ZELALEM GEBRETSADIK ANEBO ADVERSE DRUG REACTIONS REPORTING IN ETHIOPIA: ARETROSPECTİVE ANALYSIS OF PHD THESIS YEAR-2022

NEAR EAST UNIVERSITY

INSTITUTE OF GRADUATE STUDIES

DEPARTMENT OF PHARMACOLOGY

ADVERSE DRUG REACTIONS REPORTING IN ETHIOPIA: A RETROSPECTIVE ANALYSIS OF SPONTANEOUS REPORTS FROM 2013 TO 2018

PhD THESIS

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September, 2022

Approval

We certify that we have read the thesis submitted by ZELALEM GEBRETSADIK ANEBO titled "**ADVERSE DRUG REACTIONS REPORTING IN ETHIOPIA: A RETROSPECTIVE ANALYSIS OF SPONTANEOUS REPORTS FROM 2013 TO 2018**" and that in our combined opinion it is fully adequate, in scope and in quality, as a thesis for the degree of PhD of PHARMACOLOGY.

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As a result, I now affirm that all information, documentation, analyses, and conclusions contained in this thesis were obtained and presented in line with the academic policies and ethical standards of the Institute of Graduate Studies at Near East University. I further affirm that I have appropriately referenced and attributed all non-original information as required by these rules and conduct.

Zelalem Gebretsadik Anebo

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Zelalem Gebretsadik Anebo

ABSTRACT

ADVERSE DRUG REACTIONS REPORTING IN ETHIOPIA: A RETROSPECTIVE ANALYSIS OF SPONTANEOUS REPORTS FROM 2013 TO 2018

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***Objective*: To look at the frequency and characteristics of spontaneous adverse drug reaction (ADR) reports sent to the pharmacovigilance (PV) database system in Ethiopia. *Methods*: Between 2013 and 2018, healthcare professionals reported spontaneous ADR reports to the PV database, which were analyzed in a descriptive and retrospective analysis. The study identified spontaneous ADR reports that met the minimal reporting requirements in terms of reporting rate, patient characteristics, kind of ADRs, suspected medications, report sources, and reporters' profession. *Results*: The PV center received 657 spontaneous ADR reports between 2013 and 2018. The reporting pattern of ADRs altered considerably during the research period. The number of reports grew in 2013 (n=12), reached a peak in 2015 (n=205), and then abruptly decreased in 2016 (n=144), 2017 (n=142), and 2018 (n=144). Females reported a larger percentage of incidents (55.9%) than males (43.3 %). The age groups 0-14 years (154, 23.3%), 65 years and more (65%), and 15-64 years (475, 72.0%) reported the greatest ADRs, respectively (21, 3.2%). Pharmacists (81.2%) were the ones who reported the most adverse drug reactions, followed by health officials (7.1%), nurses (5.8%), and doctors (5.8%). Skin and subcutaneous**

tissue abnormalities were the most often reported ADRs. The most commonly suspected drug class was "anti-infective for systemic use'' according to anatomical therapeutic chemicals code class. The most commonly reported drug that causes ADRs was trimethoprim with sulfamethoxazole as a combination (14.5%). ***Conclusions*****: In comparison to developed countries, the amount of ADRs reported in Ethiopia was small and unpredictable, indicating that the PV system's performance and health-care personnel' understanding of ADR reporting were not sufficient. More efficient PV procedures and public policies must be established in order to enhance the frequency of spontaneous reporting.**

Key-words: pharmacovigilance; adverse drug reactions; spontaneous report

ÖZET

ETİYOPYA'DA ADVERS İLAÇ REAKSİYONLARI BİLDİRİMİ: 2013'TEN 2018'E SPONTAN RAPORLARIN GERİSPEKTİF BİR ANALİZİ

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Amaç: Etiyopya'nın farmakovijilans (PV) veri tabanı sistemine sunulan spontan advers ilaç reaksiyonu (ADR) raporlarının sıklığını ve profilini araştırmak. Yöntemler: 2013 ve 2018 yılları arasında sağlık uzmanları, tanımlayıcı ve geriye dönük bir analizde analiz edilen PV veri tabanına spontan ADR endişelerini bildirdiler. PV merkezi, raporlama oranı, hasta özellikleri, ADR türleri, şüpheli ilaçlar, rapor kaynakları ve rapor verenlerin mesleği açısından minimum raporlama kriterlerini karşılayan spontan ADR raporlarını belirledi ve analiz etti. Sonuçlar: PV merkezi, 2013 ile 2018 arasında 657 spontan ADR raporu aldı. ADR'lerin raporlama modeli, araştırma dönemi boyunca önemli ölçüde değişti. Rapor sayısı 2013'te arttı (n=12), 2015'te zirve yaptı (n=205) ve 2016'dan 2018'e hızla düştü (sırasıyla n=144, 142 ve 65). Kadınlar (%55.9) erkeklere göre (%43.3) daha büyük bir olay yüzdesi bildirmiştir. 15-64 yaş grupları (475, %72,0) en fazla ADR bildirdi, bunu 0-14 yaş (154, %23,3) ve 65 yaş ve üstü (%65) (21, %3,2) izledi. AİR'lerin çoğunluğu eczacılar (%81,2) tarafından rapor edilmiş, bunu sağlık görevlileri (%7,1), hemşireler (%5,8) ve doktorlar (%5,8) izlemiştir. En yaygın ADR'ler cilt ve deri altı doku anormallikleriydi. En yaygın olarak şüphelenilen ilaç, "sistemik kullanım için anti-enfektif" olarak adlandırılan anatomik bir terapötik kimyasal kod sınıfıydı. ADR'lere neden olan en yaygın olarak rapor edilen ilaç, kombinasyon halinde sülfametoksazol ile trimetoprimdir (%14,5). Sonuçlar: Gelişmiş ülkelerle karşılaştırıldığında, Etiyopya'da rapor edilen ADR'lerin miktarı küçük ve tahmin edilemezdi, bu da PV sisteminin performansının ve sağlık personelinin ADR raporlamasını anlamasının yeterli olmadığını gösteriyor. Spontane raporlama sıklığını artırmak için daha verimli PV prosedürleri ve kamu politikaları oluşturulmalıdır.

