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A SITUATIONAL ANALYSIS OF PHARMACOVIGILANCE SYSTEM IN GEORGIA

Master's thesis

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GEORGIA RAVIMIOHUTUSE JÄRELVALVE OLUKORRA ANALÜÜS

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Author’s declaration of originality

I hereby certify that I am the sole author of this thesis. All the used materials, references to the literature and the work of others have been referred to. This thesis has not been presented for examination anywhere else.

Author: Shota Jibuti

12.05.2018

Abstract

Introduction

Political, economic and social changes in Georgia, lower-middle-income country, had a great impact on the health care coordination. Pharmacovigilance principles and safe drug use promotion activity still stays as a one of the main problem of the country, because of specific organizational aspects. In Georgia, pharmacovigilance system was established in 1997. But currently underreporting of adverse drug reactions (ADRs) still stays one of the widespread and a scaring challenge. The core purpose of the thesis work is to evaluate an actual pharmacovigilance situation in Georgia, aimed to determine the level of general knowledge, practice performance and attitude of health care providers, in particular, medical doctors towards pharmacovigilance and the sub aim is to determine the purpose of under reporting, faced by MDs towards ADR reporting.

Methods

The cross-sectional analytical study and focus group interviews were carried out in Georgia. The developed questionnaire was designed to be anonymous, well-structured and self-administrated, sent to 170 MDs selected randomly.

Results

The results of the study undoubtedly pointed out that in spite of the MDs positive attitude there was an absence of suitable knowledge and practice to ensure ADRs reporting effectively.

Summary

The result of the conducted study shows that most of the MDs have poor and insufficient knowledge and practice performance level regarding pharmacovigilance system and ADR reporting. The study findings also demonstrates that pharmacovigilance system legislation requirements in Georgia still stay on the paper and unfortunately, currently does not work in practice.

This thesis is written in English and is 63 pages long, including 7 chapters, 5 figures and 9 tables.

Annotatsioon

GEORGIA RAVIMIOHUTUSE JÄRELVALVE OLUKORRA ANALÜÜS

Sissejuhatus

Poliitilised, majanduslikud ja sotsiaalsed muutused Gruusias, madalama ja keskmise sissetulekuga riikidel avaldasid suurt mõju tervishoiu koordineerimisele. Ravimiohutuse põhimõtted ja ohutu uimastite kasutamise edendamise tegevus jääb endiselt üheks riigi peamiseks probleemiks spetsiifiliste organisatsiooniliste aspektide tõttu. Gruusias loodi ravimiohutuse järelevalve süsteem 1997. aastal, kuid ravimite kõrvaltoimete (ADR-ide) alahindamine on endiselt üks levinumaid ja hirmutavaid väljakutseid. Lõputöö põhieesmärk on hinnata tegelikku ravimiohutuse järelevalve olukorda Gruusias, eesmärgiga määrata kindlaks tervishoiuteenuste osutajate, eriti arstide, üldteadmiste, praktika ja hoiakute tase ravimiohutuse järelevalves. Alaeesmärgiks on määrata kindlaks aruandluse aluseks olevad eesmärgid, millega MD-d puutuvad kokku seoses ADRi aruandlusega.

Meetodid

Gruusias viidi läbi fookusgrupi intervjuud ja läbilõikeline analüütiline uuring. Välja töötatud küsimustik oli anonüümne, hästi struktureeritud, ise administreeritav ning saadeti juhuslikult valitud 170-le MD-le.

Tulemused

Uuringu tulemused tõid kahtlemata välja, et vaatamata MD-de positiivsele suhtumisele puudusid sobivad teadmised ja praktika, et kindlustada tõhus aruandmine kõrvaltoimetest.

Kokkuvõte

Läbiviidud uuringu tulemus näitab, et enamikul MD-dest on puudulikud ja ebapiisavad teadmised ja praktika seoses ravimiohutuse järelevalve süsteemi ja ADRi aruandlusega. Uuringu tulemused näitavad ka seda, et Gruusia ravimiohutuse järelevalvesüsteemi õigusaktide nõuded jäävad endiselt paberile ja kahjuks praegusel hetkel praktikas ei tööta.

Lõputöö on kirjutatud ingliskeelne keeles ning sisaldab teksti 63 leheküljel, 7 peatükki, 5 joonist, 9 tabelit.

List of abbreviations and terms

PV	Pharmacovigilance
WHO	World Health Organization
ADR	Adverse Drug Reaction
US	United States
UMC	Uppsala Monitoring Centre
EEC	European Economic Community
SRS	Spontaneous Report System
RAMA	LEPL State Regulation Agency For Medical Activities
MSRA	Medical Service Regulation Agency
MD	Medical Doctor
AEs	Adverse Events
EU	European Union
HCPs	Health Care Providers
KAP	Knowledge, Attitude and Practice

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Aknowledgement

First and for most, I would like to express my great gratitude to my supervisor Janek Metsallik, who extremely supported me and provided the exact directions during the working procedures on my master thesis. I would like to note that without his irreplaceable suggestions and encouragement, it will not be possible to write this thesis appropriately.

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1 Introduction

‘‘All drugs are poisons’’

Paracelsus, no date

1.1 General overview of Pharmacovigilance

The history of pharmacovigilance begins from thalidomide disaster which was held in the 1960s and played a role of catalyst for pharmacovigilance (PV) program movement [1]. The thalidomide tragedy, which was the cause of thousands of hereditarily malformed infants born, as the consequence of unsafe medicine administration by pregnant mothers, opened eyes of world and underlined importance for more vigilance. Consequently, was founded World Health Organization (WHO) Pilot Research Project for International Drug Monitoring in 1968. The main aim of this organization was to create system, accessible globally, for identifying formerly unfamiliar or poorly understood adverse reactions of pharmaceutical products [2], in aim to prevent population. Adverse drug reactions (ADR) are well-defined by the WHO, as a human body response of pharmaceutical product administration, which is noxious and unintended and ,,which occurs at doses normally used in humans for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function”[3]. In most of the cases unexpected and rare adverse drug reactions are mostly determined in the post-marketing phase of medicines [4].

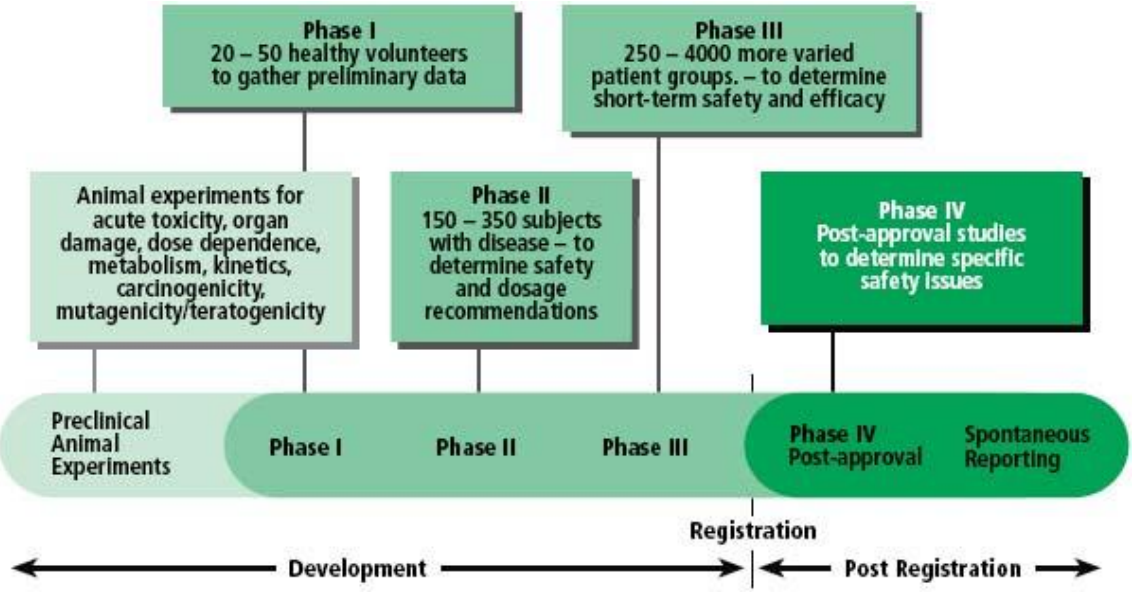

Figure 1. Clinical development of medicines.

Figure 1 shows that prior to approval of pharmaceutical products, most medicines are tested for short-term safety and efficacy on a restricted amount of carefully selected persons. Consequently, the limited numbers of individuals involved in pre-marketing phase clinical trials do not shows clear estimation of the ADR profile of a medicine [5]. ADRs may be reasons of morbidity and mortality. ADRs characterize a huge economic weight regarding of healthcare expenditure, for instance in the United States (US) ADR costs have been estimated at more than US$177 billion annually [6]. Respectively, ADRs have a major influence on the public health programs and impose unnecessary and irrational economic loads on the population.

> ‘‘Not all hazards can be known before a drug is marketed’’.
> Committee on Safety of Drugs, Annual Report 1969, 1970.

As it was mentioned above, the greatest of all medicine tragedies was the thalidomide disaster. The thalidomide catastrophe led in most of the countries to the establishment of the pharmaceutical product supervisory system for early prevention and detection of probable adverse drug reactions [7], in particular, in 2002, more than 65 countries have their own observational systems, which are coordinated by the WHO Collaborating Centre for International Drug Monitoring, familiar as the Uppsala Monitoring Centre (UMC) [2]. UMC was established in aim to support the WHO Programme for International Drug Monitoring in 1978. The main reason was to gather data regarding to the adverse effects of drugs globally, since to make sure that the first marks of probable hazard from medicines would not be missed. Currently, 131 countries are full members

and 26 associate member countries of the WHO Programme for International Drug Monitoring [8]. Nowadays, aforesaid ADRs monitoring systems are familiar as Pharmacovigilance centres. The term of Pharmacovigilance is defined by the WHO as ‘‘the science and activities relating to the detection, assessment, understanding and prevention of adverse events or any other drug-related problem’’ [9]. PV is an essential component of effective drug regulation systems, public health programmes and clinical practice [10]. According to the directive of the European Economic Community (EEC) a pharmacovigilance system was defined as “a system [that is] used to collect information useful in the surveillance of medicinal products, with particular reference to adverse reactions in human beings, and to evaluate such information scientifically” [11].
Pharmacovigilance plays a greatest role for protection of society. Correspondingly, principle goals of PV are following:

- Identify new ADRs as rapidly as possible;
- Increase and improve the information about already determined or doubted ADRs;
- Evaluate the benefits of a medicine compared to other pharmaceutical products or other therapeutic agents [12];
- “Promote understanding, education and clinical training in pharmacovigilance and its effective communication to health professionals and the public.” [13].

The WHO Drug Monitoring Program database is growing step by step and nowadays, it counts over 16 million reports of assumed adverse effects of drugs, submitted, since 1968. Georgia has become an associated member of the WHO Drug Monitoring Program in 2004 (Uppsala Monitoring Centre, 2018) and unfortunately, still remains a status of an associated member. Pharmacovigilance activity relies on Spontaneous Reporting Systems (SRS) in order to gather data regarding ADRs. The main effort of a SRS is to notice serious unfamiliar ADRs. All reports are revised and investigated to generate alarms and signals of serious, yet undetermined, medicine-associated events [14]. As a result, spontaneous reporting systems are very important for signal detection of novel medicines.

A signal of suspected causality is determined as follows: “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, which

would command regulatory, societal or clinical attention, and is judged to be of sufficient likelihood to justify verifiable and, when necessary, remedial actions" [15].
A familiar obstacle is the underreporting of ADRs in the spontaneous reporting system [16]. Dissimilar problems to notifying ADRs have been proposed in different studies [17]. There were several obstacles of ADRs reporting.

