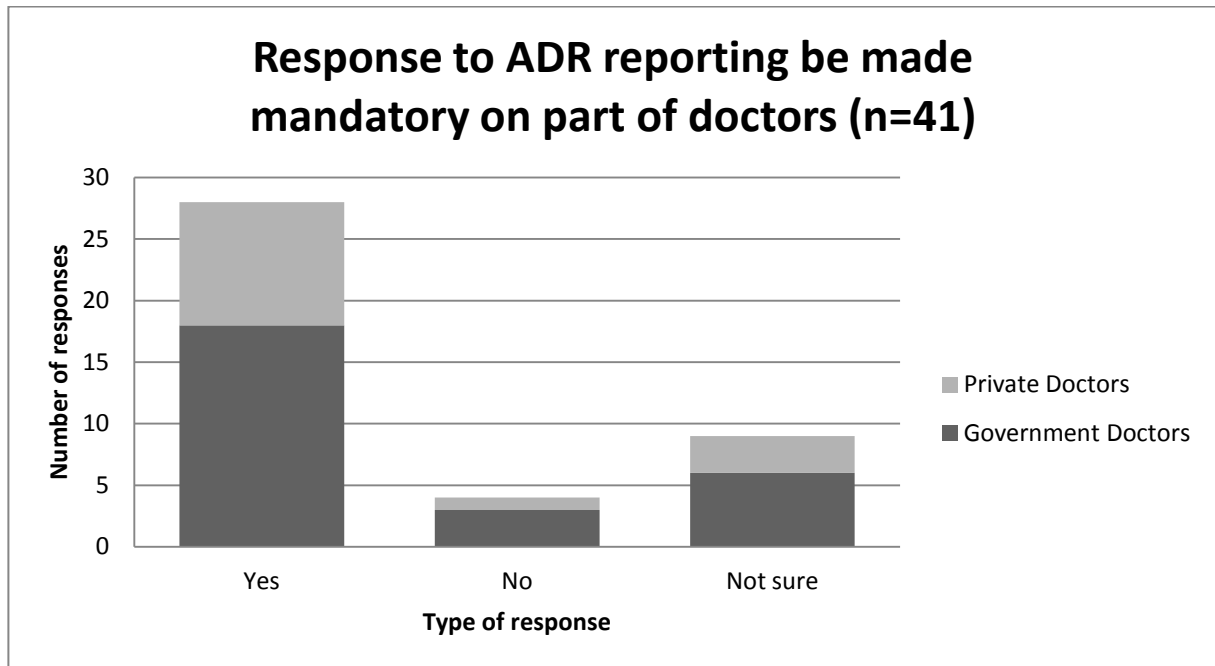
Table 3: Showing responses to questions 1-5 in section A (n=47 unless specified).

S. no	Questions	Yes	NO	Does not apply/do not remember / not sure
1	Have you observed ADRs in the past 12 months?	33	14	
2	Did you diagnose ADRs in the past 12 months?	27	10	10
3	Did you report ADRs to Pharmacovigilance centers or companies?	21	26	
4	Would you like ADR reporting be made mandatory on part of doctors? (n= 41)	28	4	9
5	Did you receive any information regarding ADR reporting in the past 12 months/ have you had past knowledge with regards to it ?	30	16	1

On the contrary, only 28 (68.2%) subjects liked the idea of ADR reporting being made mandatory, while 4 (9.7%) subjects did not like the idea, indicating the reason that they cannot devote time to report ADRs. Out of the 68.2% who liked the idea of ADR reporting be

made mandatory, most of them were inclined towards having their staff report ADRs to centers, while they themselves would diagnose and confirm ADRs. A total of 21.9% subjects were not sure if they would or would not like the idea of ADR reporting being made mandatory. Results are displayed graphically in Figure 3.

Figure 3: Bar chart showing response to ADR being made mandatory (n=41).



Nine subjects explained why they did not have an ADR reporting system established at their clinics/hospitals. It was evident that some were not aware of the system. One subject pointed to the lack of support from health administration and lack of initiative from hospital management as the reason for not having an established ADR reporting system. Most of the subjects were willing to report ADRs with the support of a clinical pharmacist.

4.3 ADR reporting - Attitude and practice

It was evident from the survey that most of the subjects had positive attitudes towards ADR reporting. Most of the subjects felt that doctors should report ADRs themselves. A total of 30 (63.8%) respondents out of 47 believed in doctors reporting ADRs to either pharmacovigilance centers or the pharmaceutical companies. With one question cross-referencing the reason for not having an established ADR reporting system at clinics/hospitals, the response of 10 subjects (21%) was that they are justified in thinking that pharmacists should report ADRs. The data is summarized and presented graphically in figure 4.