Anahtar kelimeler: farmakovijilans; Advers İlaç Reaksiyonları; kendiliğinden rapor

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LIST OF ABBREVIATIONS

ADRs: Adverse Drug Reactions

ATC: Anatomical therapeutic classes

DME: Designated medical terms

FMHACA: Food Medicine and Health Care Administration and Control authority

HCPs: Health care professionals

ICH: International Council for Harmonisation

ICSR: Individual case safety report

ICU: Intensive Care Unit

KAP: Knowledge, Attitude, Practice

MAHS: Market Authorization Holders

MedDRA: Medical dictionary for Drug regulatory authority

MHRA: The Medicines and Healthcare products Regulatory Agency

PTs: Preferred terms

PV: Pharmacovigilance

PvCPs: Pharmacovigilance Contact Points

SNNPR; Southern Nations and Nationalities people representatives

SOCs: System organ classes

SPS: Strengthening Pharmaceutical Systems

SRS: Spontaneous Report System

UMC: Uppsala Monitoring Center

US; United States

USAID: United States Agency for International Development

WHO: World Health Organization

WHO-UMC: World health organization Uppsala Monitoring Centre

CHAPTER I

Introduction

In today's modern world, the proper use of medicines and the well-being of patients are top priorities (Hitesh Mishra, 2013). The development of new drugs has revolutionized the way diseases are handled and controlled, and this has been a hugely beneficial progression in many situations. However, despite all of the benefits, evidence continues to mount that adverse drug responses are a widespread, yet sometimes preventable, cause of sickness, disability, and even death (Desai et al., 2011)**.**

Since the second quarter of the twentieth century, there has been widespread access to therapeutic advances, which has resulted in significant improvements in public health but also raised safety concerns because medicines carry a risk, and the benefit/risk ratio changes during the post-marketing phase. (Reis and Veiga, 2015).

Adverse drug reactions (ADRs) are defined by WHO (World health organization) as “any noxious and unintended response to a medicine which might occur at doses utilized for prophylaxis, diagnosis or treatment.” (Hadi et al., 2017). ADRs, which are one of the top causes of morbidity and mortality worldwide, will continue to be a public health issue if medications are used to treat a variety of conditions (WHO, 1972).

Pharmacovigilance has been increasingly important in recent years, and its relevance in the healthcare system is now well recognized. However, there are a number of difficulties that must be addressed in order to ensure that medicines are safe (Najafi, 2018). Pharmacovigilance, commonly known as "drug safety," is the science and activity concerned with the identification, assessment, and prevention of adverse effects, according to the WHO (WHO, 2012). The goal and scope of pharmacovigilance are broad, encompassing a variety of issues such as pharmaceutical errors, counterfeit and unlicensed drugs, lack of efficacy, drug interactions, and rational medication prescribing (WHO, 2012).

Improvements in public health, as well as precise evaluation and monitoring of drug safety, are critical for preventing or reducing patient risks. To reach this goal, all countries

should implement an effective pharmacovigilance and adverse event reporting system (Najafi, 2018). In the pharmacovigilance system, healthcare practitioners play a key role. They will successfully contribute to this area by early identification, management, and reporting of medicine safety issues, and will require extensive knowledge and expertise in the field of medication safety. Despite widespread concerns about medication safety, healthcare professionals are still unaware of pharmacovigilance and adverse event reporting. Only 2-4 percent of all adverse events and 10% of significant ADRs are recorded globally, according to studies (Sales et al., 2017).

Furthermore, recent research have revealed that adverse drug reactions (ADRs) are underreported by healthcare practitioners, particularly in underdeveloped countries (kidu Gidey, Mohammed Seifu, Berhane Yohannes Hailu, Solomon Weldegebreal Asgedom, 2020). Any suspected adverse reaction, particularly those suspected reactions to newly authorized drugs and significant incidents, should be reported by healthcare professionals such as physicians, pharmacists, dentists, and nurses. As a result, pharmaceutical safety evaluations must be considered an integral element of healthcare professionals' daily clinical practice (Almandil, 2016).

The spontaneous reporting system (SRS) is an important aspect of pharmacovigilance and is used to generate ideas regarding probable drug side effects that need to be investigated further. It is extremely useful in detecting extremely unusual or delayed reactions that were missed during the clinical trial's brief duration (Hans & Gupta, 2016; Najafi, 2018). However, SRS has its limitations. SRS is frequently linked to reports of poor quality, known reactions, and the inability to establish a causative association. Furthermore, due to insufficient numerator data and an unreliable denominator, SRS limits the ability to calculate rates (Fontanarosa et al., 2004). Furthermore, SRS has been linked to underreporting, which could have an impact on new medications and dangerous reactions (Moride et al., 1997). Despite its problems, SRS is widely regarded as the most cost-effective approach of medication safety monitoring (Hazell & Shakir, 2006).

The Uppsala Monitoring Center (UMC), established under the auspices of the WHO Program for International Drug Monitoring, collects global data on ADRs (WHO, 2006). The UMC's individual case safety reports (ICSR) database system, VigiBase, receives

national ADR reports from all member nations (Shankar, 2016). UMC keeps a close eye on the VigiBase for any potential signals or alerts from national pharmacovigilance agencies. ADR profiles, on the other hand, change from country to country due to variances in genetics, population nutrition and culture, and medical procedures(Russo et al., 2013). Furthermore, pharmacovigilance systems differ amongst WHO member nations (Aagaard et al.,2012).

In 2002, Ethiopia's Food, Medicines and Healthcare Administration and Control Authority (FMHACA) formed its own pharmacovigilance system. Following this, Ethiopia joined the WHO's international drug monitoring program in 2008. Since the inception of the pharmacovigilance system, the number of ADR reports received by the center from healthcare practitioners has been low. (Adimasu, 2014).

Ethiopian population have a distinct genetic makeup when compared to Caucasians, Orientals, and other Black peoples, according to studies. (Ermias et al., 2011). The monitoring of the safety of these drugs contributes to the collection of evidence on the safety of medicines used by Ethiopians. In Ethiopia, only a few studies have been undertaken to analyze health care professionals' knowledge, attitude, and practice regarding ADR reporting. The findings reveal that health care professionals have a good attitude toward ADR reporting but insufficient knowledge and practice.(Gurmesa & Dedefo, 2016; Seid *et al*., 2018). According to Ermias et al., (2011), analysis of case reports done from 2002-2007, showed that the level of ADR case reporting in Ethiopia is very low. Although there is little evidence that ADRs and other adverse events are reported in Ethiopia, it is likely that the problem is significant due to widespread irrational drug usage, such as the predilection for injections, antibiotic misuse, traditional/herbal medicine use, and extensive self-medication. In Ethiopia, there is a scarcity of data on healthcare personnel' knowledge, attitudes, and behaviors surrounding ADR reporting at the health facility level (Necho Mulatu, 2014). As a result, the purpose of this research was to examine national ADR reports submitted to pharmacovigilance centers by health care providers during the study period.