In Georgia, Pharmaceutical activity is regulated by the LEPL State Regulation Agency for Medical Activities [18]. According to the mentioned law and order of Minister, pharmacovigilance system is intended to work with a spontaneous voluntary ADR reporting system [19]. The RAMA notes that based on the Law, doctors from curative-prophylactic networks, specialists from medical facilities and agencies from the MoLSHA participate in the monitoring of the adverse effects of drugs [18]. But, above-mentioned regulation stays still on the paper and for that reason polypharmacy (the administration of many different remedies at the same time) and the non-existence of pharmacovigilance remains a problem in the country [20]. Correspondingly, pharmacovigilance system in Georgia like others developing countries across the world, is characterized with underreporting from health care professionals. One of the main players on the market, pharmaceutical company representatives, stated that currently the management of the pharmacovigilance system is not effective [20]. For that reason Georgia stays as an associated member of the WHO Program for International Drug Monitoring, because of the law number of reported ADRs.

Currently, slight information is known regarding the Georgian health care provider's attitude, awareness, knowledge and reporting performance towards ADRs reporting system.

Consequently, the aim of the present pilot study is to gain understanding into the attitude, awareness, knowledge and reporting performance and to discover the reasons behind underreporting of ADRs among of health care provider's, in particular, medical doctors in Georgia.

1.2 Problem Statement

Spontaneous Report Systems is used for signal detection and enables the investigation of unfamiliar ADRs not determined during clinical trials. SRSs give opportunity to assess safety of medication in the actual clinical use situation. Also, SRS plays a great role in pharmacoepidemiological research addressed on drug safety evaluation [21]. ADRs spontaneous reporting systems are the main mechanisms for the complete post-marketing observation of medicine-induced risks [22]. However, a major limitation of this system is that only minor portion of total number ADRs are reported [23]. Respectively, voluntary nature of this system reporting represents the main reason of ADR underreporting phenomena [24]. Nowadays, underreporting stays one of the scaring obstacles of pharmacovigilance comprehensive activity [25]. According to the scientific literature several reasons have been proposed for underreporting among health care provides. The most important causes are following: lack of awareness about the voluntary reporting system, doubt concerning the causal relationship between the medicine and ADR, prejudiced attitudes on ADR reporting, lack of structured pharmacovigilance systems, nonexistence of enough time [26]. Based on the literature, it has been proved that knowledge attitude and practice of the medical doctors working towards spontaneous ADR reporting were very low [27] [28].

Generally Medical practitioners are playing the most important role for identifying and report important ADRs [2]. Among health care professionals, doctors are the most responsible persons who will report ADRs, but unfortunately, Georgian population still suffers with underreporting of ADRs.

Correspondingly, pharmacovigilance system in Georgia like other developing countries across the world is characterized with underreporting from health care professionals. One of the main players on the market, pharmaceutical company representatives, stated that currently the management of the pharmacovigilance system is not effective [20]. For that reason Georgia stays as an associated member of the WHO Program for International Drug Monitoring, because of the law number of reported ADRs.

Currently, slight information is known regarding the Georgian health care provider's attitude, knowledge and reporting performance towards ADRs reporting system.

Consequently, the aim of the present study is to gain understanding into the attitude, knowledge and reporting performance and to discover the reasons behind underreporting of ADRs among of health care provider's, in particular, medical doctors in Georgia.

1.3 Sensible of the study

Georgian Pharmacovigilance system was set up in 1997 in partnership with Pharmacological Committee of the Ministry of Health of Georgia and WHO for observing the safety profile of drugs during post-marketing period and to decrease the risks of health complication and in parallel increase a rational pharmacotherapy in Georgian population [29]. The main source of gathering information regarding ADRs were MDs [19] working in hospitals and outpatient departments [29].

As it was mentioned above, experience and well documented scientific literature shows that the key success of Pharmacovigilance systems active functioning relies on spontaneous reporting systems, which implies health care provider's active participation in ADRs reporting [30].

Georgia, like other developing countries across the world is characterized with underreporting from health care professionals [20]. Quite many researches have conducted in different industrialized countries related to the health care practitioners' knowledge, practice performance and attitude concerning adverse drug reactions reporting and pharmacovigilance systems in general. Unfortunately, there are no any scientific studies conducted in this field in Georgia that helps to get the bright picture about the actual PV situation in the country. Nowadays, polypharmacy stays one of the hugest problems on the pharmaceutical market in the country. Georgian pharmaceutical market counts approximately 12 000 registered pharmaceutical products, with different forms, dosage and packaging of the drug [31].
Consequently, aforesaid shows crucial necessity to carry out complete research, in aim to assess current PV system condition regarding to the evaluation of health care practitioners role, benefits and incidence of underreporting of ADRs concerning to the future improvements of the existing PV system state and rational, cost-effective usage of medicines.

1.4 Importance of the study

There are numerous consequences in the provided research, which can offer rational and helpful information regarding existing ADR reporting situation among the health care professionals to the policy makers.

- It should be mentioned that provided study is the first in Georgia and gives opportunity to the policy makers to have an access to the current data of PV system, which on the one hand can be beneficial for the development of the existing PV policy and on the other hand for the future modification of the PV system.

- The outcomes of the research will help in modernization the ADR reporting practice by underling the weaknesses and obstacles in the existing PV scheme.

- This study will give opportunity to collect information in the place regarding safety profile of pharmaceutical products that offers possibility to prevent the risks of health complications in the population of Georgia.

- Since, presented study defines concrete involvement required in improving ADRs reporting, through determining the probable issues leading to underreporting. It will be the beneficial for the State as well as for the private insurance companies, in order to decrease the budget expenditure for the treatment with irrational and non-effective drugs.

- Consequently, study will be beneficial in economical perspective as well for the population of Georgia.

Since, the study highlights the practice performance of MDs, knowledge and attitudes towards ADRs reporting, it gives opportunity to the policy makers to decrease the risks of health complications and improve treatment efficiency with improvement of reporting procedures.

1.5 Hypothesis and research questions

Hypothesis: In Georgia, pharmacovigilance systems and activities to regulate and monitor ADRs of pharmaceutical products are not in place.

Consequently, the main exact aims of this research are following:

- To assess medical doctors attitude, knowledge and reporting performance concerning ADR reporting system and to define obstacles of ADR reporting in medical doctors;
- To discover the Georgian health care provider's, in particular, medical doctors attitude, knowledge and reporting performance towards ADRs reporting system;
- To evaluate existing situation related to the pharmacovigilance system in Georgia and provide suggestions for future improvements of the system.

2 Literature overview

2.1 Literature review

A literature research was conducted in MEDLINE, EMBASE and Google Scholar databases and also searching was carried out of textbooks on pharmacovigilance and pharmacoepidemiology, aimed to define the core problems of the thesis topic. The search was orientated to articles in English, published from 1997-2018, with free full text accessibility. The terms used in search procedures were as follows: “adverse drug reaction” OR “adverse drug reactions” “spontaneous reporting”, OR “spontaneous reports” OR “pharmacovigilance” OR “spontaneous report” AND ‘Post-marketing surveillance” OR “Postmarketing surveillance” OR “adverse drug reaction reporting systems” AND “under-reporting” OR “underreporting” OR “under reporting”. The texts books used for research were as follows: Stephens’ Detection and Evaluation of Adverse Drug Reactions: Principles and Practice, Sixth Edition; Ronald D. Mann and Elizabeth B. Andrews’: Pharmacovigilance, Second Edition.

Reference titles and abstracts were reviewed and assessed to identify additional studies containing specific impact on the underreporting of ADRs, Pharmacovigilance knowledge, attitude and practice performance of health care providers in developed, middle-income and developing countries. A literature review was done in March-April 2018.

Because of the research, there were listed initial 918 scientific records. The author of the thesis work started to apply the inclusion/exclusion criteria (see Appendix 7). Respectively, 28 citations were excluded, made the final list of 124 citations. After removing the duplications, the final sample was decreased to 63 articles. The precise flow chart of the articles can be seen in Appendix 8.

2.2 Theoretical background –Milestone events

The past of Pharmacovigilance has old roots and consists with unfortunate events, which have played an important role in the development of pharmaceutical products regulation. Several medicine related safety concerns influenced society world-wide to open eyes and revise ancient perceptions and think more broadly, because of the drug related tragedies and issues ,which had huge damaging impact on the public health [37]. Kind of most significant disasters will be discussed briefly below, because of them biggest importance for the establishing contemporary pharmacovigilance system.

The Elixir Sulfanilamide tragedy - 1937

There were not mandatory requirements in the United States for novel drugs to undertake preclinical safety trials before the market authorisation until 1938. Toxicity test of Sulfanilamide was conducted later in animals and humans, in order to cure streptococcal infections in January of 1937 [38].

In September of 1937, after the production and distribution of Elixir Sulfanilamide (antibiotic) for the medication purposes have caused the death of more than 100 individuals (most of them were child) with acute kidney failure in the United States [39]. Consequently, aforesaid catastrophe led to the establishment the imperative provisions, which was a required preclinical safety trial before the drug authorisation on the pharmaceutical market. Respectively, the Food, Drug and Cosmetic Act have been signed after the several months of this incidence, which automatically replaced the old, insufficient drug safety requirements [40].

Thalidomide disaster - 1961

After the 25 years of above mentioned tragedy, additional extensive drug related disaster, from which the Europe, Australia and Canada were not secured, was the antinausea and sedative drug, thalidomide, which was known to cause congenital defects in the infants, whose mothers had administrated the medicine throughout pregnancy. The first ,,Thalidomade Baby" was born in Germany in 1957. Before the medicine-defect association was assumed (1961), by two autonomous medical doctors, McBride in Australia and Lenz in Germany, more than 10,000 infants worldwide were born with genetic abnormalities [41]. By this time, United States were prevented with

already accepted, relatively strict drug-safety regulations and FDA's medical officer had prevented the drug's approval, despite pressure to do so. For that reason, fortunately, only a few babies were born with debilitating malformations [42]. The thalidomide disaster totally transformed the technique medicines are tested [43]. After this tragedy, governmental organizations and authorities have started to arrange national PV centres to avoid such a disaster happening again [44]. Nowadays, pharmacovigilance centres are concentrated to collect adverse drug reaction reports related to medicines, which are mostly provided by medical practitioners or by drug manufacturers [45].

Practolol – 1971

Practolol like thalidomide was characterised with its unique nature of the toxicity. Presently, it is well documented that it was an uncommon and formerly non-reported ADR, in particular „Oculomucocutaneous syndrome", which has made suspicion related to the safety profile of the drug [46]. The per oral form of this medicine had a widespread variety of ADRs, such as e.g. tachyarrhythmias, but first signs of this impending tragedy were reported in reports regarding exfoliative dermatitis [47]. As it was reported by Felix et al. in 1974, an entire of 21 patients were suffering from medicine-induced ADRS, in particular, with rashes, which have been overseen over the previous two years [48]. After several months more quantity of ADRs were reported regarding corneo-conjunctival damage [49] and finally as the consequences of serious adverse events drug was withdrawn from the UK market [50]. As a result, kind of outcome underlined brightly that it is essential to report adverse drug reactions in aim to avoid future complications.

Cerivastatin - 2001

According to the cerivastatin mechanism of action, it is characterised as a cholesterol-lowering drug, which was withdrawn from the several markets, including USA in 2001 because of its linkage with rhabdomyolysis [51]. It was reported that a combined administration of cerivastatin and gemfibrozil could be a cause of drug-drug interaction that noticeably raises the risk of rhabdomyolysis [52]. Unfortunately, such cases were not reported by the manufacturer or by marketing authorization holder until numerous years after the drug initial marketing [53]. Accordingly, there have been 31 life-treating conditions caused by severe rhabdomyolysis in the patients administrating the medicine

in the US [54]. After that incidence, it become essential that pharmaceutical products safety portfolios to be reviewed by the autonomous expert committees.