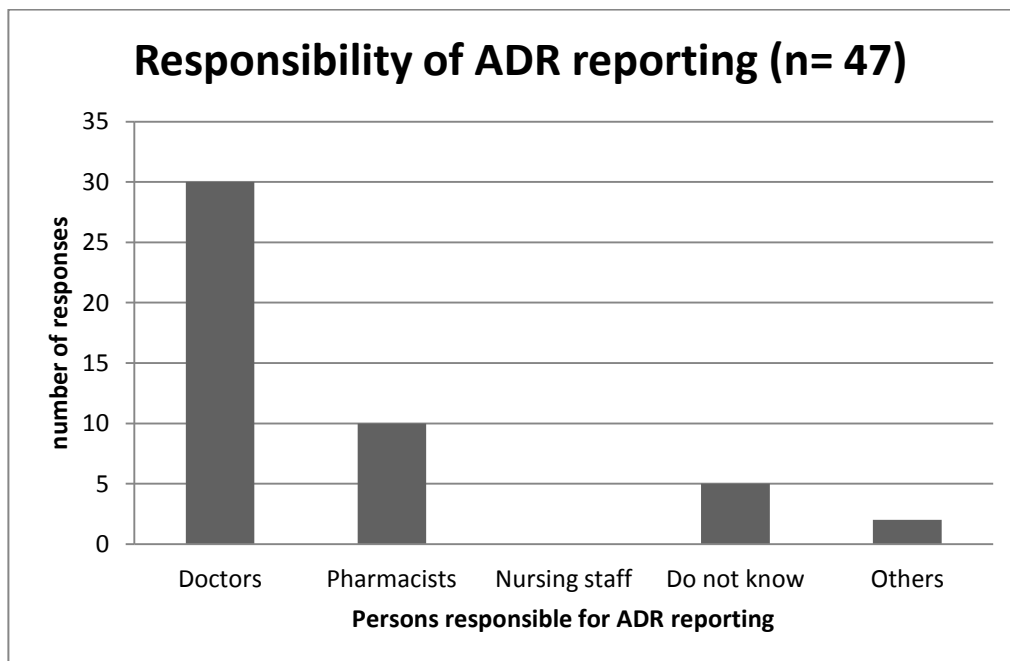


Figure 4: Bar graph representing the perspective of the subjects to ADR reporting being made mandatory on part of doctors.

4.4 Types of ADRs generally reported by subjects

Upon analysis, a significant difference was observed between the two groups (government and private practitioners) of doctors with regards to the type of reactions/medical occurrences they would generally report to either pharmacovigilance centers or pharmaceutical companies.

When asked if they would report any suspected serious reactions to an established product that they have observed, almost all the government doctors 27(96.4% within group) said they would definitely report such reactions, while only 1(3.6% within group) respondent said he/she might report such reactions. On the other hand, 14(73.7% within group) private practitioners answered they would definitely report and 5(26.3% within group) responded they might report (Table 4).

With regards to reporting all suspected reactions to new products, 19 (67.9% within group) government doctors said they would definitely report and 9(32.1% within group) said they might report. It was observed that a total of 12(63.2% within group) private practitioners said they might report all new suspected reactions to new products, while only 7(36.8% within group) answered they would definitely report such reactions. There lies a significant difference between the government and private practitioners in this regard (Table 4).

Similar to the responses registered for the first question in this section, 27 (96.4% within group) government doctors answered they would definitely report all life-threatening reactions and only 1(3.6% within group) responded he/she might report them. On the contrary, there were 6(31.6% within group) private practitioners who said they might report the reactions despite them being life threatening (Table 4).

Government doctors were consistent in their knowledge of what kind of reactions they feel should be reported, and a similar 27(96.4% within group) respondents said would definitely report reactions causing disability, and 1(3.6% within group) respondent said they might report reactions causing disability.

A mixed response was recorded when the subjects of this survey were asked if they definitely would, might or definitely would not report ADRs that cause initial or prolonged hospitalization. Close to 40% (within group) in either of the groups responded they might report such reactions, and specifically 3(15.8% within group) private practitioners said they definitely would not report such ADRs that cause initial or prolonged hospitalization. All the data were analyzed and summarized in Table 4.

Table 4: Chi-square analysis with calculated percentages within groups.