Statement of the Problem

ADRs have clearly emerged as a major global health problem that requires substantial attention at all levels of the healthcare system, according to studies from throughout the world. The pharmacovigilance system aids regulatory agencies in allowing safe medications to enter the market and benefit patients. The device is utilized to detect signals and allows for the investigation of unknown ADRs that were not discovered during clinical trials. The approach also allows for the assessment of pharmaceutical safety in real-world clinical situations and is one of the key mechanisms for comprehensive post-marketing monitoring of medicine-induced risks (Suyagh et al., 2015).

On the other side, one of the system's fundamental flaws is that only a small percentage of overall ADRs are reported (Hazell & Shakir, 2006). Correspondingly, voluntary nature of this system reporting represents the main reason of ADR underreporting phenomena (Härmark & Van Grootheest,2008).Currently, underreporting stays one of the scaring obstacles of pharmacovigilance comprehensive activity (Visacri et al., 2015). According to the scientific studies several reasons have been listed out for underreporting among health care providers. The most significant factors are a lack of understanding of the voluntary reporting system, doubts regarding the causal association between the medicine and adverse events, prejudicial attitudes against ADR reporting, a lack of established pharmacovigilance systems, and a lack of sufficient time (Mariley Perez Garcia and Albert Figuersa, 2011). According to the literatures, health care providers' knowledge, attitude, and practice regarding spontaneous ADR reporting were extremely low (Gurmesa & Dedefo, 2016) (Alharbi et al., 2016).

It is critical to protect the public's health and safety from harmful medication reactions in general. It is highly reliant on health-care professionals reporting medication-related adverse occurrences to drug regulators. The evaluated ADRs information is then utilized to improve evidence-based practice and underlies regulators' and market authorization holders' decisions to reduce drug safety risks (Ampadu et al., 2016).

Significance of Study

I. The study revealed rational and helpful information regarding existing ADR reporting pattern and ADR profile of national database.

II. The outcomes of the research helped in strengthening the ADR reporting practice by underling the weaknesses and obstacles in the existing PV scheme.

III. This study would have given opportunity to collect information in the place regarding safety profile of pharmaceutical products in the market that offers possibility to prevent the risks of health complications in the target population

Hypothesis / Research Questions

Research Questions

I. What percentage of adverse drug reactions are reported?
II. Which patient population has an increased risk of adverse drug reactions?
III. Who should report adverse drug reactions?
IV. What factors can contribute to the increased incidence of adverse drug reactions?
V. What organs are affected by adverse drug reactions?

Answers

Hypothesis: -There is limited information on ADRs reporting pattern analysis and its performance.

I. Only 6–10% of all ADRs are reported, according to estimates. As a result, underreporting has been a major impediment to spontaneous reporting of ADRs, posing a significant challenge to pharmacovigilance efforts as well as having a negative impact on public health (Adisa & Omitogun, 2019). In Ethiopia, increasing access to complex treatment of concomitant infectious and non-communicable diseases is leading to a higher prevalence of drug-related problems due to medication errors, product quality defects, and irrational use of medicines

among patients on chronic follow-up in ambulatory care clinics, as well as significant causes of mortality rate among patients presenting to emergency departments (Hailu & Mohammed, 2020).

II. While the occurrence and impact of ADRs in the general adult population have been widely investigated, little is known about ADRs in the elderly. It is well recognized that older people have a higher disease burden and, as a result, use more medications. ADRs are more likely to occur as a result of increased pharmaceutical use and health complexity. A variety of age-related physiological changes impacting the pharmacokinetics and pharmacodynamics of drugs, as well as increases in medication quantity and concomitant diseases, may raise the risk of ADRs in older people (Alhawassi et al., 2014)(Mekonnen et al., 2018). Adverse drug responses (ADRs) become more common as people get older, with patients 65 and older being admitted to the hospital twice as often as their younger counterparts (Giardina et al., 2018). Adverse drug reactions (ADRs) are common in older adults, with falls, orthostatic hypotension, delirium, renal failure, gastrointestinal and intracranial bleeding being amongst the most common clinical manifestations. ADR risk increases with age-related changes in pharmacokinetics and pharmacodynamics, increasing burden of comorbidity, polypharmacy, inappropriate prescribing and suboptimal monitoring of drugs (Lavan & Gallagher, 2016).

III. Healthcare Professionals are the preferred source of information in pharmacovigilance, for example physicians, family practitioners, medical specialists, and dentists. Nurses and other health workers may also administer medicines and should report relevant adverse drug reactions experienced by the patients. Pharmacists can play an important role in the stimulation of reporting and in the provision of additional information (for example, on co-medication and previous medicine use). Patients & their relatives can also report their experienced adverse drug reactions directly to regulatory authority, or through their healthcare professionals. In this case seek the patient permission to contact their healthcare professionals for additional information and data verification. Marketing authorization holder (MAH), being primarily responsible for the safety

of their products, they are obligated to report serious adverse drug reactions they receive about their products to regulatory authority. While the Non-serious ADRs should be included in the periodic safety update reports (PSURs)(Naranjo et al., 1981)

IV. Extremes of age, gender, multiple medicines, disease status, previous history of ADR or allergy, hereditary variables, excessive doses, and a variety of other factors can all raise the risk of ADRs (Alomar, 2014).

V. Adverse drug reactions can affect a number of different organs, including the liver, skin, kidney, heart and muscle, and, with some drugs, more generalized hypersensitivity reactions can occur(Pirmohamed, 2004). The most commonly affected organ system was gastrointestinal , and the most common class of drugs responsible was anti-infectives (Kourorian et al., 2009).

Objectives of the study

The general purpose/objective of the study to investigate the frequency and profile of spontaneous ADRs reports submitted to Ethiopia's pharmacovigilance (PV) database system

Specifically the aims of the present study were the following;

I. To conduct analysis and characterize the patterns of ADR reports submitted to pharmacovigilance center of country and to generate information and gain understanding on ADRs reporting pattern.

II. The study also will do comparative analysis on the quantity and quality of reports submitted among health care professionals.