Rofecoxib - 2004; Aprotinin -2007; Benfluorex -2009; Rosiglitazone - 2010

Rofecoxib has been withdrawn from the pharmaceutical products market in 2004, since it increased issues related its cardiovascular toxicity, in particular, increasing opportunity of myocardial infarction [55, 56]. Several years later, following drugs has been withdrawn from the market: Aprotinin has been withdrawn in 2007 for increased mortality and renal impairment; Benfluorex in 2009 for pulmonary hypertension and valvulopathy; Rosiglitazone – 2010 for the cause of cardiovascular disease [57].

Throughout the years, numerous adverse drug reactions have led to modernizations in pharmacovigilance and encouraged the foundations of different international establishments across the world, which are mainly based on spontaneous reporting systems and serves to the protection of public health [57].

2.3 Definition of pharmacovigilance

The term of Pharmacovigilance is defined by the WHO as ‘‘the science and activities relating to the detection, assessment, understanding and prevention of adverse events or any other drug-related problem’’ [9]. As it was mentioned in the previous chapter, PV is an essential component of effective drug regulation systems, public health programmes and clinical practice [10]. According to the directive of the European Economic Community (EEC), a pharmacovigilance system was defined as “a system [that is] used to collect information useful in the surveillance of medicinal products, with particular reference to adverse reactions in human beings, and to evaluate such information scientifically” [11].

As it was mentioned above, pharmacovigilance plays a greatest role for protection of society. Correspondingly, principle goals of PV are following:

- Identify new ADRs as rapidly as possible;
- Increase and improve the information about already determined or doubted ADRs;
- Evaluate the benefits of a medicine compared to other pharmaceutical products or other therapeutic agents [12];

- "Promote understanding, education and clinical training in pharmacovigilance and its effective communication to health professionals and the public." [13].

2.4 Definition of ADR

According to the WHO adverse drug reaction definition, that is already validated more than 45 years and used most commonly is "a response to a medicine which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy or for modification of physiologic function" [58].

Aforesaid definition is commonly used, but there are others as well, for instance, Prof I Ralph Edwards and Jeffrey K Aronson in their article (Lancet, 2000) defined ADR as "an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product" [59]. Edwards and Aronson (Lancet, 2000) assumed that WHO definition, which is presented above, is imprecise, since it consists of all adverse drug reactions. Edwards & Aronson stated that definition provided by WHO does not take into account the minority of ADRs and covers extensive range of ADRs.

2.5 Classification of ADRs

Currently, there are two generally used systems for adverse drug reactions classification. The original classification of ADR proposed by Rawlins and Thompson in 1991, which separated ADRs into two types: Type A (Pharmacological/dose-related - Augmented) and type B (idiosyncratic/ non-dose-related - Bizarre) [59]-[60]-[61]. Later, two additional types (type C and type D) of reaction have been added, in particular, reactions associated to both dose and time and delayed reaction [59]. Later, in 2003, two furthermore types (E and F) were added. Aronson & Ferner detected that some ADRs do not constantly fit well into just one of above mentioned categories and suggested a classification based on dose-relatedness, time-relatedness and susceptibility of the patient [62]. Respectively, table 1 shows present ADRs classification and examples follows [63]:

Types of Reaction	Mechanism
Type A (Augmented)	Reactions are predicted from the identified pharmacology of the medicine. Presented reactions are dose-dependent.
Type B (Bizarre)	Reactions are not predicted. They appear (but in reality are not) relatively dose-independent, as very minor amount of doses might already provoke warning signs.
Type C (Chemical/Chronic)	Reactions are associated to the active substance structure and its metabolism.
Type D (Delayed)	Reactions occur after many years of drug cure.
Type E (End of treatment)	Reactions appear after medicine withdrawal.
Type F (Failure)	Reactions frequently produced by drug-drug interactions.

Table 1. Classification of Adverse Drug Reactions.

2.6 Definition of averse drug event

Adverse Drug Event (AE) is defined by WHO as ,,any untoward occurrence that may present during treatment with a pharmaceutical product but that does not necessarily have a causal relation to the treatment" [59]. According to the statement an adverse event is consider as an adverse consequence that appears while a patient is administrating a medicine, but same time is not or not essentially attributable to it [59].

2.7 Epidemiology of adverse drug reactions

The thalidomide tragedy stimulated the attention and importance related to the drug safety monitoring and encouraged the interest regarding ADRs reporting. Subsequently the aforesaid disaster, various studies have been conducted to research the incidence of ADRs in the clinics and public settings. A meta-analysis of studies conducted by Lazarou and colleagues in the United States showed surprising outcome and assumed that ADRs were the fourth to six dominant cause of patients death in 1994, causing more than 105 000 deaths per year [64]. But there was study heterogeneity among studies [65].

An additional modern systematic review has shown that 7% of entirely admissions are due to ADRs, with the total impact in the England being 15-20 out of 400 clinic-bed equivalents and has approximately 15% mortality rate [66]. Respectively, average annual rate of charges due to ADRs-associated patient admission is almost £400 million a year to the National Health System in United Kingdom. The research also assumed that ADR incidence rate might reduce since 1985 [67].

Another extensive pilot study, which was conducted in 18 000 patients presented that 7.5% of hospital admissions were the cause of ADRs in England [68].
The prospective cohort telephonic study was conducted in Boston (USA) by Ghandi and colleagues. The results have shown that 25% of patients (162) had adverse drug reactions with a total of 181 events (27 events per 100 patients) [69].

2.8 Frequency of ADRs during hospital admission & Population mortality associated to ADRs

Various studies have been conducted in developed countries in the previous years, stated that ADRs are a significant purpose of morbidity, mortality and hospital admissions, in where under under-reporting remains an important issue [70]. The Study that was carried out in England between the period of 1999 and 2008 reported that there were approximately 560,000 ADRs-related hospital admissions, representing almost 1% of total hospital admissions. This study has showed that quantity of ADRs increased per year by 77% and mortality ratio amplified by 10% in hospitals. The study obviously indicated that form 6,830,067 emergency admissions 1.1% (75,076) were drug associated [70].

Another study was conducted beforehand, which covered the period between of 1998-2005, reported that ADRs have huge harmful influence on public health and economic implications. Conducted study stated that here were approximately 448000 ADRs demonstrating 0.50% of whole hospital incidents and over this period the amount of ADRs has increased by 45%. The total number of incidents in all age group patients was 76,692 that were directly medicine related [71]. In addition, Pirmohamed and colleagues considered that in England ADRs were accountable for approximately 6.5% of total severe hospital admissions and minimum 5,000 deaths annually [72].

In the USA, ADRs are one of the challenging and scaring causes of death in the population. It was documented by Lazarou and colleagues, that ADRs were responsible over 100 000 deaths in the USA in 1994 [64].

Furthermore, a Swedish population based study reported that approximately 3.1% of fatalities were associated to ADRs in the general population. It was documented that this ratio included patients who has died outside hospitals as well with life-threating complications linked to the ADRs [73].

Another prospective cohort study, carried out In Japan, that covers roughly 3500 patients, identified around 1,050 ADRs during hospital admissions. Among ADEs, around of 2%, 5% and 33% were fatal, life-threatening and serious, correspondingly. The study reported that among discovered ADRs, approximately 15% were avoidable [74].

The literature findings demonstrate that there is not substantial difference related to the ADRs incidence rate and drug related mortality of the population. It was also reported that around 15 % of ADRs were absolutely preventable. Correspondingly, underreporting seems most leading cause of population mortality and severe drug-associated complications [70]-[74].

There is lack of similar studies carried out in law and middle-income countries associated with the subject of interest. The reasons could be various, in particular, in developing countries pharmacovigilance systems do not work properly. A very few researches have conducted aimed a systematic assessment of the pharmacovigilance setting in developing countries [75]. Another reason may be insufficiency of studies designed to evaluate the frequency of the ADRs. Even though, several studies were found out. In particular, the South Indian study reported that a total of 3.7% of the in-hospital patients experienced the ADRs. Respectively, 0.7% of the hospital admissions were due to ADRs and 1.8% of patients had the ADRs, caused mortality [76].

South African study has revealed that ADRs related causes accountable for mortality of patients were 2.9% [77].

3 Methods

3.1 Research Plan

As mentioned in the previous chapter, the primary goal of the research is to identify all existing problems linked to the ADRs reporting in Georgia, which could interrupt the improvements of PV system in Georgia, and to give a recommendation how to resolve the defined problematic questions. In Georgia, pharmacovigilance systems and activities to regulate and monitor ADRs of pharmaceutical products hypothetically are not in place. The issues in question are: lack of Knowledge, attitudes and reporting performance regarding ADRs reporting among the MDs and not knowing the existence of a PV national program system is a major reason of underreporting in Georgia

The research questions was formed based on the thesis' core objectives and stated as follows: What is the present characteristic of medical doctor's attitudes knowledge and reporting performance regarding ADRs reporting system in Georgia? The sub-research questions of the conducted study are as follows: What is the present characteristic of medical doctors' attitude towards ADRs reporting in Georgia?; What sort of knowledge level do medical doctors' have towards ADRs reporting in Georgia?; Do the medical doctors' have practice performance skills regarding ADRs reporting in Georgia?; What is the existing condition of pharmacovigilance system in Georgia? To answer the research questions author has used qualitative and quantitative research methods.

Qualitative method used to discover and collect basic data regarding knowledge, practice performance and attitude of the Medical Doctors concerning Pharmacovigilance activities and ADRs reporting in Georgia. Additionally, the research aimed to get clearer perception of a given causes and the supposed barriers of under-reporting in medical doctors.

Quantitative method used in order to evaluate knowledge, practice performance and attitude of the Medical Doctors concerning Pharmacovigilance activities and ADRs

reporting in Georgia. Respectively, the study would make available useful and beneficial idea regarding aforesaid concerns related to ADR reporting, which can be used for future PV improvement perspectives in Georgia. Quantitative research method assists to interpret and better understand the complex reality of a given situation and the implications of quantitative data.

Based to the study design, the author has used aforesaid research methodologies aimed to accomplish the final results. The author collected the data, conducted the interviews and prepared the literature review in the March-April 2018. The study design and literature research was attained based on supervisor's recommendations. The author has collected basic and supplementary data based on the interviews from MoLHSA, leading Manufacturer of Pharmaceutical Products in Georgia, Association of Pharmaceutical Companies Representatives, Tbilisi State Medical University, Committee of experts on Quality and Safety Standards for Pharmaceutical Practices and Pharmaceutical Care of EDQM in April 2018.

3.2 Approach

Presented study consists with following central parts:
Qualitative method - was used to discover and collect basic data regarding knowledge, practice performance and attitude of the Medical Doctors concerning Pharmacovigilance activities and ADR reporting in Georgia. Additionally, the research conducted in aim to get clearer perception of a given causes and the supposed barriers of under-reporting in medical doctors.

Quantitative method was used in order to evaluate knowledge, practice performance and attitude of the Medical Doctors concerning Pharmacovigilance activities and ADR reporting in Georgia. Respectively, the study would make available useful and beneficial idea regarding aforesaid concerns related to ADR reporting, which can be used for future PV improvement perspectives in Georgia.

3.3 Interviews – Qualitative approach

Qualitative approach was used when interviewing the focus group. The author chose a qualitative research, since this methodological approach could identify private sectors

and Regulatory Authority's view and would enable the improvement of concepts for potential interventions.

The researcher has conducted face to face interviews, used general interview guide approach. The interviews give exceptional occasion to obtain the all essential information related to the research topic. The interviews supported to collect the specific information and attitude related issues linked to the existing PV system situation in Georgia. The respondents for the interviews were carefully chosen, aimed to screen all components of the research. The author has collected basic and supplementary data based on the interviews from MoLHSA, leading Manufacturer of Pharmaceutical Products in Georgia, Association of Pharmaceutical Companies Representatives, Tbilisi State Medical University, Committee of experts on Quality and Safety Standards for Pharmaceutical Practices and Pharmaceutical Care of EDQM in April 2018.

The core purpose of the interviews was to discover the real-life situation related to PV situation in Georgia. For this reason, interviews covered approximately 5 to 8 open questions, particularly prepared for each respondent, grounded on their practical experience. The respondents described the existing PV related situation in Georgia and suggested the solutions for the improvements and developments of the system.