s.no	Type of ADRs	Type Of doctors	Recorded responses			Total	Chi-square value	p-value	Df
			Definitely Would report	Might Report	Definitely Would not report				
1	Serious suspected reactions to established products	Govt.	27 (96.4%) 0.5 (SR)	1 (3.6%) - 1.4 (SR)	-	28	5.258	0.022	1
		Pvt.	14 (73.7%) - 0.6 (SR)	5 (26.3%) 1.7 (SR)	-	19			
2	All suspected reactions to new products	Govt.	19 (67.9%) 0.9 (SR)	9 (32.1%) - 1.0 (SR)	-	28	4.405	0.036	1
		Pvt.	7 (36.8%) - 1.1 (SR)	12 (63.2%) 1.2 (SR)	-	19			
3	Life threatening reactions regardless of product age	Govt.	27 (96.4%) 0.6 (SR)	1 (3.6%) -1.6 (SR)	-	28	7.005	0.08	1
		Pvt.	13 (68.4%) -0.8 (SR)	6 (31.6%) 1.9 (SR)	-	19			
4	Disability (significant, persistent or permanent) - regardless of product age	Govt.	27 (96.4%) 0.5 (SR)	1 (3.6%) -1.4 (SR)	-	28	5.258	0.22	1
		Pvt.	14 (73.7%) -0.6 (SR)	5 (26.3%) 1.7 (SR)	-	19			
5	Hospitalization (initial or prolonged) regardless of product age	Govt.	17 (60.7%) 0.4 (SR)	11 (39.3%) 0.1 (SR)	0 (0%) - 1.3 (SR)	28	4.803	0.91	2
		Pvt.	9 (47.11%) - 0.5 (SR)	7 (36.8%) - 0.1(SR)	3 (15.8%) 1.6 (SR)	19			

(SR = Standard Residual, df = Degree of freedom).

From table-4, it can be inferred that the Chi-square significance between the government doctors and private practitioners, with regards to the type of ADRs they would generally report, was significant with $n=47$, $df=2$, (total) $\chi^2=26.729$, $p < 0.05$. There was no significant difference though between the government doctors and private practitioners with regards to reporting such ADRs that lead to either initial or prolonged hospitalization, with a $\chi^2=4.803$, $p > 0.05$ at a 2 level degree of freedom.

Though the Chi-square turned out to be significant for variables 1, 3 and 4, each of the 2x2 tables had at least 2 cells with expected count < 5 that make the data invalid. Upon observation, with a standard residual 1.7, 1.9 and 1.7 (all close to 2) respectively, these groups of private practitioners influenced this outcome.

4.5 Factors that encourage ADR reporting

Reactions to new products and seriousness of the reactions were the two factors that encouraged ADR reporting as per the results. On the other hand, unusual reactions and degree of confidence in diagnosis of ADRs were not a major factor that influenced ADR reporting.

A total of 27(96.4% within group) government doctors felt that seriousness of the reactions to products does influence their reporting of ADRs, while a similar percentage, 14 (94.7% within group) of private practitioners, felt the same. There was no significant difference between these two groups in this regard with a χ^2 value of 2.156 at a 2 level degree of freedom and $p > 0.05$ (Table 5).

There was also no significant difference in the opinion of both groups regarding the influence of degree of confidence in the diagnosis of ADRs. A total of 8(28.6% within group) government doctors and 7(36.4 % within group) private practitioners felt there is no necessity

to report the degree of confidence in diagnosing ADRs and that it does not influence their reporting of ADRs. (Table 5).

However, there was a significant difference between government doctors and private practitioners regarding the influence of unusual reactions on reporting with a χ^2 value of 7.404, $p < 0.05$ (n= 47). Table 5 illustrates the analysis of factors influencing ADR reporting.

Table 5: Chi-square analysis of factors that encouraged ADR reporting.

S.no	Factors	Type of Doctors	Recorded responses			Total	Chi-square	P-value	Df
			Not required	Required	Unsure				
1	Unusual reactions	Govt.	1 (36%) -1.4 (SR)	23 (82.1%) 0.2 (SR)	4 (14.3%) 1.0 (SR)	28	7.404	0.025	2
		Pvt.	5(26.3%) 1.7 (SR)	14 (73.7%) - 0.2 (SR)	0 (0%) - 1.3 (SR)	19			
2	Reactions to new products	Govt.	0 (0%) - 1.3(SR)	24 (85.7%) 0.3 (SR)	4 (14.3%) 0.2 (SR)	28	4.749	0.093	2
		Pvt.	3(15.8%) 1.6 (SR)	14 (73.7%) - 0.3 (SR)	2 (10.5%) - 0.3 (SR)	19			
3	Seriousness of the reactions	Govt.	1 (36%) 0.5 (SR)	27 (96.4%) 0.0 (SR)	0 (0%) - 0.8 (SR)	28	2.156	0.340	2
		Pvt.	0 (0%) - 0.6 (SR)	18 (94.7%) 0.0 (SR)	1 (5.3%) 0.9 (SR)	19			
4	Degree of confidence on diagnosis of ADRs	Govt.	8(28.6%) - 0.3 (SR)	18 (64.3%) 0.5 (SR)	2 (7.1%) - 0.2 (SR)	28	2.432	0.488	3
		Pvt.	7(36.8%) 0.4 (SR)	9 (47.4%) - 0.6 (SR)	2 (10.5%) 0.3 (SR)	18			

(SR = Standard Residual, df = Degree of freedom).

Similar to the earlier section, Chi-square turned out to be significant for the first variable despite an expected count of 4 cells < 5 (1.62). Cumulative $\chi^2 = 16.741$, $n = 47$, $p > 0.05$.