Definition of Key Terms;

Terms that study focuses on are the following: -

ADRs;

A negative affect that is said to be induced by a medicine. This term has been thrown around a lot to cover a wide range of negative events, many of which aren't really "reactions" in the strict sense and haven't been subjected to any sort of causation analysis. The word should only be used in late-stage research when the link between a drug and an adverse effect has progressed beyond 'unmeasurable' or 'uncertain'(WHO- ART, 2005).

Pharmacovigilance;

Medicines and vaccines have transformed the prevention and treatment of diseases. In addition to their benefits, medicinal products may also have side effects, some of which may be undesirable and / or unexpected. Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine/vaccine related problem. All medicines and vaccines undergo rigorous testing for safety and efficacy through clinical trials before they are authorized for use. However, the clinical trial process involves studying these products in a relatively small number of selected individuals for a short period of time. Certain side effects may only emerge once these products have been used by a heterogenous population, including people with other concurrent diseases, and over a long period of time(WHO- ART, 2005).

Medical Dictionary for Regulatory Activities:-

MedDRA is the medical terminology created under the auspices of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)(WHO, 2011). The Medical Dictionary for Regulatory Activities (MedDRA) is an internationally used set of terms relating to medical

conditions, medicines and medical devices. It was created to assist regulators with sharing information. It is also used by industry, academics, health professionals and other organisations that communicate medical information.

Individual case safety report (ICSR);

When a patient taking one or more drugs experiences an unfavorable impact, reports are sent by health professionals or patients. Adverse drug reaction (ADR) reports and adverse event (AE) reports are two terms that have been used to describe these reports(WHO-ART, 2005).

Uppsala Monitoring Center;

The Uppsala Monitoring Centre advances pharmacovigilance science and promotes medications and patient safety programs around the world. We collaborate with the World Health Organization and engage stakeholders who share our aim of enhancing medicines safety with the global pharmacovigilance community as an independent, non-profit organization. We examine the benefits and dangers of medications for patients as a leader in the research and development of innovative scientific approaches, and we offer goods and services used by health authorities and the pharmaceutical industry around the world. The center have been supporting the WHO Programme for International Drug Monitoring with scientific advancement and operational support for over 40 years (UMC,2021).

Preferred terms;

"Preferred Terms" (PTs), is a distinct descriptor (single medical concept) for a symptom, sign, disease diagnosis, therapeutic indication, investigation, surgical or medical procedure, and medical social or family history characteristic(MedDRA, 2016).

Anatomical therapeutic Chemical (ATC) classification*;*

The Anatomical Therapeutic Chemical (ATC) Classification System defines active ingredients of medications based on the organ or system on which they work, as well as their therapeutic, pharmacological, and chemical qualities. Its purpose is to help with drug monitoring and research to improve medication quality. It does not imply pharmacological efficacy or recommendation (WHO, 2020). It is controlled by the World Health Organization Collaborating Centre for Drug Statistics Methodology (WHOCC), and was first published in 1976(Strengthening Pharmaceutical Systems (SPS) Program & USAID, 2009)(WHO, 2020)(WHO- ART, 2005).

System organ class*;*

The highest level of the MedDRA terminology is the system organ class, which is distinguished by anatomical or physiological system, aetiology (disease origin), or purpose. The majority of these are illnesses of a specific body part. For instance: Cardiac disorders are abnormalities with the heart. Renal and urinary ailments refer to issues with the kidneys and bladder.(ICH, 2022).

***VigiBase*;**

VigiBase is a global Individual Case Safety Report (ICSR) database maintained by the World Health Organization (WHO). It contains ICSRs received by participating member states enrolled in WHO's international drug monitoring program. It is the world's largest repository of medication safety data. The Uppsala Monitoring Centre (UMC; Uppsala, Sweden) has been maintaining VigiBase on behalf of WHO since 1978 (Iavindrasana et al., 2006). Vigibase is used to collect information on a pharmaceutical product's safety profile. Pharmaceutical companies, academic institutions, and regulatory agencies use these data to spot statistical signals, update periodic reports, compare ICSR data to business databases, and investigate reporting patterns (UMC, 2021). The data (pre-dominantly post-marketing serious and non-serious cases) is collected from each of its

110 member states which currently comprises to over 10 million ICSRs (October 2014)(UMC, 2021). About a hundred thousand ICSRs are added each year.

Spontaneous Report System;

Spontaneous reporting is defined as "an unsolicited communication by a healthcare professional or consumer to a company, regulatory authority, or other organization (e.g., WHO, Regional Centre, Poison Control Centre) that describes one or more adverse drug reactions in a patient who was given one or more medicinal products and that does not derive from a study or any organized data collection scheme," according to the WHO (ICH, 2022). By nature, spontaneous reporting is a passive method to pharmacovigilance (PV), relying solely on individuals' motivation to report suspected adverse drug reactions (ADRs) to a local or national pharmacovigilance center. SRSs can be paper-based (like the UK's 'Yellow Card' system) or computerized (online reporting or mobile applications). Individual Case Study Reports are single reports from individual patients submitted to pharmacovigilance centers using these methods (ICSRs). The data from several ICSRs is then combined to find potential’ signals, or connections between a pharmaceutical product and a previously unknown reaction. The detection and confirmation of these signals can reveal previously unknown unfavorable or good effects of a medicine using a variety of approaches. SRS is distinguished by the fact that they (WHO- ART, 2005), encompassing the entire product life cycle of each medicine.

CHAPTER II

Literature Review

Historical Development and Milestones in Pharmacovigilance

The global history of pharmacovigilance can be divided into a succession of milestones that lead to the re-evaluation of previous notions and the introduction of new concepts within the discipline (Lembit Rägo, 2008). A few drug-related safety concerns sped up the concerned parties' reactions. These safety concerns stemmed from a catastrophic health tragedy in which the public's health was jeopardized. One of the most notable examples, which affected an approach to established practice, is discussed below.

Sulphanilamide elixir, 1937

The use of Sulphanilamide in the form of elixir had resulted in fatal incidents in the United States. Diethylene glycol, the elixir's solvent, was found to be hazardous, and dozens of people died as a result. As a result of this disastrous experience, the Federal Food, Drug, and Cosmetic Act of 1938 was enacted (Canadian Medical Association, 1937).

Thalidomide - 1961

The usage of thalidomide was linked to an increase in the incidence of phocomelia in European countries. The medicine was first studied on animals before being tried on humans, with exceptionally minimal toxicity in both animal and clinical testing (Kim & Scialli, 2011). Malformations in tens of thousands of children, on the other hand, resulted in a tragic scenario, prompting a re-evaluation of a method for collecting, evaluating, and disseminating information on ADRs (WHO, 2010).