3.4 Questionnaires development and Design

The KAP questionnaire was arranged based on the frameworks to be evaluated as part of the research. The questionnaire was developed based on studies conducted previously [78, 79, 80] and slightly was modified to make it suitable for Georgian location. The developed questionnaire was designed to be anonymous, well-structured and self-administrated, sent to 170 MDs selected randomly. The final questionnaire (see Appendix 6) has four blocks: A) social demographic data of the respondents; B) ADRs reporting practice related questions; C) adverse drug reaction reporting practice related questions and several hypothetical ADR situations; D) Attitude related questions. The conducted questionnaire based study design developed stage by stage, aimed to cover all essential materials and to outline the significance of accessible scientific sources. The presented study has been designed as a validated, cross-sectional, observational, questionnaire based survey involving MDs working in different regional hospitals in

Georgia.

3.5 Data collection and Statistical analysis

All questions sent by Google form were coded and then imported to Social Sciences SPSS version 20 for analysis. Descriptive analysis was used to analyses the socio-demographic data. A correlation analysis was performed to test association.

Information from the paper-based survey was firstly after the field-work and then entered into spreadsheets (Microsoft Office Excel®) and then exported into a Statistical Package for the Social Sciences SPSS version 20 for analysis.

3.6 Location

The study was conducted in Georgia, situated in the South Caucasus, on the southern foothills of the Greater Caucasus mountain range. There is a short border with Turkey to the south-west and a western coastline on the Black Sea. The northern border with the Russian Federation follows the axis of the Greater Caucasus. To the south lies Armenia and, to the south-east, Azerbaijan. Georgia has an area of 69 700 km^2. The size of the Georgian population is disputed; official statistics estimate that the population is 4.4 million people with an average population density of 61 inhabitants per square kilometre [81].

The study was conducted in Tbilisi inhabited by a population of 1,114,600 [82] and in different regions of Georgia, in particular, Kvemo Kartli (Rustavi) and Guria (Ozurgeti, Lanchkhuti). A total of over 23000 medical practitioners, distributed throughout the cities of Georgia, providing medical care (through various specialties) to the population [83].

Rustavi is a city in the southeast of Georgia, in the province of Kvemo Kartli, situated 25 km (16 mi) southeast of the capital Tbilisi. According to the 2014 Census it has a population of 125,103. Ozurgeti is the capital of the western Georgian province of Guria. According to the 2014 Census, population of 14,785 individuals. Lanchkhuti is a city in western Georgian region of Guria. According to the 2014 Census, population of about 8000 individuals. The research was conducted over a period of one month from March-April, 2018.

4 Results of the Interviews

Face to face interviews reported supported to obtain the all essential information related to the research topic. The author has collected basic and supplementary data based on the five interviews from MoLHSA, leading Manufacturer of Pharmaceutical Products in Georgia, Association of Pharmaceutical Companies Representatives, Tbilisi State Medical University, Committee of experts on Quality and Safety Standards for Pharmaceutical Practices and Pharmaceutical Care of EDQM.

All participants of the interviews declared that pharmacovigilance system is not working actively and efficiently in Georgia for years now and it still stays just on the paperwork and is not enforced in day to day practice. As respondents stated, there could be several objective and subjective reasons for pharmacovigilance system not working in a way as it should be. For instance all of the respondents mentioned that there are no sufficient requirements within the legislation. From their point of view current legislation differs from the legislation of the developed countries. In contrast of the EU member state countries legislation of Georgia seems very specific and out of date, that need future improvements and harmonization according to the EU requirements. The respondents also considered that MDs are unaware and characterised with lack of knowledge and practice performance skills within this filed. As they mentioned, the major leading factor related to the poor knowledge and appropriate reporting behaviours could be the non-existence undergraduate and postgraduate curriculums concerning PV system at Universities. The respondents underlined the problem regarding weak mutual interaction between health care supervision authorities and MDs. They also supposed that managerial board of the clinics insufficiently control MDs related to this field, because of the lack of interest ineffective legislation. Some of the participants noted that since PV system does work successfully, polypharmacy cases are widely disseminated in the country, which directly are linked to irrational pharmacotherapy. According to the interviews, the significant reason of the underreporting of ADRs is lack of technical support within the regions and less awareness of the MDs towards ADRs reporting.

The interviews also suggested that in Georgia there are number of ethics and compliance cases, which imply the encouragement of medical practitioners by the unconscientious pharmaceutical companies to prescribe series of unnecessary drugs at the same time. All of these lead to polypharmacy and underreporting of ADRs.

Underreporting of ADRs is not doubtful in Georgia. Representative of MoLSHA declared that RAMA has not received at least one ADR submitted neither by medical doctors, nor pharmacists in 2017. According the respondents opinion the causes of this problem are insufficient qualification of HCPs, respectively inadequate understanding of future implications and indifference behaviours within the medical doctors that are directly linked to the lack of strict regulations in the legislation.

The interviews highlighted that, presently RAMA is not able to ensure an analysis regarding PV issues, since Georgia is not a member of WHO drug monitoring program and in order to guarantee sophisticated working of this system need of daily, regular interaction with international organizations and Uppsala Monitoring Center. Also study has stated that there is no PV department or unit in the RAMA.

The study revealed a readiness of the EU pharmaceutical companies' representatives with regard to develop and maintain the PV system in Georgia. As it was noted, aforesaid pharmaceutical companies are operating and investing a lot of funds in Georgia with the aim to study the safety profile of their products.

The study findings also showed that a PV system works more or less in the drugstores in Georgia. Pharmacy chains have special forms related to the drug side effects and this information. If patient refers to the pharmacists with concrete complications aforesaid ADR forms are filled by pharmacist.

The interviews specified that there is no an adequate funding and financial resources aimed to implement PV system in place and RAMA requires as specialists trained and experienced in this particular field as well as working places.

Based on the respondents' statements, the study has revealed that there was no adequate political will and correspondingly, sufficient support from the state for this particular field.

5 Results of the Questionnaire based survey

5.1 Social-Demographics data of the Respondents

A total of 170 physicians were included to the research. 120 MDs (response rate: 70.6%) responded to the questionnaire-based survey. Of the 120 MDs only 14 (11.7%) were general practitioners and 78.3% were specialists in hospital practice (e.g. surgeons, internal medicine, obstetrics and gynaecology and etc. (see Appendix 7) from different cities (Figure 2).

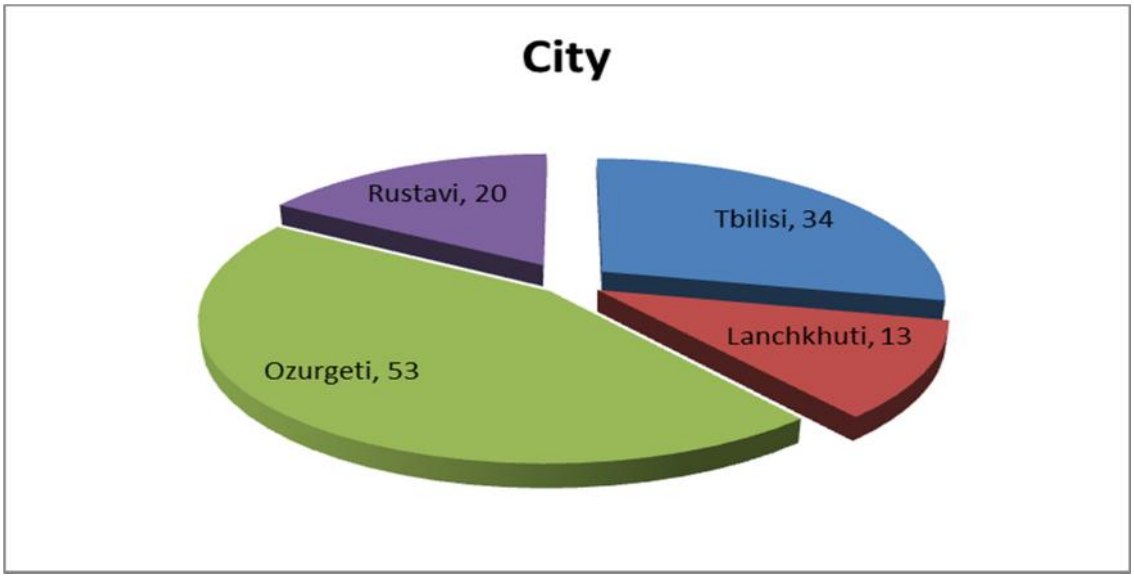

Figure 2. Response frequencies within the cities.

The majority of MDs (63 %) were aged between 45 and 60 years of age, 29 MDs aged were among 36-44 years of age, whereas 21 were aged more than 60 years old and 7 of MDs were in age 24-35 (Figure 3).

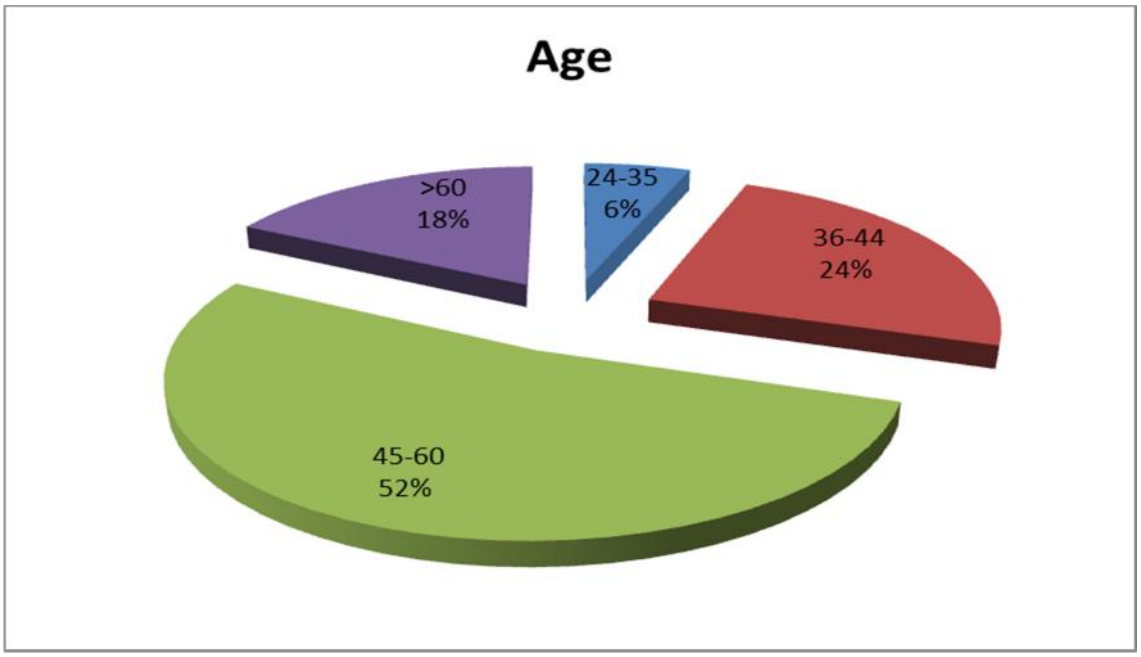

Figure 3. Age frequency within the respondents.

Research results showed that female MDs answered to the questionnaire were 3 times more (75%) than male (25%) respondents (see Figure 4).