4.6 Factors affecting ADR reporting

Unavailability of ADR reporting forms was considered as one of the major factors affecting the overall reporting rate as represented by the data. However, the rest of the factors also turned out to be contributing to the low ADR reporting rate.

Chi-square association was found to be insignificant with a cumulative $\chi^2 = 18.669$, $p > 0.05$, $n = 47$ except for variable (factor) 6, which turned out to be significant with $\chi^2 = 8.196$, $p < 0.05$. But, the data would be considered invalid as none of the calculated standard residuals were ≥ 2.0 , and also for the 6 variables in question, the expected count was found to be a minimum of 2 cells less < 5 .

However, for the sixth variable, the Chi-square was significant at $p < 0.05$ with a value 8.196. But, there was not much difference in the standard residual value, and the private practitioners in particular contributed to the significance which reiterates the inequality in the distribution of the sample. Results are tabulated in table 6.

Table 6: Chi-square analysis of factors affecting the ADR reporting (system or practice)

S. no	Factors	Type of Doctors	Responses			Total	Chi-Square	p-value	Df
			Agree	Disagree	Neither agree nor disagree				
1	System of reporting is too bureaucratic	Govt.	7 (25%) - 0.1 (SR)	6 (21.4%) 0.6 (SR)	15 (53.6%) - 0.3 (SR)	28	0.979	0.613	2
		Pvt.	5 (26.3%) 0.1 (SR)	2 (10.5%) - 0.7 (SR)	12 (63.2%) 0.3 (SR)	19			
2	Too busy to send an ADR report	Govt.	1 (3.6%) - 1.1 (SR)	15 (53.6%) 0.0 (SR)	12 (42.9%) 0.6 (SR)	28	4.110	0.128	2
		Pvt.	4 (21.1%) 1.4 (SR)	10 (52.6%) 0.0 (SR)	15 (26.3%) - 0.7 (SR)	19			
3	Report forms not available when needed	Govt.	14 (50%) - 0.8 (SR)	11 (39.3%) - 0.6 (SR)	3 (10.7%) - 0.3 (SR)	28	2.636	0.268	2
		Pvt.	5 (26.3%) - 1.0 (SR)	11 (57.9%) 0.7 (SR)	3 (15.8%) 0.4 (SR)	19			
4	Feel that you would be exposed to legal liability by reporting an ADR	Govt.	2 (7.1%) 0.2 (SR)	23 (82.1%) 0.1 (SR)	3 (10.7%) - 0.3 (SR)	28	0.305	0.858	2
		Pvt.	1 (5.3%) - 0.2 (SR)	15 (78.9%) - 0.1 (SR)	3 (15.8%) 0.4 (SR)	19			
5	Believe that only safe drugs are	Govt.	1 (3.6%) - 0.9 (SR)	24 (85.7%) 0.2 (SR)	3 (10.7%) 0.4 (SR)	28	2.443	0.295	2

	marketed	Pvt.	3 (15.8%) 1.1 (SR)	15 (78.9%) - 0.2 (SR)	1 (5.3%) - 0.5 (SR)	19			
6	Unsure how to report an ADR	Govt.	7 (25%) 1.4 (SR)	17 (60.7%) 0.1 (SR)	4 (14.3%) - 1.2 (SR)	28	8.196	0.017	2
		Pvt.	0 (0%) - 1.7 (SR)	11 (57.9%) - 0.1 (SR)	8 (42.1%) 1.4 (SR)	19			

(SR = Standard Residual, df = Degree of freedom).

Chapter 5: Discussion

In the interest of public safety, the formidable strength of ADR reporting systems is its ability to continuously and spontaneously collect all such undesired reactions associated with drugs throughout their life cycles. Though the concept of pharmacovigilance emerged in the mid 1900's, it has been observed, throughout the world, that many factors influence doctors in reporting ADRs, and often the reporting rate was low.

In India, the concept of pharmacovigilance is relatively new, compared to the other developed nations like the UK and USA. Despite reviewing the NPP in the year 2010, there was a predominant under-reporting of ADRs in India, according to studies by Rishi, Patel and Bhandari (2012) and Karkhar and Bowelakar (2012). Other studies conducted in the cities of Mumbai, Mysore and Muzzafarnagar, as reported by Desai et al. (2011) have shown high knowledge but poor practices with regards to ADR reporting. This study was an attempt to understand and compare, between government doctors and private practitioners, the knowledge, attitudes and practices with regards to ADR reporting in a Tier-II city. This study has found that both the government and private doctors have an adequate knowledge and possessed positive attitudes towards ADR reporting systems, but their practices were poor (with some exceptions).

The overall response rate was 21.3%, which is less compared to other survey's administered by Desai et al.(2011), who documented a 61% response rate and another similar survey by Gupta and Udupa (2011) who reported a response rate of 77.2% (which were similar to rates documented in studies from Germany, United Kingdom, Italy, Nigeria and the Netherlands). But, the ratio of male to female respondents to this survey was comparable to

other studies that recorded similar frequencies of male and female participants. However, this response rate was indicative of the factors affecting the practice of ADR reporting by both groups of doctors. Having said that, this could be a rather satisfactory response rate following repeated reminders sent every two weeks, given the limitations of this study.