Practolol -1975

Patients experienced oculomucocutaneous syndrome after taking practolol. It's possible that recording all adverse events reported by patients, not just those classified as ADRs to medications, might have discovered practolol's ocular toxicity before the drug was released. As a result of this experience, come to the conclusion that all events should be recorded. (Wright, 1975).

Cerivastatin-2001

Rhabdomyolysis was first documented in a patient using a combination of cerivastatin and gemfibrozil in 1999. Cerivastatin was taken off the market in the United States and Europe in August 2001, and then in Japan, due to an increase in rhabdomyolysis reports (Lau et al., 2001). Since then, there has been increased pressure to keep independent advisory panels in place to conduct their own reviews and make suggestions (Ray & Weiss, 2012; SPS Program & USAID, 2009).

Rofecoxib-2004

When it became clear that the medicine caused substantial cardiovascular side effects, it was taken off the market in September 2004. While the VIGOR study offered strong evidence for rofecoxib's gastrointestinal safety, it also raised concerns about its cardiovascular toxicity, including a particularly concerning increase in the risk of myocardial infarction in 2000. However, according to a cumulative meta-analysis published in 2004, rofecoxib should have been discontinued several years earlier (Jüni et al., 2004).

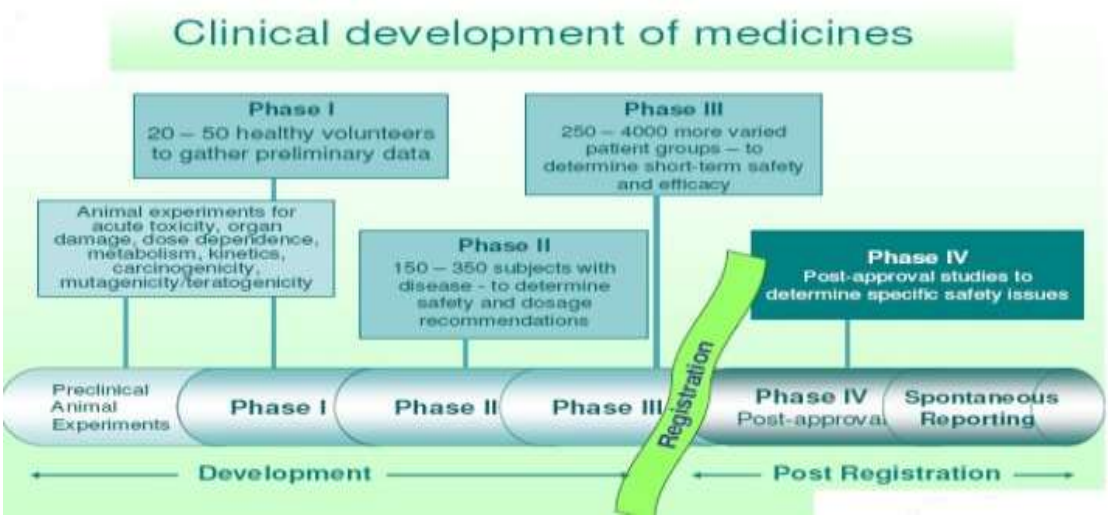
Emerging drug safety concerns in the 20th century hastened the development of international organizations, each with its own projects and programs, to define standards and assure effective collaboration in the surveillance of medicinal product safety (Jindrich, 2014).

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 (Elshafie *et al*., 2018).

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 (WHO,2012), 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" (WHO-UMC, 2009). In most of the cases unexpected and rare adverse drug reactions are mostly determined in the post-marketing phase of medicines.

Figure 1.

Clinical Development of Medicines.



The above figure 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.

As a result, the small number of people participated in pre-marketing phase clinical trials makes it difficult to estimate a medicine's ADR profile (Wysowski & Swartz, 2005). 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 (Campbell *et al*., 2014). Respectively, ADRs have a major influence on the public health programs and impose unnecessary and irrational economic loads on the population.

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 (Moore, 2017) 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) (WHO, 2012). 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 (Jindrich, 2014)].

Pharmacovigilance is defined by the World Health Organization (WHO) “as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem”. Pharmacovigilance's goals are to improve patient care and safety in connection to the use of medications, as well as to support public health programs by providing reliable, balanced information for the proper assessment of a medicine's risk-benefit profile (WHO, 2004).

Patients' safety and the safe use of medications are top issues in today's environment (Mishra *et al*., 2016)). Any Drug Regulatory Authority and Pharmaceutical Company's primary mission is to ensure the quality, efficacy, and safety of all marketed goods. Data

from in vitro testing to guarantee conformity with approved standards, as well as data from animal research, preclinical and clinical trials involving humans, can be used to determine the first two criteria (Deolekar et.,al 2016)).

However, it is a well-known reality that pre-marketing clinical trials lack the statistical power to detect infrequent ADRs and lack the necessary follow-up to detect delayed adverse drug reactions or long-term consequences. As a result, pharmacovigilance is crucial in determining the safety profile of marketed medications, as pre-marketing clinical trials are frequently insufficient to adequately establish these criteria (Deolekar et al., 2016).

If correctly followed and performed on a wide scale, pharmacovigilance has grown from a minor appendix of drug regulation to a major activity. Adherence to this approach will ensure higher patient safety and help to eliminate preventable ADRs (Deolekar et al., 2016); Rohilla et al., 2012). However, a lack of reporting and understanding of the need of pharmacovigilance remains a concern. Table 1 lists some recent notable medication safety concerns, as well as the data that led to their discovery.