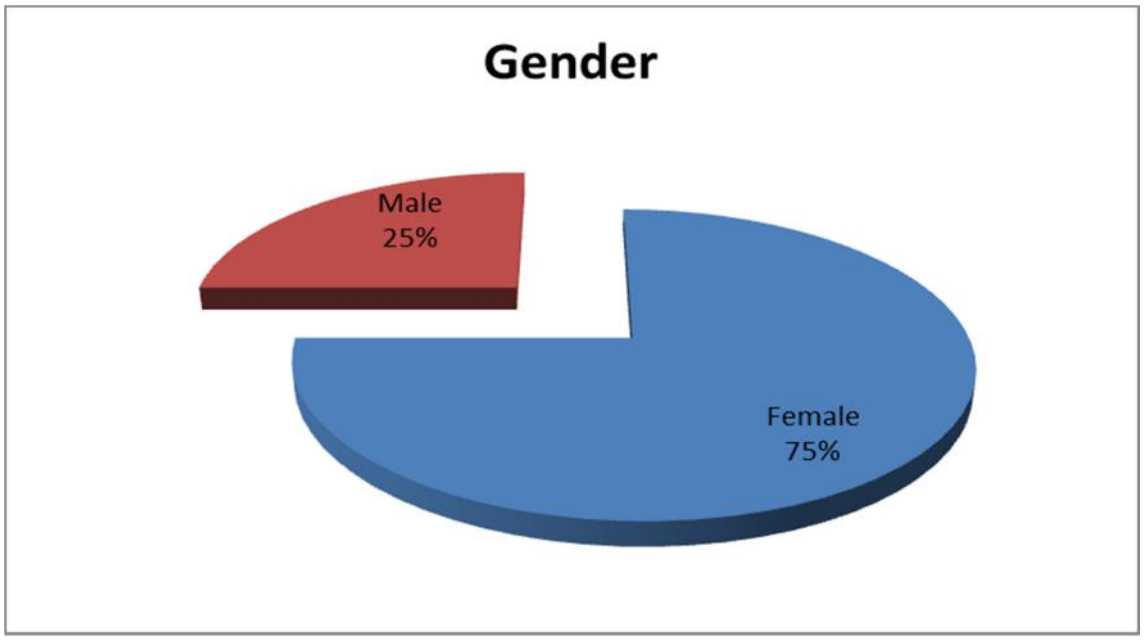

Figure 4. Gender rate of respondents.

The social demographics of the enrolled MDs in the research are presented in Table 2:

How long have you been practicing?		
	Frequency	Percent
1-5 year	7	5.8
5-10 year	8	6.7
>10 year	105	87.5
Number of prescription dispensed per day?		
	Frequency	Percent
<10	36	30.0
10-20	36	30.0
> 5	41	34.2
< 5	7	5.8
Number of patient served per day?		
	Frequency	Percent
<5	18	15.0
5-10	52	43.3
10-15	26	21.7
>15	24	20.0
Time spent with patient?		
	Frequency	Percent
5-10 minute	10	8.3
10-15 minute	35	29.2
>15 minute	75	62.5

Table 2. Social demographic characteristics of respondents.

5.2 Knowledge related data

A quite high proportion of the subjects enrolled in the research, specified that they have supposed (60.8%) the ADRs but not reported it, while about 85% of the total quantities of respondents were not aware of the existence of the ADRs reporting national program in Georgia (see Appendix 9). As it mentioned above 60.8 per cent of MDs had suggested ADRs but had not reported them. The major reasons that discouraged ADR reporting ($p<0.05$) are presented in the Figure 5 that shows that there is statistically significant relationship among position of non-reporters and all the variables assessed.

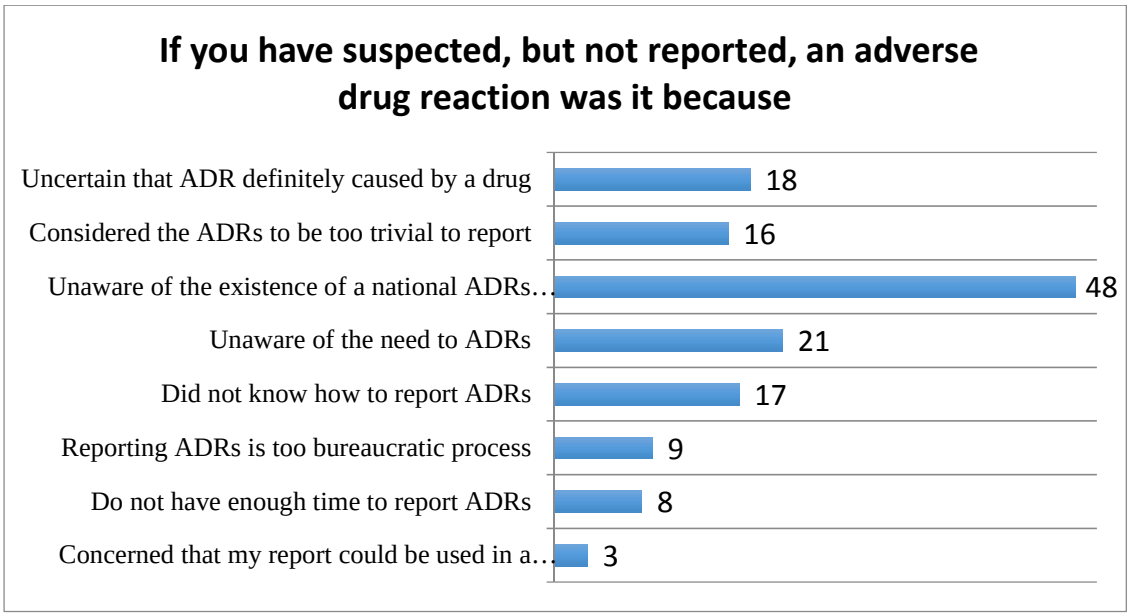

Figure 5. Discouraged reasons of ADR reporting.

The major predictor was the variable concerning to uncertainty (48%) of the existence of national ADR reporting program. 18% of MDs were not aware that the ADRS had been definitely caused by a medication. 16% of MDs considered ADRs too trivial.

Most of the participants of the survey were not familiar with the term of pharmacovigilance and ADR and for instance, 80.8% (97), and 72.8% (88) correspondingly (Tab. 3-4).

Are you familiar with the term Pharmacovigilance?		
	Frequency	Percent
Yes	23	19.2
No	52	43.3
Difficult to Answer	45	37.5

Table 3. Familiarity with term of pharmacovigilance.

What do you understand by the term ADR? Please, specify		
	Frequency	Percent
Adverse drug reaction is a disease or harmful effect, which occurs at doses normally used in man	33	27.5
Rash, candida, anaphylactic reaction	50	41.7
Difficult to answer	37	30.8

Table 4. Definition of ADR.

According to the present study, around 85% of the participants were unaware of the ADRs reporting program in Georgia (see Table 5).

Are you aware of any ADRs reporting program in Georgia?		
	Frequency	Percent
Yes	18	15.0
No	102	85.0
Total	120	100.0

Table 5. ADRs reporting program in Georgia.

Moreover, 96.7% (116) respondents did not know how to make a ADRs report (see, Table 6).

Do you know how to report an ADR?		
	Frequency	Percent
Yes	4	3.3
No	116	96.7
Total	120	100.0

Table 6. Mechanism of ADRs reporting.

Furthermore, 100 % of respondents did not know the location of the International Center for Drug monitoring (see, Table 7).

Do you know in which country the International center for ADR monitoring is located? If "Yes", please, specify			
		Frequency	Percent
Valid	1 UK	1	.8
	2 USA	1	.8
	Total	2	1.7
Missing	System	118	98.3
Total		120	100.0

Table 7. Location of International Center for ADR monitoring

5.3 Practice related data

The survey has revealed that the MDs had a poor practice related skills, in particular 46.7% of them had diagnosed less than ten (45.8%) ADRs but majority of them (91.7%) not reported it to RAMA, respectively Tab.9-10. 6.7% had sent ADRs to pharmaceutical product license holders and 1.7% to pharmaceutical product manufacturer.

Have you ever diagnosed an adverse drug reaction in a patient under your care in the past 12 months? (If Yes" go to question 4, (if "No'" go to question 5)?		
	Frequency	Percent
Yes	56	46.7
No	64	53.3

Table 8. Diagnosed ADRs in a patients under the care in the past 12 months.

Have you ever sent a report of a suspected adverse drug reaction to?			95% Confidence Interval		P value
	Frequency	Percent	Lower	Upper	
Pharmaceutical product license holder	8	6.7	2.9%	15.1%	6.1%
Pharmaceutical product manufacturer	2	1.7	.1%	4.9%	2.4%
Have not sent	110	91.7	84.2%	96.6%	6.2%
Total	120	100.0	100.0	100.0	*p<0.05*

Table 9. Reporting rate of a suspected adverse drug reaction.

5.4 Attitude related data

Though the survey documented that the MDs had a low knowledge level regarding to the PV national program and centre, but they still expressed a positive attitude concerning ADRs reporting. About 90.8% (109) participants agreed that MDs should be involved in ADRs reporting process. Although 83.3% (100) considered that monitoring drug safety profile was undoubtedly essential. Correspondingly, around 89.2% (107) believed that MDs should be involved in training programs related to PV and ADR reporting. Approximately 57% (68) respondents disagreed with the statement that the “It is not necessary to report ADRs of OTC products supplied by the clinic in where I do work”. Study has revealed that there were no statistically important alterations distinguished between the responses of the respondents to these statements and the demographics (see, Appendix 9). However, most of the respondents acknowledged to the fact that the ADRs, which lead to congenital abnormality, patient disability and incapability, leading to hospitalization, life threating situations and death of the patient considered as highly essential issues and compulsory to be reported (see Appendix 9).

5.5 Limitations of the study

The major limitation of presented study is that the results were restricted to only four cities of Georgia and did not cover large portion MDs. The outcomes would have been more significant if the study was conducted in all regions and cities in Georgian.

6 Discussion

The current analysis of the focused group interviews and questionnaire based survey responded by a Medical Doctors of Georgia documented the extent level of the lack of knowledge and practice performance related to the mandatory pharmacovigilance reporting system of suspected ADRs.

My hypothesis was confirmed according to the presented study results, in particular, study findings demonstrated that there are obvious complications, problems and obstacles with regard to the ADRs reporting by MDs in Georgia. The study consequences revealed that MDs had poor knowledge and practice performance toward ADRs reporting and pharmacovigilance activity in general. Furthermore, the study outcomes discovered that pharmacovigilance system in Georgia is not in place and it does not work in practice.

6.1 Awareness related to PV program

The study reported that 85% of the total numbers of respondents were not aware of the existence of the ADRs reporting national program in Georgia despite the fact that it had been founded in 1997 in partnership with Pharmacological Committee of the Ministry of Health of Georgia. On the other hand, approximately 92% of the MDs have never sent ADR reports to RAMA. Present study reported that around 83.3% of MDs were not familiar with criteria established by RAMA specifying which ADRs should be reported. The study also demonstrated the fact that 98.3 % of MDs were not aware in which country is located the International Center for Drug monitoring. Based on the information retrieved from the representative of MoLSHA (see, Interview 3), it is evident that RAMA has not received any ADR from MDs in 2017

According to this fact, it seems that the requirements defined by the legislation are not obvious to the MDs. Since, the 83.3% of the respondents were not aware with criteria established by RAMA concerning ADRs reporting in Georgia. The author of the study

assumes that existing problem could be the cause of the lack of communication between the Regulatory Authority and MDs in Georgia.

Correspondingly to the challenging facts presented above, the author sees the necessity from the RAMA for the forceful proclamations, information sharing, providing specific journals and bulletin articles, that will be easily accessible to MDs, in order to increase awareness among MDs. Beside this, it will be beneficial if the RAMA ensures regular, permanent and constant feedback to MDs that will encourages the willingness among MDs to report ADRs continuously. The author strongly believes that in order to improve and increase reporting level the first step should be to maximize the communication and minimize the misconceptions between RAMA and MDs and increase the trust on the common level. This will support to provide adequate explanation and sufficient information by supervision body towards MDs.