A total of 27 (57.4%) government doctors and 14 (29.7%) private doctors responded to this survey. The comparison could have been effective had the percentage of respondents in the private practitioners group increased. It was understood that many doctors working in the government run hospitals also had a private practice of their own, but instead, chose to be identified as government doctors. A choice was given in this regard to study subjects in the study consent: if they wished to be identified as a private practitioner or as a government doctor when they fulfilled both, and as a result we see a higher number of responses registered in the group of government doctors.

The average practice experience of government doctors was high with 6.75 years of experience, while the private practitioners only had an average of 3.5 years of experience (Figure1). This could be attributed to the fact that government institutions (hospitals/clinics) relied on experienced doctors to treat patients in need of treatment and believed that the more the experience, the greater the skill a doctor has. An interesting observation was that there was a greater number of female government doctors with greater than 10 years of experience compared to male doctors. Many of the private practitioners had an experience ranging between 1-10 years, and there were only two private practitioners who reported they had greater than 10 years of experience (Table 2). A proper statistic, with regards to this difference in the experience gained, could only be obtained with a bigger sample size. Nonetheless, it had been observed that knowledge of ADRs and their reporting systems is

directly proportional to the experience gained through years of medical practice, based on a report by Upadhyaya et al. (2012) who stated that medical students had poor knowledge of ADRs/their reporting systems, while in another study, Rehan, Vasudev and Tripathi (2002), stated a need to incorporate a detailed concept of pharmacovigilance in the undergraduate medical curricula besides periodically strengthening this concept among the doctors.

Though the sample population was selected randomly (Figure 2), there were only a few respondents from specializations like cardiology, oncology, neurology etc. where there is large scope for occurrence of ADRs, owing to the fact that drugs used in the treatment of cardiovascular events or cancers or neuronal disorders are often potent chemical entities and exert a wide range of undesirable effects on the organ system and/or body. This low response to the survey from doctors belonging to these super-specialties might be due to their busy schedules. However, in the context of ADR reporting, it is important to devote quality time in reporting all those ADRs associated with the prescribed drugs despite busy schedules.

A majority of the doctors, indicated by the survey, observed less than 25 ADRs in a period of six months, which was a positive reflection on the knowledge, skill and awareness about ADRs among the doctors. However, only 57% of the doctors ever diagnosed ADRs and only 48% ever reported them. A majority (28%) of the respondents said they reported ADRs to pharmaceutical companies and only few reported ADRs to pharmacovigilance centers. This is a concern, as it reflects the failure of the NPP program. Few doctors reporting to pharmacovigilance centers might indicate poor knowledge with respect to the NPP program, which is consistent with the finding of 34% doctors' lack of information on the current ADR reporting systems established in the country. Though all the subjects of this study exercised adequate knowledge of the country's guidelines pertaining to ADR reporting, lack of

information on the current practices of ADR reporting reflects their low interests in reporting the otherwise burdensome ADRs. This emphasizes the need to extravagantly propagate the established NPP program and the ADR reporting systems by creating awareness among the prescribers of the program and the systems. This is possible by regularly organizing CME programs with an emphasis on pharmacovigilance as a majority of the study subjects stated their intention to update their knowledge with respect to the guidelines and/or regulations on ADR reporting via CME programs, indicating a broad scope for change in their present attitudes towards reporting ADRs.

On the contrary, only 48% of doctors reported ADRs to either pharmacovigilance centers or pharmaceutical companies which is comparatively low. In a pilot study conducted by Kharkar and Bowalekar (2012), 19% of their subjects were found to have reported diagnosed ADRs to ADR/pharmacovigilance centers while a majority of their respondents, (89.7%) were said to have reported ADRs to pharmaceutical companies/DGCI/ other NGO's who have a statutory obligation to report to the drug authorities concerned. These figures are, however, low compared to other countries like the UK where a high spontaneous ADR reporting rate was recorded. Also reporting rates in relation to prescription volumes was best among the European countries (Rishi et al., 2012). Ramesh and Parthasarathi (2009), estimated that only 10% of serious ADRs and 2-4% of non-serious ADRs are being reported, which is a rather high rate of under-reporting. Though doctors did not personally cite reasons for underreporting, they could be among the "seven deadly sins" summarized by Inman (1996) as :

- Ignorance - not obtaining information on how to report ADRs despite their feeling that they are unsure how to report ADRs

- Diffidence - feeling foolish to report suspected ADRs
- Fear of exposure to legal liability
- Lethargy - being of the opinion that they are too busy to report ADRs
- Guilt of unknowingly causing harm to the patient
- Ambition of collecting the information on ADRs to publish them to their credit and
- Complacency - being of the opinion that only safe drugs are marketed

Among these, lethargy could be assumed to be the reason for underreporting in this tier-II city, as there was a low response to this survey from doctors practicing super-specialties, as mentioned earlier, and also that there were 12.7% (6) responses registered by other medical/health care staff on behalf of the doctors they work for, though this survey was only administered to doctors. This indicates that the doctors were either ignoring to respond to the survey, or were too busy to respond, and hence had their staff answer the questionnaire. This is supported by the results that 9.7% (4) respondents did not like the idea of ADR reporting to be made mandatory on part of doctors (Table 3).