Table: 1

Drug Safety Concerns That Have Risen In Europe Since 1995

Drug	**Safety concern**	**Key evidence**	**Regulatory Decision taken**
Trovofloxacin	Hepatoxicity	Spontaneous ADRs	Withdrawn
Tolcapone	Hepatoxicity	Spontaneous ADRs	Suspended
Cisapride	QT prolongation; heart arrhythmias	Spontaneous ADRs	Patient registration licences subsequently cancelled

Bupropion	Seizures, drug interaction	Spontaneous ADRs	Posology change, Warnings
Cerivastatin	Rhabdomyolysis	Spontaneous ADRs	Withdrawn
Hormone replace therapy	CVS risk; cancer long term	Epidemiological studies	Warnings and restriction of indication
SSRIs	Suicidal behavior in children	Clinical trials	Warnings accompanied by clinical guidance
COX IIs	CVS risk	Clinical trials	Warnings and clinical guidance
Topical macrolides immunosuppressant	Risk of cancer	Spontaneous reports	Restriction of use, Risk management plan SSRI

Despite the growth in access to medications in Africa over the last three decades, data on the impact of adverse drug reactions (ADRs) is still scarce, owing primarily to the countries' level of development. Nonetheless, ADRs are thought to be the cause of 4.5 to 8.4% of hospital admissions, 1.5 to 6.3 % of hospitalizations, 6.3 to 49.5 % of ADRs occur during hospitalization, and 14% of ADRs in the Moroccan Anti Poison and Pharmacovigilance Center database are classified as preventable errors (Hye et al., 2012)(Wa et al., 2011)(Bencheikh & Benabdallah, 2009). Another study in a Tunisian hospital found that 9.2 % of ADRs occur during hospitalization, with 27 % to 69.6 % of them being preventable or due to ignorance (Nabiha et.,al 2013).

PV is a critical science for public health protection and a crucial instrument for ensuring consumer quality, effectiveness, and safety, contributing to the rational use of medications. As a result, this is the framework for every country's demand for a functional PV system.

PV systems in African countries, like those in developed countries, are primarily relied on spontaneous reporting, and Ethiopia is no exception. In Ethiopia, the Food, Medicines and Healthcare Administration and Control Authority (FMHACA) created a pharmacovigilance system in 2002. Ethiopia was thereafter accepted into the WHO's international drug monitoring program. Since the inception of the pharmacovigilance system, the number of ADR reports received by the center from healthcare practitioners has been limited in number (Worku and Mulatu, 2014).

The primary goal of recording and reporting ADRs is to prevent future patient harm. Although there is little evidence that ADRs and other adverse events are reported in Ethiopia, it is likely that the problem is significant due to widespread irrational drug usage, such as the predilection for injections, antibiotic misuse, traditional/herbal medicine use, and extensive self-medication (Adimasu, 2014). In Ethiopia, there is a scarcity of data on healthcare personnel' knowledge, attitudes, and behaviors surrounding ADR reporting at the health facility level.

Adverse Drug Reactions (ADRs)

The reporting of ADRs is a major concern for pharmacovigilance. The WHO defines an ADR "as a noxious and unanticipated response to a medicine in people or animals, including loss of efficacy that happens at any dosage and can also emerge from overdose, misuse, or abuse of medicine". (Deolekar et al., 2016; Palaian, Ibrahim, & Mishra, 2011; Zolezzi & Parsotam, 2005; Mishra and Kumar, 2013). Any unfavorable experience linked with the use of a medicinal product in a patient is referred to as an adverse drug event (ADE). ADRs and other occurrences (including medication errors) linked to the prescribing, preparation, dispensing, or administration of drugs are included in this comprehensive definition (Zolezzi & Parsotam, 2005).

One of the most common drug-related issues is adverse drug reactions (ADRs) (Alsaleh et al., 2017) , and are a major cause of morbidity and mortality around the world (Khalil & Huang, 2020). ADRs are among the top 10 primary causes of death in various nations (Abubakar et al., 2014). A meta-analysis of 69 prospective and retrospective studies involving 419 000 patients undertaken in various parts of the world indicated that ADRs

were responsible for around 6.7 % of all hospitalizations (Mehta, 2011). Adverse events account for a significant portion of hospital admissions, ranging from 3.2 % in France to 6.7% in the United States, 12 % in Sweden, and 6.5% in the United Kingdom. (Suleman, 2010).

Several studies, such as those conducted by(Mehta, 2011) and(Sultana et al., 2013) have also found that the cost of managing ADRs place a significant burden on health care budgets. Some countries reportedly spend up to 15 - 20 % of their hospital budget dealing with drug complications(M. Ramesh et al., 2003; Mehta, 2011; Sultana et al., 2013). As a result, in addition to the obvious morbidity and mortality instances caused by these often preventable consequences, ADRs place a huge financial strain on global health care systems, as they lengthen hospital stays and raise overall treatment costs (KB & NG, 2014). The understanding of medication safety as a key public health priority has been aided by meta-analyses and reviews of these studies (Mehta, 2011).

ADR reporting

The reporting of suspected ADRs is critical to the success or failure of any pharmacovigilance system (Berhe et al., 2015). ADRs are monitored using a variety of ways, the most prevalent of which is voluntary or spontaneous reporting (Abdela et al., 2019), and is considered the corner stone of any pharmacovigilance system (Alharf et al., 2018).

The most effective methods of obtaining ADR information, particularly in the case of new and serious ADRs, are spontaneous and voluntary reporting systems, which are fundamental components of drug safety surveillance programs (Sultana et al., 2013). HCPs are expected to identify and report any suspected ADRs to their NPC or the pharmaceutical company that manufactures the medicine in this manner of reporting. (Mishra et al., 2016).

Despite the critical relevance of this type of reporting, the spontaneous reporting system has a key drawbacks known as under-reporting (Sultana et al., 2013).In this category, the rate of under-reporting is expected to be between 90 and 95 %. (Mishra et al., 2016). Reporting rarely exceeds 10 % of cases – proving that this instance of reporting is woefully

under-utilized(Mishra et al., 2016). Under-reporting causes a delay in the early discovery of ADRs, which can increase the patient's morbidity and mortality (Sultana et al., 2013). Overall, Under-reporting of ADRs is by far the most common and serious issue confronting effective pharmacovigilance programs (Mishra et al., 2016).

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 (Lazarou et al., 1998). But there was study heterogeneity among studies (Wiffen, 2002).

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 (Pirmohamed, 2004). 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 (Pirmohamed, 2004).

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 (Brvar et al., 2010).

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) (Brvar et al., 2010).

Post-approval monitoring facilitates observation of the drug profile for longer durations and for unapproved indications, effects of co-morbidities, co-administrations and the likely possibility of non-compliance with drug administration instructions.

Signal detection is one of the primary goals of pharmacovigilance (Settles, 2001, Hauben & Reich, 2005). A signal is defined by the WHO "as reported information on a possible

causal relationship between an adverse event and drug, the relationship being unknown or incompletely documented previously". Depending on the seriousness of the event and the quality of the data, more than one report is usually required to generate a signal. Signals should be followed up with extensive investigations, including pharmacoepidemiologic studies, if they are discovered (Settles, 2001) and appropriate regulatory action (Hauben & Reich, 2005).