6.2 Awareness about ADR and Reporting

The conducted research findings noted that approximately 92% of the MDs have never sent ADR reports to RAMA. The study also shows that 60.8 per cent of MDs had suggested ADRs but had not reported them. The major reasons of discouraging factors towards ADR reporting were as follows: Uncertainty that ADR definitely caused by the particular drug (18%); 16 per cent of the MDs considered the ADR was too trivial to report; around 48 % of physicians were not aware of the existence of a national ADRs reporting scheme; about 21 % were not aware of the need to ADR reporting; 17 % did not know how to report ADRs; 9 per cent considered ADR reporting as too bureaucratic process; 8% mentioned that they did not have enough time to report ADRs and 3% thought that their reports could be used in a legal cases against to them.

Based on the findings it is obvious that further information and education is required in this field, in order to ensure relevant knowledge regarding ADR reporting and stimulate reporting culture. This fact influences and supports to the ideas that in the country there is an illumination deficit of the facts regarding ADRs.

The study results suggest more attention to the training and education programs directed to the issues concerning to pharmacovigilance activities in the undergraduate and postgraduate medical curriculum should be introduced as well. It will be beneficial if

Ministry of Education of Georgian and MoLSHA will collaborate actively and implement appropriate educational curricula at Medical Universities. This progressive action and view will support to increase the awareness and knowledge levels as well as responsibilities among HCTs that will be guarantee to decrease underreporting rate and protect the public health.

6.3 Effectiveness of the existing legislation

As it was noted above 9 per cent of MDs considered ADR reporting as too bureaucratic process and 3% thought that their reports could be used in a legal cases against to them. This fact influences and supports to the idea that current legislation is quite weak and out of date. Based on the study results current legislation differs from the legislation of the developed countries and seems relatively bureaucratic. In contrast of the EU member state countries legislation of Georgia seems very specific and out of date, that need future improvements and harmonization according to the EU requirements in order to make ADR reporting simpler and convenient.

6.4 Attitude and Readiness to report suspected ADRs

The study shows that most of the participants of this research demonstrated very positive feedback towards the ADRs reporting. About 90.8% (109) participants agreed that MDs should be involved in ADRs reporting process. Although 83.3% (100) considered that monitoring drug safety profile was undoubtedly essential. Correspondingly, around 89.2% (107) believed that MDs should be involved in training programs related to PV and ADR reporting. This result shows the readiness of MDs for the future improvements of PV system. These outcomes recommend that there is an urgent need to educate all the MDs concerning the ADR reporting procedures.

One of the significant outcomes discovered in the research was the positive correlation between attitudes and knowledge towards ADRs reporting. Consequently, if the knowledge of ADRs reporting will be improved it also ensures practice performance improvement that would be mirrored on ADRs reporting arrangements in a positive way.

6.5 Hypothetical idea regarding awareness towards pharmacists ADRs reporting

The study findings has showed that 6.7% of MDs has sent ADR reports to 2 Pharmaceutical product license holders and 1.7 per cent informed regarding ADRs to Pharmaceutical product manufacturers. Also, the research noted that PV system works more or less in the drugstores in Georgia. Pharmacy chains have special forms related to the drug side effects and this information. Consequently, the author of the presented study assumes that PV system works more or less on the pharmacy chains level in Georgia. Respectively, it will be beneficial if policymakers take into consideration this fact in the nearest future will involve pharmacists in the PV activity and respectively will strength their role in this field.

7 Summary

The results of the present study shows that most of the Medical doctors have poor and insufficient knowledge and practice performance level regarding pharmacovigilance system. Respectively, activities of pharmacovigilance are not regulated as it is recommended by the international organization and WHO and present legislation is out of the date and requires improvements and harmonization with the EU legislation.

The most essential finding of the study demonstrates that none of the suspected ADRs is not reported, which shows a highest frequency of the underreporting of serious, life treating and fatal reactions in Georgia.

The study findings also demonstrates that pharmacovigilance system legislation requirements in Georgia still stay on the paperwork and unfortunately, currently it does not work in practice.

The Author of the study believes that the outcomes of the study would be useful for development strategies to progress ADR reporting rate in Georgia. Consequently, there are suggestions provided as follows:

The MoLSHA with partnership of Ministry of Education of Georgia should discover methods to implement an appropriate educational curricula at Medical Universities, in order to increase the awareness and knowledge levels as well as responsibilities and reporting culture mong HCTs that will be guarantee to decrease underreporting rate and protect the public health.

Policy makers of Georgia should provide improved, non-bureaucratic and harmonized legislation according to the EU requirements, in order to make ADR reporting simpler, convenient and effective.

To establish PV unit or department in Georgia, in order to ensure safety of circulated drugs on pharmaceutical market and prevent public health and provide cost-effective health care.

To discover pharmacists and nurses knowledge, practice performance and attitude regarding ADRs reporting. Respectively, to strengthen their role towards PV activity that will be highly beneficial for the existing situation in Georgia.

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Appendix 1 – Interview with Mr. Nikoloz Gongadze

Respondent is Nikoloz Gongadze – Chief of Pharmacology Unite of State Regulation Agency for Medical Activities of the Ministry of Labour, Health and Social Activities of Georgia. Head of Chair of Pharmacology, Tbilisi State Medical University

- Shota Jibuti: How would you evaluate present pharmacovigilance working procedures in Georgia?

- Nikoloz Gongadze: Pharmacovigilance system is not working actively in Georgia for years now. It could be seen a signs of the system gradually improvement.

- Shota Jibuti: What are the reasons for pharmacovigilance system not working in a way as it should be?

- Nikoloz Gongadze: There are several objective and subjective reasons related to the issue. Subjective reasons are as follows:

1. Lack of awareness within health care professionals in this field;
2. Not sufficient requirements within the legislation;
3. Lack of basic knowledge within the medical doctors in this field
4. Weak mutual interaction between health care authorities and HCP.
5. Insufficient requirements and relative control from the managerial board in the clinics;
6. Lack of technical support within the regions and less awareness;
7. Inadequate understanding of future implications
8. Polypharmacy moments, which are directly linked to irrational pharmacotherapy
9. Unfortunately, lack of interest of pharmaceutical companies related to the implementation and improvement of the system

- Shota Jibuti: From your perspective, what are the ways to improve the quality of the system?

Nikoloz Gongadze: In order to improve the quality of the system the following activities are required:

1. Increase the sense of responsibly within the HCP
2. Evaluation of attitude and knowledge level within HCP;
3. Active involvement of decision makers from the ministry of health;
4. Enhancement of the applicable supervision procedures, which gradually will become more strict;
5. Implementation of Training programs in this field
6. Implementation of the education programs at universities in this field
7. Implementation of the long-term continues education programs related to the rational usage of medicines that will support the only high quality pharmaceutical products registration. Initial steps have been made in this field that implies GMP standards implementation in the legislation
8. Share EU countries experience and their step by step harmonization;
9. Implementation of the system for statistical analyses regarding drug induced side-affects, complications and life threating incidents;

Release of special medical journal in this field that will be accessible for HCPs.

Appendix 2 – Interview with Irakli Margvelashvili

Respondent is Mr. Irakli Margvelashvili – Executive director of Association of Pharmaceutical Companies Representatives in Georgia

- Shota Jibuti: What do you consider as a week ring on Georgian pharmaceutical market?

- Irakli Margvelashvili: From my point of view, I would emphasise the following: The most week ring is poor quality control of pharmaceutical products, because of the defective legislation and registration procedures of pharmaceutical products that are not harmonized with EU directives.
I would also like to mention nonexistence of pharmacovigilance systems in Georgia. In reality, the process and procedure is written in the paperwork and is not enforced in day to day practice.
I would also outline the poor interaction between regulatory authorities and health care providers.
From my perspective, we have two main leading problems, quality control and nonexistence of pharmacovigilance systems.

- Shota Jibuti: How do think, what are the causes of above mentioned leading problems?

- Irakli Margvelashvili: There are several significant reasons: To begin with, regulatory environment is very specific in Georgia, for instance, when the developed countries, in particular EU countries talk about the harmonization of legislation, our law still stays very unique and specific. I mean that harmonization implies a standardization of the legislation. For example, the Georgian law ,,On drugs and pharmaceutical activities" (adopted in 2009), does not cover quality control of drugs at all. Theses essential issues have been move back to the background. Taking all above into account, I can say that we do not have the opportunity to enforce the control mechanisms and oversight the pharmaceutical products distribution pathway.

- Shota Jibuti: What level of changes do you consider in the present legislation?

-Irakli Margvelashvili: It seems to me that existing legislation, regarding pharmaceutical products quality standard control and pharmacovigilance activity requires essential, cardinal changes in order to ensure the protection of public health.

- Shota Jibuti: Is the polypharmacy considered as a problem in the current environment in Georgia?

- Irakli Margvelashvili: Polypharmacy is a big problem in Georgia. I would like to underline my words that nowadays, polypharmacy is the major problem. I can openly declare this, not only as an expert, but as well as from the experience of my family.

- Shota Jibuti: Can you please, name the main contributors to the problematic issues?

- Irakli Margvelashvili: In the first instance, this is related to the nonexistence of the pharmacovigilance system. Pharmacovigilance system also refers to the medical practitioners' knowledge about drugs and the drug related side effects.

Secondly, an insufficient qualification of HCPs. Of course, it does not refer to everyone, but there is lack of knowledge in quite big population of HCPs, which automatically causes problems of polypharmacy, or in other words, the administration of many different remedies at the same time. Also, it should be noted, that there are a lot of cases, where prescriptions contain such kind of medicines, which are characterized with drug-drug interaction and it is forbidden to administer these drugs together at the same time.

Thirdly, there are number of ethics and compliance cases, which imply the encouragement of medical practitioners (this does not refer to all doctors) by the unconscientious pharmaceutical companies to prescribe series of unnecessary drugs at the same time. All this leads to polypharmacy.

- Shota Jibuti: What are the reasons of above mentioned cases?

- Irakli Margvelashvili: There are several reasons, for instance, indifference behaviours within the doctors, or lack of strict regulations in the legislation.
When we talk about the continuous medical education, this does not mean to be aware of the nosology of the novel treatment methodology only. It also implies the education about

side effects of drugs. This knowledge should be shared by leading pharmaceuticals companies, as it is in the United States where such educational programs are financed by the pharmaceutical companies by 70%. But who is responsible to control the educational level? By all means, Government must be fully responsible for this activity. In the current situation, we do not have opportunities to supervise aforesaid issues, because we do not have mechanism, which can make an analysis of treatment outcomes. It means that we do not have information related to the treatment outcomes.

- Shota Jibuti: You as the executive director of Association of Pharmaceutical Companies Representatives in Georgia, do you have any information, about the level of attention made related to the complaints of patients about the side effects of drugs in the drugstores?

- Irakli Margvelashvili: As I am aware, if patient goes to the pharmacy with the complaints of concrete drug, he or she will be carefully listened. May be not in all pharmacy chains, but as I know most of the pharmacy chains have special forms related to the drug side effects and this information is written there, but to be honest I do not have an information regarding next procedures. So, in their field could be said that PV systems works more or less. It should be also noted, that how well the patient explains his or her feelings and condition to the pharmacist.

- Shota Jibuti: Do you have information about the existence of Pharmacovigilance department/service at the Ministry of Labour, Health and Social Affairs?

- Irakli Margvelashvili: As I am aware, State Regulation Agency for Medical activities is made up with qualified staff. But in this field, it is no to possible to make an analysis since for the active sophisticated working of this system there is a need of daily interaction with international organizations, for instance, such as Uppsala Monitoring Center. Moreover, as I am familiar, Georgia is not part of drug monitoring system and does not have regular connections with them.
I would also like to note, that based on statistics, on average 15 000 000 prescriptions are written in Georgia annually. And it is interesting to know from such amount of prescriptions, there has not been stated 5 adverse drug reaction to become a full member of WHO Drug Monitoring Center. This is the response and this fact highlights that this

system does not work in Georgia and without this it is not possible to oversight and supervise modern pharmaceutical products distribution pathways and inspection.

Also, as an executive director of Association of Pharmaceutical Companies Representatives in Georgia, I would like to note that pharmaceutical companies are very keen to develop and maintain the system in Georgia. These Pharmaceutical companies are investing a lot of funds in Georgia with the aim to study the safety profile of their products. But this does not mean to make bureaucratic barriers and system does not start working in reality.