Interestingly, however, 68.2% respondents liked the idea of ADR reporting be made mandatory on part of doctors and 21.9% of them were not sure if they liked this idea, which was similar to the findings by Rishi et al. (2012). Out of the 68.2% who would like ADR reporting be made mandatory, many inclined toward taking the help of their support staff, especially clinical pharmacists, in reporting ADRs. This was inferred from the explanation of one of the respondents, who said, "An ADR reporting system need to be established at the clinic, with an office directly under the supervision of a clinical pharmacist." Another

respondent also stated the absence of clinical pharmacist in their clinic, as one of the reasons for not having an established ADR reporting system at their place.

This also indicates that most of the respondents (68.2%) had positive attitudes towards ADR reporting/systems, which is consistent with the findings in a study carried out by Rishi et al. (2012). The respondents' intention of the involvement of clinical pharmacists' in reporting ADRs, found in this study, was similar to a study conducted by Amrita and Roomi (2011) who reported, from various other studies, that for the success of pharmacovigilance programs involvement of pharmacists is essential. According to Grootheest et al. (2004), underreporting of ADRs could be lowered with considerable surveillance of the system by pharmacists. So, involving pharmacists in reporting ADRs can be considered pivotal in tackling the menace of underreporting in the first place. Pharmacists also play a major role in the detection of ADRs and contribute their part in reducing the occurrence of ADRs as found by Shulman, Shulman and Haines (1981). In their study, they found that pharmacists detected 83 potential ADRs, and suggested general practitioners to change the prescription to avoid ADRs in another 53 cases. They also found pharmacists being instrumental in detecting 76 unwanted prescription errors in their meta analysis of 1,366 patient medication records, collected over a period of 3 years, at a local pharmacy. They suggested that a closer collaboration between doctors and pharmacists would be mutually beneficial, while addressing the issue of ADRs.

In this study, a significant difference was observed ($N= 47$, $df= 2$, [total] $\chi^2= 26.729$, $p < 0.05$) between the government doctors and private practitioners with regards to the knowledge they possess about ADRs and ADR reporting systems. The government doctors had, comparatively, more knowledge about the types of ADRs that need to be reported than

the private practitioners. However, it appears that both government and private doctors need to reinforce their knowledge on the current systems of ADR reporting and keep themselves abreast of knowledge with regards to the types of ADRs associated with drugs they usually prescribe. Most of the respondents from either group, if not few, said they might report, or definitely would not report, drug reactions causing initial or prolonged hospitalization. In this regard, there is a definite need to make these doctors understand the economic burden caused by such hospitalizations on the state government or health administration. It is important to note that in the year 2007, the average cost per ADR per patient was calculated to be ₹ 481 (€6) by Arulmani et al. On the contrary, this difference could not be taken for granted, as a particular cell in the 2X2 table (Table 4) represents a group of private practitioners who influenced the outcome. As such, a definite statistic eliminating such influences could only be obtained with a larger sample size or a greater number of responses.

While most of the doctors identified reactions to new products and seriousness of the reactions as factors while reporting ADRs, many private practitioners did not consider unusual reactions to products worth reporting, which most of the time could turn out to be serious ADRs associated with drugs (Table 5). In this regard, government doctors had a good knowledge. These findings were in contrast with those in the study conducted by Rishi et al. (2012) where physicians were found to be more likely to report suspected ADRs for serious, unknown reactions/events for new drugs (81%) and serious, unknown reactions for established drugs (73%). When assessing the factors considered to affect the ADR reporting by doctors (Table 6), unavailability of ADR report forms, feeling that the system is too bureaucratic and busy schedules were cited predominantly, which are in line with the findings of Rishi et al. (2012) where 22.3% of respondents cited their busy schedules as reason for

underreporting and 2.1% of respondents cited the bureaucratic system as being the reason. Interestingly 8.5% (4) respondents believed only safe drugs are marketed, while a vast majority thought not all marketed drugs are safe. This obviously warrants a need to strictly enforce pharmacovigilance in their practice. Though many considered all marketed drugs are not safe, underreporting of ADRs still exist.