Several methods have been used to quantify the frequency of ADRs. They include Solicited and unsolicited ADR reporting. Clinical trials, non-interventional research, registries, post-approval named patient usage programs, various patient assistance and illness management programs, patient or healthcare provider surveys, or information gathering on efficacy or patient compliance are all examples of solicited reports of potential ADRs. Solicited reports should be classed as study reports for the purposes of safety reporting, and they should have an adequate causality evaluation to determine whether they fit the criteria for expedited reporting (Finkelstein et al., 2009) .

Reports from other sources, such as spontaneous reports, literature reports, or reports from other sources, are referred to as unsolicited reports (e.g. media) (Finkelstein et al., 2009). A spontaneous report is an unsolicited communication from a healthcare professional, patient, or consumer to a competent authority, marketing authorisation holder, or other organization that describes one or more suspected ADRs in a patient who was given one or more medicinal products and is not based on a study or any other organized data collection schemes (Finkelstein et al., 2009).

No single method can cover all the requirements for the efficient collection of ADR data and therefore a multiplicity of methods is needed (Fletcher, 1991). Spontaneous reporting is the most common method used in pharmacovigilance and the best one to generate signals on new or rare ADRs (Requejo et al., 1998). This reporting scheme has contributed significantly to successful post-marketing drug safety surveillance and can be regarded as the cornerstone of pharmacovigilance. There are numerous limitations of the scheme, including the poor quality of submitted reports, difficulty in calculating rates because of incomplete numerator (adverse events) data along with inaccurate denominators (number of prescriptions) and limited ability to determine causality. However, the main limitation is under-reporting (Requejo et al., 1998).

The prevalence of ADRs and population mortality related with ADRs during hospitalization

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 (Pourpak et al., 2008). 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 (Pourpak et al., 2008)

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 (Patel et al., 2007). In addition, Pirmohamed,2004 considered that in England ADRs were accountable for approximately 6.5% of total severe hospital admissions and minimum 5,000 deaths annually.

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 (Lazarou et al., 1998).

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 (Palaian et al., 2011).

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 (Morimoto et al., 2011).

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 preventable. Correspondingly, underreporting seems most leading cause of population mortality and severe drug-associated complications (Pourpak et al., 2008) (Patel et al., 2007) (Pirmohamed, 2004) (Morimoto et al., 2011).

There is lack of similar studies carried out in low and middle-income countries associated with the subject of interest. The reasons could be various 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 (Olsson & Dodoo, 2015).

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(Ramesh et al., 2003). South African study has revealed that ADRs related causes accountable for mortality of patients were 2.9% (Mouton et al., 2015).

Under-reporting by HCPs

HCPs play an important role in the detection, appraisal, and spontaneous reporting of ADRs, according to several studies. Several global studies were done to analyze HCPs' attitudes and behavior toward their national ADR reporting schemes, with the goal of finding reasons for underreporting and determining initiatives that may be taken to raise reporting rates (Alharf et al., 2018; Ramesh et al., 2003; Zolezzi & Parsotam, 2005, (Sultana et al., 2013).

In a review of 37 studies from 12 countries, undertaken to estimate the extent of under-reporting of ADRs to spontaneous reporting systems by (Hazell & Shakir, 2006) reported a median under-reporting rate of 94% across these studies. Mariley Perez Garcia and

Albert Figuersa, 2011, in a study of physicians and pharmacists in Venezuela, reported poor knowledge of the voluntary ADR reporting system in that country. They concluded that study of the actual knowledge of pharmacovigilance could form the basis for specifically designed interventions aimed at overcoming misconceptions and improving reporting rates.

In Jamaica, ADR reports are made to the regulatory authority, the Standards and Regulation Division, Ministry of Health. The standardized ADR reporting form is the PharmWatch" form (Williams & Adebayo, 2008)). A study of the knowledge and attitude of healthcare professionals toward pharmacovigilance and ADR reporting identified training as a significant factor in the improvement of the reporting of ADRs (Campbell et al., 2014).

Various research have examined the primary impediments to enhanced ADR monitoring and reporting, which can be summarized as follows:

- Personal and organizational liability fears
- Inadequate surveillance and reporting resources
- Reporting methods that are labor-intensive, complex, and time-consuming
- There was some ambiguity in determining whether the medicine was the cause of the adverse event.
- HCPs who are unaware of the established reporting procedures and protocols
- ADRs are sometimes misunderstood as being too minor or unimportant to be reported.
- ADRs are incorrectly thought to be too common to be reported.
- HCPs make the mistake of assuming that the drug's major ADRs are well-documented and that additional reporting of incidents isn't necessary.
- Reporters receive little feedback when they submit their reports, which may deter potential reporters who believe their work goes unnoticed or underappreciated.
- There are no financial incentives, rewards, or motive to report.
- Inability to discriminate between large and small ADRs due to a lack of knowledge and confidence (Bawazir, 2006; Zolezzi and Parsotam, 2005; John et al., 2012)

Analysis of ADRs reports Patterns

Adverse Drug Reactions (ADRs) reporting is a mechanism in place to protect the public's health and safety from adverse drug reactions. It is mainly reliant on health professionals (HPs) reporting adverse medication reactions to regulatory agencies (Ermias et al., 2011).

High-income nations had the greatest ADR reporting rates and low-income countries had the lowest, with significant variability among countries in each group, according to a global study on analyses of spontaneous reports to VigiBase. The greatest ADR reporting rates (range 3–613 reports/million inhabitants/year) were found in high-income nations, whereas the lowest (range 0–21) were found in low-income countries. The bulk of adverse drug reactions (ADRs) were recorded for nervous system pharmaceuticals, followed by cardiovascular meds in this study. Antiinfectives for systemic use caused more ADRs in low-income countries than in high-income countries, and antineoplastic and immunomodulating medicines caused more ADRs in high-income countries than in lower-income countries (Aagaard et al., 2012).

A study undertaken in Ethiopia to investigate the scope of ADR examined 249 ADR instances between 2002 and 2007. It found that an average of 0.5 ADR cases per million people were reported annually. 36 % of the 249 cases were for those aged 31 to 40. In terms of sources, the majority of reports (63 %) were from health facilities in the capital city. Physicians were involved in 76 % of the instances reported. Antiretroviral medications were shown to be involved in 70% of the instances. Dermatological diseases were the most commonly reported side effects. (Ermias et al., 2011).