Appendix 3 – Interview with Mrs. Naili Shengelidze

Respondent is Naili Shengelidze – Head of Registration department of State Regulation Agency for Medical Activities of the Ministry of Labour, Health and Social Activities of Georgia

- Shota Jibuti: Do we have pharmacovigilance unit in Georgia?

- Naili Shengelidze: According to the law, we have regulations regarding pharmacovigilance system.

- Shota Jibuti: Does the legislation require involving medical practitioners as well as pharmacists in the field of the pharmacovigilance activity?

- Naili Shengelidze: If we take into consideration the Georgia law ,,On Drugs and Pharmaceutical Activity", both medical practitioners and pharmacists are required to develop the reports related to adverse drug reactions.

- Shota Jibuti: What about the pharmacovigilance unit at RAMA?

- Naili Shengelidze: We do not have specific independent pharmacovigilance unit, but we have one person in registration division and one person in the division of inspection, who are participating in the data mining of ADRs in case of necessity.

- Shota Jibuti: How many ADR reports have you submitted during previous year?

- Naili Shengelidze: Usually this kind of information is received from other countries' pharmaceutical markets. There is a lack of information related to the ADRs in Georgia. For example, we do receive letter from clinics and outpatient departments, with the content that there were not stated any ADRs. In 2017, we have received 588 reports, mainly CIOMS forms about ADRs, mainly from the pharmaceutical products license

holders. We have not received any ADR report neither from medical doctors, nor from pharmacists.

I also would like to note that we use every opportunity to make a statement during broadcasting on TV channels and in Radio, where we make proclamations regarding the importance of the ADRs reporting. I would like to mention, that Government of Georgia has invited international consultant organization ,,Global Alliance", with the aim to evaluate existing problems around different issues. Georgian Government is trying actively to eradicate gaps from the legislation and make a harmonization with EU legislation. We would like to raise these issues in the foreground and to implement it; we do require specialists, funding and etc. I other words, we need financial support, as well as working places, in aim to ensure effective working of this system. We know that the issue is very problematic and important and as the consequence, RAMA is doing its' best for the regulation of this system.

- Shota Jibuti: Nowadays, do you have active collaboration with Uppsala Monitoring Center?

- Naili Shengelidze: According to the information provided by International organizations, we are conducting relevant activities. We have close collaboration with pharmaceutical product manufacturers, big pharmaceutical companies and with their representatives. They regularly send us valuable information about ADRs and kind of data is the basis to withdraw particular drugs from the pharmaceutical market or cancel the registration, until we are aware of risks.

- Shota Jibuti: Do you have precedent in sending the repots related to ADRs in the Uppsala Monitoring Center?

- Naili Shengelidze: We don't have received any report, which gave us sufficient cause for sending the report to Uppsala Monitoring Center.

- Shota Jibuti: According to information provided above, RAMA receives more reports (which are gathered in different countries) from pharmaceutical products license holders than HCPs, in your opinion what are the reasons?

- Naili Shengelidze: As far as I am concerned, reasons could be lack of knowledge and awareness within medical doctors and pharmacists in this field, as well as lack of

understanding about the importance of the subject. We have circulated information letters within inpatient and outpatient departments and clinics and for response, in 99% we got answer that such kinds of ADRs have not been stated in their authorities. Respectively, with the aim to increase the awareness and knowledge level, we have to take a whole series of measurements and for this we need support from the population, International organizations and medical institutions.

- Shota Jibuti: From your point of view, what are the measures to be implemented to improve the quality of the system working and problem solving?

- Naili Shengelidze: Somehow, it looks simple: we should make amendments in the legislation. We have to involve medical practitioners, pharmacists, representatives of pharmaceutical companies in the improvement procedures of the system. We also should create separate group of individuals, who will be responsible for the setting up and running of the pharmacovigilance system.

Appendix 4 – Interview with Mr. Giorgi Antadze

Respondent is Giorgi Antadze – General Director of the GM Pharmaceuticals

- Shota Jibuti: How would you evaluate the quality of pharmacovigilance system in practice in Georgia?

- Giorgi Antadze: It seems to me, that PV system's working quality is on the middle stage, since the political course of our country is outlined and we all are waiting for the harmonization of our legislation with the EU legislation and directives. But it should be noted, that actually nothing has been done in the field of pharmacovigilance in Georgia at this moment. There are a quite a lot of discussions and projects, but I cannot see the results in practice. From my perspective, currently we live still in old system and should admit, that transition in the new system already seems late and we should move forward very fast, with the aim to reimburse wasted time.

- Shota Jibuti: From your perspective, what steps should be followed to solve the problem? And can you also describe the level of interaction with regulatory authority?

- Giorgi Antadze: In my view, we have close interaction with regulatory authority, because of the enforced regulations and we are trying at maximum to collaborate with the authority. For instance, at present, there is an ongoing discussion regarding the implementation of Good Manufacturing Practice in Georgia. For this reason, regulatory body involved in this project is 'WHO' and is planning to train staff with the support and help of WHO. We also would like to support RAMA in this project and for the training processes we are proposing our factory's material-technical bases. We are quite sophisticated in this field, because we have done kind of training in 2005.

- Shota Jibuti: What do you think about the present pharmacovigilance system in Georgia?

- Giorgi Antadze: From my point of view, present status of this system, including organizational aspects is absolutely insufficient and unsatisfying. The system is outlined

in the paperwork only, but the mechanism by itself does not work at all. We can blame participants of this system, because of their inert activity, but we also should mention that there were not requirements in order to improve or just starting up the system. Otherwise, this system has huge perspective and importance and will be beneficial not only to the State and patients, but for the pharmaceutical products registration procedures as well. The sufficient activity of the PV system will give us opportunity to evaluate adequately the safety profile of our medicines.

- Shota Jibuti: Are you receiving reports related to ADRs of the drugs, which are manufactured in your factory?

- Giorgi Antadze: Since we are working according the EU's Good Manufacturing Practice requirements, we have a special unit related to PV system in our company. We receive, gather and evaluate ADRs. But I would like to note, that if this system is being worked normally we would have an opportunity to avoid a lot complications, waste of time and energy and unnecessary charges as well. At present, we have to spend huge effort with the aim to gather valuable information regarding ADRs.

- Shota Jibuti: In your opinion, what are the reasons for HCPs not sending reports to the regulatory authority?

- Giorgi Antadze: From my perspective, there are series of various reasons: they are not familiar with this field; they don't have sufficient resources and time. They do not have desire to take additional responsibilities. HCPs do not have sufficient motivation. If there is a strong and adequate support from the State, this field will become more important.

- Shota Jibuti: How do you think, does active involvement of pharmacists improve the working quality of the system?

- Giorgi Antadze: If we take into consideration the experience of Western countries, the role of pharmacists should be more high level.

Appendix 5 – Interview with Mr. Zaza Chapichadze

Respondent is Zaza Chapichadze – Chief Specialist of Pharmaceutical Department of State Regulation Agency for Medical Activities Ministry of Labour, Health and Social Affairs of Georgia. Expert of the Committee of experts on Quality and Safety Standards for pharmaceutical practices and pharmaceutical care (CD-P-PH/PC) of European Directorate for the Quality of Medicines & HealthCare (EDQM)

- Shota Jibuti: How would you assess present pharmacovigilance working procedures in Georgia?

- Zaza Chapichadze: Pharmacovigilance system does not work sufficiently in Georgia for years.

- Shota Jibuti: What do you think, what are the actual reasons, which lead pharmacovigilance system not working in a way as it should be?

- Zaza Chapichadze: In my view, there are some important reasons related to these matters, for instance, lack of awareness and knowledge in this field within medical doctors and pharmacists. No adequate requirements within the legislation. It should be noted, that our legislation requires modernization and improvements, in order to be harmonized with the EU law.

- Shota Jibuti: How do you perceive the methods to improve the quality of the system?

- Zaza Chapichadze: From my perspective, in order to improve the quality of the system the following activities are required: At first, we should increase the awareness and knowledge of relevant and actual participants of this system and also, raise the sense of responsibility within the HCP towards the ADRs reporting. In parallel, we should modernize and/or implement EU directives and legislation. I mean to share EU countries practical experience, knowledge and step by step advance suitable observation procedures, which progressively will become more precise and reasonably strict.

Secondly, it seems to me that it will be quite beneficial if medical universities will implement relevant educational programs related to necessity and importance of the pharmacovigilance system and gradually will change the behaviour of medical students, which will become doctors in the nearest future. Thirdly, it will be beneficial to involve international organizations, for example WHO, also policy makers from the Ministry of Health.

Appendix 6 - Survey Questionnaire:

Questionnaire for proposed research survey:

Block A

Social demographic data of the respondents:

1) Gender

1. Male
2. Female

2) Age

1. 24 – 35
2. 35- 45
3. 3. 45-60
4. >60

3) Which type of classification best describes your current area of practice?

1. Paediatrics
2. Surgery
3. Internal medicine
4. Cardiology
5. Family Doctor
6. Dermatology
7. Oncology
8. Neurology
9. Ophthalmology
10. Emergency medicine
11. Urology

12. Obstetrics and Gynaecology
13. Otorhinolaryngology
14. Rheumatology
15. Pulmonology
16. Family medicine
17. Anaesthesiology
18. Infections disease
19. Immunology
20. Allergology
21. Radiology
22. Other… please, specify …

4) How long have you been practicing?

1. < 1 year
2. 1-5 years
3. 5-10 years
4. >10 years

5) Number of prescription dispensed per day?

1. <10
2. 10-20
3. > 5

6) Number of patient served per day?

1. <5
2. 5-10
3. 10-15
4. >15

7) Time spent with patient?

1. <5
2. 5-10
3. 10-15

4. >15

Block B: Adverse drug reaction reporting practice related questions and several hypothetical ADR situations:

1) Have you ever diagnosed an adverse drug reaction? (if "Yes" go to question 2, (if "No'" go to question 3)

1. Yes
2. No

2) During past 12 months, have you observed any adverse drug reaction with any drug?

1. Yes
2. No

3) Have you ever diagnosed an adverse drug reaction in a patient under your care in the past 12 months? (If Yes" go to question 4, (if "No'" go to question 5)

1. Yes
2. No

4) If yes, on an average how many ADRs would be diagnosed under your care in a period of 12 months?

1. < 25
2. 25-50
3. 50- 100
4. >100

5) Have you ever sent a report of a suspected adverse drug reaction to:

1. State Regulation Agency for Medical Activities;
2. Pharmaceutical product license holder;
3. Pharmaceutical product manufacturer

6) Have you ever suspected an adverse drug reaction but not reported it? (if "Yes" go to question 7, (if "No'" go to question 8)

1. Yes
2. No

7) If you have suspected, but not reported, an adverse drug reaction was it because: (tick as many as applicable):

1. You were uncertain that the reaction had been definitely caused by a drug?
2. You considered the adverse drug reaction to be too trivial to report?
3. You were unaware of the existence of a national adverse drug reaction reporting scheme?
4. You were unaware of the need to report adverse drug reactions?
5. You did not know how to report adverse drug reactions?
6. Reporting adverse drug reactions is too bureaucratic process?
7. You do not have enough time to report adverse drug reactions?
8. You were concerned that your report could be used in a legal case for damages by the patient?

8) Are you aware of any criteria from the State Regulation Agency for Medical Activities specifying which adverse drug reactions you should report?

1. Yes
2. No

9) Would you report an adverse drug reaction if the medicine had been prescribed for your patient by another physician?

1. Yes
2. No

10) Would you report an adverse drug reaction if phe patients had purchased the medicine (without prescription) themselves?

1. Yes
2. No

11) Have you ever counselled patient regarding food /drug interaction in the last 12 months?

1. Yes
2. No

Block C: Knowledge related questions

1) Are you aware of any ADRs reporting program in Georgia?