These results suggest a need to improve the practice of pharmacovigilance in the best interest of public safety in this tier-II city. With an insight into the factors affecting ADR reporting, there could be a possibility to come up with suggestions that might help improve the present trend in pharmacovigilance in this tier-II city of Warangal, of course with the limited information gathered via this survey. Some of the suggestions are:

- Offering incentives to doctors for regularly reporting ADRs. This will definitely up-gear the practice of reporting, as many doctors think devoting time to reporting ADRs might, in a way, affect their time spent in earning money
- Periodically conducting CME programs with good emphasis on the concept of Pharmacovigilance and the concept of ADRs. It can be observed from the results that about 28% of the respondents stated their willingness to update their knowledge through CME programs. This in particular, will have an immense response as many doctors do attend CME's to update their medical knowledge
- Establishing spontaneous ADR reporting systems (electronic/paper - like the yellow card system established by the CSM in UK) in hospitals and clinics and

offering training, in the first place, on the working of such systems to doctors and their medical staff

- Assuring all the doctors that they will not be held legally liable for discrepancies in any such ADR reports
- Improving the system of pharmacies from merely filling prescriptions and dispensing to taking part in decision making during writing prescriptions as a primary care team member (Amrita and Roomi, 2011)
- Offering clinical pharmacists good training in ADRs and their reporting systems and also incorporating the same in their curricula. Clinical Pharmacists often make good supervisors for ADR reporting systems given their knowledge about drugs and their interactions (Amrita and Roomi, 2011)
- Periodically sending feedback to reporters on all the data gathered by NPP. This will definitely have a positive impact as it gives assurance to all the reporters that each and every ADR report is being considered, in-turn, to update their knowledge. Doing so will also improve the working of NPP, ultimately paving the way to its success (Amrita and Roomi, 2011)
- Sending warning letters or notifications to doctors regarding serious ADRs associated with drugs, immediately upon obtaining information from drug authorities/Pharmacovigilance centers (Amrita and Roomi, 2011)
- Educating patients about ADRs and encouraging them to participate directly in spontaneous ADR reporting. As it is believed that patients themselves will have a better understanding of how ADRs / related events affect their lives/life styles (Blekinsopp, Wilkie, Wang and Routledge, 2006)

Chapter 6 : Conclusion

There is a significant difference between government doctors and private practitioners in the tier-II city of Warangal, with regards to the knowledge of ADR reporting systems. Government doctors exhibited good knowledge of ADRs and current ADR reporting systems established in the nation, while private practitioners had a little knowledge of current systems in place. However, all the doctors surveyed do have knowledge of the guidelines and/or regulations pertaining to ADR reporting in India. Both groups of doctors had positive attitudes towards reporting ADRs, as a majority of them were open to the idea of ADR reporting being made mandatory on the part of doctors. However, some of them inclined towards having their support staff like pharmacists and/or nursing staff, report ADRs on their behalf which was also evident from 6 responses registered by non doctors in a survey drafted only for doctors. There is a need to improve the concept of pharmacovigilance in this city, which requires the participation of CDSCO via the NPP program.

The underreporting of ADRs in this city can be attributed to several factors as discussed earlier, but it would be inappropriate to generalize those factors and suggest ways to improve the situation based on a pilot study like this, which has certain limitations according to Launiala (2009). This was evident when a smaller group of private practitioners influenced the statistics. However, implementing the discussed suggestions would surely improve ADR reporting in this city, by motivating doctors to rigorously participate in pharmacovigilance programs in the best interest of public safety. There is also a need to conduct more research, with a larger sample size, including the adjacent cities, to the immediate North and South of this City. This would give a good sample size of doctors as these cities make the central zone

of the District of Warangal. Also, with a larger sample size, there is a possibility of a greater response rate and close to equal participation within both the groups of doctors.

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5- How long have you been practicing?

- a. < 1 year b. 1-5 years
c. 5-10 years d. > 10 years

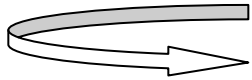
Section A: Adverse Drug Reaction (ADR) Reporting

1- During the past 12 months, have you observed any adverse drug reaction with any drug?

- a. Yes b. No

2- If a Physician, have you ever diagnosed an adverse drug reaction in a patient under your care in the past 12 months?

- a. Yes b. No c. Does not apply



If yes, on an average how many ADRs would be diagnosed under your care in a period of 6 months?

- a. < 25 b. 25 - 75
c. 75 -125 d. > 125

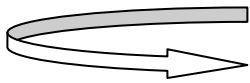
3- During the past 12 months have you reported an ADR either to a Pharmacovigilance center or a Pharmaceutical Company?

- a. Yes b. No.

4- To whom did you send adverse drug reaction reports?

- a. To nearest Pharmacovigilance centers
b. To pharmaceutical company
c. Both

5- Did you receive any information regarding ADR reporting in the past 12 months or have you had past knowledge of ADR reporting system?



- a. Yes b. No c. Do not remember

If yes, what type of information?

- Written information in medical handbooks
- Verbal information from colleagues
- Through CEP programs

If No, Are you familiar with your country’s Guidelines and/or regulations pertaining to ADR Reporting?