1. Yes
2. No

2) Do you consider ADRs reporting as a natural task for a health care professional?

1. Yes
2. No

3) Are you familiar with the term Pharmacovigilance? (if "Yes" Please, specify…)

1. Yes
2. No
3. 99 – Difficult to answer

4) What do you understand by the term ADR? (if "Yes" Please, specify…)

5) Do you know how to report an ADR?

1. Yes
2. No

6) Do you know in which country the international center for ADR monitoring is located?

1. Yes (if "Yes" Please, specify…)
2. No
3. 99 – Difficult to answer

Block D: Attitude related questions – Do you agree or disagree with the statement provided bellow?

1) Medical Doctors should be involved in ADRs reporting process.

1. Agree
2. Disagree

2) It is important for community medical professionals to attend training programs in.

1. Agree
2. Disagree

3) Reporting ADRs is part of the professional role of a Medical Doctor

1. Agree
2. Disagree

4) I believe that the monitoring drug safety is important.

1. Agree
2. Disagree

5) It should be confirmed that ADR is related to the drug before reporting.

1. Agree
2. Disagree

6) It is not necessary to report ADRs of OTC products supplied by the clinic in where I do work.

1. Agree
2. Disagree

7) It is important to report ADRs leading to hospitalization.

1. Agree
2. Disagree

8) It is important to report ADRs leading to a life threatening situations.

1. Agree

2. Disagree

9) It is important to report ADRs leading to congenital abnormality.

1. Agree
2. Disagree

10) It is important to report ADRs leading to persistent disability or incapacity

1. Agree
2. Disagree

11) It is important to report ADRs leading to patients' death.

1. Agree
2. Disagree

12) It is important to report ADRs in order to answer the questions that may arise in my practice.

1. Agree
2. Disagree

13) Reporting of ADRs is important to show patients that their concerns are taken seriously.

1. Agree
2. Disagree

Appendix 7 – Search strategy

Table 1. Database search results

Database	Citations retrieved
PubMed	**50**
EMBASE	**3**
Google Scholar	**10**

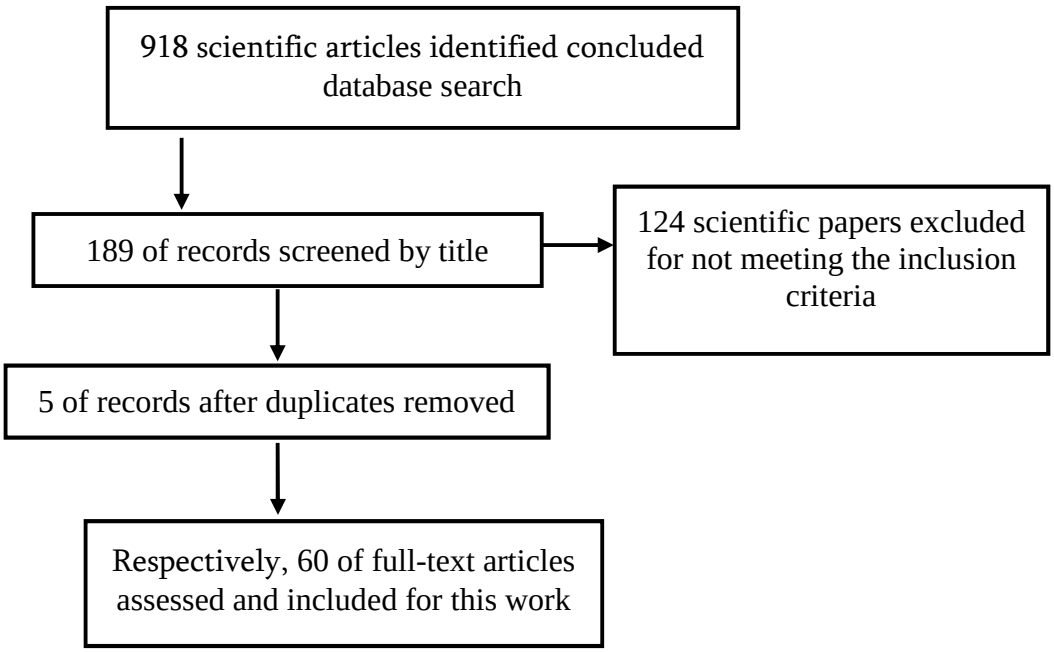
Source: the author.

Table 2. Inclusion and exclusion criteria

Screening questions	Is the citation about Pharmacovigilance Systems?
Language and text	Only citations with full text and in English will be included
Timeline	Only citations from last 22 years will be included

Source: the author.

Appendix 8 – Flow diagram for research selection of the articles



Source: authors.

Appendix 9 – Questionnaire-based Survey Results

City		
	Frequency	Percent
1 Tbilisi	34	28.3
2 Lanchkhuti	13	10.8
3 Ozurgeti	53	44.2
4 Rustavi	20	16.7
Total	120	100.0
A1. Gender		
	Frequency	Percent
1 Female	90	75.0
2 Male	30	25.0
Total	120	100.0
A2. Age		
	Frequency	Percent
1 24-35	7	5.8
2 36-44	29	24.2
3 45-60	63	52.5
4 >60	21	17.5
Total	120	100.0
A3. Which type of classification best describes your current area of practice?		
	Frequency	Percent
1 Pediatrics	15	12.5
2 Surgery	18	15.0
3 Internal medicine	11	9.2
4 Cardiology	6	5.0
5 Family medicine	14	11.7
6 Dermatology	2	1.7
7 Oncology	1	.8
8 Neurology	8	6.7
9 Ophthalmology	3	2.5
10 Emergency medicine	2	1.7
11 Urology	3	2.5
12 Obstetrics and Gynecology	15	12.5
13 Otorhinolaryngology	2	1.7
14 Rheumatology	1	.8
17 Anesthesiology	2	1.7

18 Infections disease	4	3.3
20 Allergology	3	2.5
22 Other… please, specify …	7	5.8
23 Psychiatrics	2	1.7
24 Endocrinology	1	.8
Total	120	100.0
A4. How long have you been practicing?		
	Frequency	Percent
2 1-5 year	7	5.8
3 5-10 year	8	6.7
4 >10 year	105	87.5
Total	120	100.0
A5. Number of prescription dispensed per day?		
	Frequency	Percent
1 <10	36	30.0
2 10-20	36	30.0
3 > 5	41	34.2
4 < 5	7	5.8
Total	120	100.0
A6. Number of patient served per day?		
	Frequency	Percent
1 <5	18	15.0
2 5-10	52	43.3
3 10-15	26	21.7
4 >15	24	20.0
Total	120	100.0
A7. Time spent with patient?		
	Frequency	Percent
2 5-10 minute	10	8.3
3 10-15 minute	35	29.2
4 >15 minute	75	62.5
Total	120	100.0
B1. Have you ever diagnosed an adverse drug reaction? (if "Yes" go to question 2, (if "No'" go to question 3)		
	Frequency	Percent
1 Yes	77	64.2
2 No	43	35.8
Total	120	100.0
B2. During past 12 months, have you observed any adverse drug reaction with any drug?		
	Frequency	Percent
1 Yes	62	51.7
2 No	58	48.3
Total	120	100.0

B3. Have you ever diagnosed an adverse drug reaction in a patient under your care in the past 12 months? (If Yes" go to question 4, (if "No'" go to question 5)?		
	Frequency	Percent
1 Yes	56	46.7
2 No	64	53.3
Total	120	100.0
B4. If yes, on an average how many ADRs would be diagnosed under your care in a period of 12 months?		
	Frequency	Percent
1 < 10	55	45.8
2 10-15	1	.8
Total	56	46.7
System	64	53.3
Total	120	100.0
B5. Have you ever sent a report of a suspected adverse drug reaction to?		
	Frequency	Percent
2 Pharmaceutical product license holder	8	6.7
3 Pharmaceutical product manufacturer	2	1.7
4 Have not sent	110	91.7
Total	120	100.0
B6. Have you ever suspected an adverse drug reaction but not reported it? (if "Yes" go to question 7, (if "No'" go to question 8)		
	Frequency	Percent
1 Yes	73	60.8
2 No	47	39.2
Total	120	100.0
B7. If you have suspected, but not reported, an adverse drug reaction was it because:	Responses	Column Responses %
1 You were uncertain that the reaction had been definitely caused by a drug	18	12.9%
2 You considered the adverse drug reaction to be too trivial to report	16	11.4%
3 You were unaware of the existence of a national adverse drug reaction reporting scheme?	48	34.3%
4 You were unaware of the need to report adverse drug reactions	21	15.0%
5 You did not know how to report adverse drug reactions	17	12.1%

6 Reporting adverse drug reactions is too bureaucratic process	9	6.4%
7 You do not have enough time to report adverse drug reactions	8	5.7%
8 You were concerned that your report could be used in a legal case for damages by the patient	3	2.1%
Total	140	100.0%

B8. Are you aware of any criteria from the State Regulation Agency for Medical Activities specifying which adverse drug reactions you should report?		
	Frequency	Percent
1 Yes	20	16.7
2 No	100	83.3
Total	120	100.0

B9. Would you report an adverse drug reaction if the medicine had been prescribed for your patient by another physician?		
	Frequency	Percent
1 Yes	56	46.7
2 No	64	53.3
Total	120	100.0

B10. Would you report an adverse drug reaction if phe patients had purchased the medicine (without prescription) themselves?		
	Frequency	Percent
1 Yes	75	62.5
2 No	45	37.5
Total	120	100.0

B11. Have you ever counselled patient regarding food /drug interaction in the last 12 months?		
	Frequency	Percent
1 Yes	104	86.7
2 No	16	13.3
Total	120	100.0

C1. Are you aware of any ADRs reporting program in Georgia?		
	Frequency	Percent
1 Yes	18	15.0
2 No	102	85.0
Total	120	100.0

C2. Do you consider ADRs reporting as a natural task for a health care professional?		
	Frequency	Percent
1 Yes	105	87.5

2 No	15	12.5
Total	120	100.0
C3. Are you familiar with the term Pharmacovigilance?		
D3. Reporting ADRs is part of the professional role of a Medical Doctor		
	Frequency	Percent
Agree	100	83.3
2Disagree	20	16.7
Total	120	100.0
D4. I believe that the monitoring drug safety is important		
	Frequency	Percent
1Agree	115	95.8
2 Disagree	5	4.2
Total	120	100.0
D5. It should be confirmed that ADR is related to the drug before reporting		
	Frequency	Percent
1 Agree	118	98.3
2 Disagree	2	1.7
Total	120	100.0
D6. It is not necessary to report ADRs of OTC products supplied by the clinic in where I do work.		
	Frequency	Percent
1 Agree	52	43.3
2Disagree	68	56.7
Total	120	100.0
D7. It is important to report ADRs leading to hospitalization.		
	Frequency	Percent
1 Agree	117	97.5
2 Disagree	3	2.5
Total	120	100.0
D8. It is important to report ADRs leading to a life threatening situations.		
	Frequency	Percent
1 Agree	117	97.5
2 Disagree	3	2.5
Total	120	100.0
D9 It is important to report ADRs leading to congenital abnormality		
	Frequency	Percent
1 Agree	118	98.3
2 Disagree	2	1.7
Total	120	100.0
D10. is important to report ADRs leading to persistent disability or incapacity		
	Frequency	Percent
1 Agree	118	98.3

2 Disagree	2	1.7
Total	120	100.0
D11. It is important to report ADRs leading to patients'death.		
	Frequency	Percent
1 Agree	116	96.7
2 Disagree	4	3.3
Total	120	100.0
D12. It is important to report ADRs in order to answer the questions that may arise in my practice		
	Frequency	Percent
1 Agree	109	90.8
2 Disagree	11	9.2
Total	120	100.0
D13. Reporting of ADRs is important to show patients that their concerns are taken seriously.		
	Frequency	Percent
1 Agree	99	82.5
2 Disagree	21	17.5
Total	120	100.0