- a. Yes b. No

If No, Would you consider updating your knowledge about your countries’ established system of ADR reporting through CEP programs?

- a. Yes b. No

6- If you have a private practice, do you have any established ADR reporting system at your clinic?



- a. Yes b. No c. Does not apply

If No, What was the reason for not having an ADR reporting system in place at your clinic? Please specify _____

Please proceed to section C.

Section B: ADR System at hospital/clinic

7- How long current ADR system has been operating in your hospital/ clinic?

- a. < 1 year b. 1-2 years
 c. 2-5 years d. > 5 years

8- Are records of ADR reports stored in the hospital/clinic?

- a. Yes b. No c. Do not know

9- Does your system involve screening laboratory results to detect ADRs?

- a. Yes b. No c. Do not know

10- Are ADR reporting forms available in the hospital?

- a. Yes b. No

11- Is there any acknowledgement for reporting an ADR in your hospital?

- a. Yes b. No

12- Who is the person responsible for screening ADR reports and

Submitting the same to the nearest Pharmacovigilance Centre?

- a. Doctors b. Pharmacists
 c. Nurse d. Other (specify) _____
 e. Do not know

Section C: Type of ADR's you would generally report to either Pharmacovigilance centers or Pharmaceutical companies (who manufacture the product that causes such ADRs)?

s.no	Types of ADRs	Definitely would report	Might report	Definitely would not report
1.	Serious suspected reactions to			

	established products			
2.	All suspected reactions to new products			
3.	Life-threatening reactions (risk of death) regardless of product age			
4.	Disability (significant, persistent or permanent) regardless of product age			
5.	Hospitalization (initial or prolonged) regardless of product age			

Section D: Which of the following factors do you think are required to be submitted in an ADR

Report?

S.no	Factors	Required	Not required	Unsure
1.	Unusual reactions			
2.	Reaction to new products			
3.	Seriousness of the reactions			
4.	Degree of confidence in diagnosis of ADR			

Section E: Factors that pose as a hindrance to you in reporting ADRs?

s.no	Factors	Agree	Neither agree nor Disagree	Disagree
1.	System of reporting too bureaucratic			
2.	Too busy to send an ADR reports			
3.	Report form not available when needed			
4.	Feel that you would be exposed to legal liability by reporting an ADR			
5.	You believe that only safe drugs are marketed			
6.	Unsure how to report an ADR			

Appendix B: Letter of Approval from HSRC

Approval Letter from the Chair of CHHS – HSRC:

Date: Thu Oct 11 2012

Subject: MS #1083 - College of Health and Human Services Human Subjects

From: Gretchen Dahl Reeves

Decision: Accept Submission

Dear Shanthan,

Congratulations! After careful review, your proposal "Pharmacovigilance: A comparative study about the knowledge of Adverse Drug Reaction (ADR) reporting that Private practitioners and Govt. Doctors gained in a random locality in India" has been accepted by the College of Health and Human Services Human Subjects Review committee. We stress that you do not stray from your proposed plan.

The current version of your paper is available here:

http://commons.emich.edu/cgi/preview.cgi?article=1083&context=chhs_hs

To submit revisions, use the Revise Submission link on that page.

Good luck with your research effort.

Sincerely,

Gretchen Reeves, PhD.

Chair, CHHS-HSRC

Appendix C : Cover Letter

Good Morning !

I am Shanthan Pingili, pursuing my MS in Clinical Research Administration at Eastern Michigan University (USA) and as part of my Thesis I've proposed a survey research here in India. My survey is designed to compare the knowledge of ADR reporting system that private and government doctors have gained and also to assess the factors that affect the proper functioning of the above said system in this tier-2 city of Warangal.

You were randomly selected for this survey and I request your participation. The questionnaire is self-explanatory and should not take more than 5 - 10 minutes to answer. This is an anonymous survey and no identifying information, what so ever, is being requested. This is an absolutely no risk survey and your esteemed participation will help in understanding the current status of ADR reporting system in this city of Warangal. To collect valuable statistical data, government doctors who also practice privately, can wish to be identified either as a government doctor or as a private practitioner.

The responses registered prior to December 15, 2012 are considered for data analysis. All subjects who register their responses are deemed as included in this study. If you wish not to participate in this survey, do not register your responses and are deemed as excluded from this survey study.

Below is the Link for the survey questionnaire:

Pharmacovigilance: A comparative study about the knowledge of Adverse Drug Reaction (ADR) reporting that Private practitioners and Govt. Doctors gained in a random locality in India.

<https://docs.google.com/spreadsheet/viewform?formkey=dDZBZjI4ek5uT3I0ZGtUd2FfeVBoaWc6MQ>

In case you lost the link, email me at shanthan.bharadwaj@gmail.com and I will re-send the link to this survey.

Thank You for your time and support.

PN: your advice/suggestions regarding this survey is sincerely appreciated.

Regards

Shanthan B Pingili

MS in clinical Research Administration

Eastern Michigan University