Another study in Turkey that examined at the ADR reporting pattern found that the annual Report rate (RR) increased gradually from 2005 to 2014. Skin and subcutaneous tissue abnormalities were the most commonly reported ADRs. Antineoplastic and immunomodulating medicines were the most usually suspected medications. Over time, there was no discernible change in the pattern of ADR reporting, patient characteristics, or suspected medication classes. Spontaneous reporting was the most prevalent source of information. The number of reports from studies gradually increased. Physicians provided

the majority of the reports. Pharmacists' RRs have risen dramatically in recent years (Ozcan et al., 2016).

When compared to adults, ADR is more common among geriatric (5%) and pediatric (9.5%) patients, accounting for 2.1% of hospital admissions (Napoleone, 2010). In India a study was conducted on analysis of adverse drug reaction in extremes of age group indicated that out of 3690 ADRs, 160 (4.33%) were in geriatric patients while in pediatric patients (16.25%). In geriatric patients, the gastrointestinal system was the most frequently affected body system (33.13%), followed by the nervous system (16.25%), while in 231 pediatric patients, the skin and appendages were the most frequently affected body system (31.6%), followed by the gastrointestinal system (25.11%). (Amin, Shah, Desai, Shah, & Maheriya, 2018). Another retrospective study of ADR reactions reported on a tertiary hospital in India found that the majority of patients who had had ADRs (94.2%) were between the ages of 19 and 64, and male patients (58.6%) were impacted more than female patients (41.4). The biggest number of ADRs were reported by the pulmonary medicine department, followed by the dermatology department. The skin was the most afflicted system (46.5%), followed by the gastrointestinal (30.45%), CNS (21.26%), respiratory (9.0%), and remaining systems. Rifampicin has the highest rate of ADR (13.79%), followed by zidovudine (13.21%), nevirapine (12.64%), and diclofenac sodium (12.64%). (8.0 %). The most common ADRs were probable (94.8%), followed by possible (5.2%) (Saxena et al., 2017) .

A study of Italian nurses' ADR reporting from the country's pharmacovigilance database revealed that nurses had the ability to improve the detection of ADRs. The percentage of significant ADR reports by nurses (22.9%) was lower than the 44.9 % of reports by physicians, while the proportion of likely ADR reports was higher among nurses than among hospital physicians (76%vs 67%). Nurses place a greater emphasis on application site diseases and nervous system reactions than physicians, whereas physicians report blood, platelet, and liver disorders more commonly. Six medicines appear in both the top ten drugs reported by nurses and the top ten drugs reported by hospital doctors (Conforti et al., 2017).

Healthcare Professionals and Pharmacovigilance

In the pharmacovigilance system, healthcare practitioners play a critical role. They require extensive knowledge and skill in the subject of medication safety, as well as the ability to contribute to this area through early detection, management, and reporting of drug safety issues (O'Callaghan et.,al 2018). In addition, healthcare workers should be well-educated in the importance and procedure of reporting adverse events. In this field, they should have a mix of training and research capabilities. Despite widespread worries about pharmaceutical safety, healthcare practitioners are still unaware of the importance of pharmacovigilance and adverse event reporting (Ali et al., 2017; Pourpak et al., 2008). Additionally, recent studies have shown that healthcare professionals, particularly in less developed nations, underreport adverse drug reactions (ADRs). According to studies, only 2-4% of all adverse events and 10% of serious ADRs are registered internationally. Any suspected adverse reaction, particularly those suspected reactions to newly authorized drugs and significant occurrences, should be reported by healthcare professionals such as physicians, pharmacists, and nurses. As a result, pharmaceutical safety evaluations must be considered an integral element of healthcare professionals' daily clinical practice (Najafi, 2018).

Because SRS is voluntary, health care professionals such as doctors, dentists, nurses, and pharmacists play a critical role in ensuring that ADRs are properly documented and reported. The primary factors of ADR reporting are health care providers' knowledge of and access to local ADR reporting systems, clinical abilities in detecting an ADR, and attitude toward reporting ADRs (Hadi et al., 2017).

In the pharmacovigilance system, healthcare practitioners play a critical role. They will successfully contribute to this area through early recognition, management, and reporting of medicine safety issues. They will require extensive knowledge and expertise in the field of medication safety. Furthermore, healthcare personnel should be well-informed about the importance and protocol of reporting adverse events. They should have a mix of training and research experience in this field. Despite widespread worries about medication safety, healthcare practitioners are still unaware of pharmacovigilance and adverse event reporting. Furthermore, recent research have found that adverse drug

reactions (ADRs) are underreported by healthcare providers, particularly in underdeveloped countries. Only 2-4 percent of all adverse events and 10% of significant adverse reactions have been documented (Almandil, 2016).

According to a study conducted in Saudi Arabia on pharmacists' perspectives on spontaneous adverse drug reaction reporting, pharmacists recognize that ADR reporting is a part of their professional obligation and have a favorable attitude toward reporting ADRs. However, current research reveals that pharmacists still have crucial knowledge gaps when it comes to ADR reporting, particularly in countries where pharmacists' involvement in the health-care system is limited (Hadi et al.,2017). Another study in Saudi Arabia looked at the knowledge and attitudes of 332 healthcare professionals about ADR reporting and pharmacovigilance, and found that they had poor knowledge of pharmacovigilance, which could have influenced reporting rates. More than half of the participants (55%) were unaware of the correct definition of PV; 207 (65.5%) were aware of the purpose of post-marketing surveillance; however, only 113 (36.9%) were aware that the National Pharmacovigilance and Drug Safety Center is the official body in Saudi Arabia for monitoring adverse drug reactions (Alshammari et al., 2015).

A direct survey of Venezuelan health professionals revealed that physicians and pharmacists have limited knowledge of the voluntary ADR reporting mechanism. These findings support the concept that underreporting is largely due to a lack of awareness of drug side effects and a lack of knowledge of the existence of a PhV system. 62.3 % of the 515 participating physicians had "bad" knowledge, while 66.7 % of the 78 participating pharmacists had "poor" knowledge (Garcia and Figuersa, 2011).

In Nepal, a cross-sectional study on health professionals' knowledge, attitude, and behaviors regarding pharmacovigilance found that the MTH's healthcare professionals had a poor KAP toward ADRs and pharmacovigilance. Doctors received a total of 40.06 points, pharmacists 38.92 points, and nurses 35.82 points. 59 (62.3%) of the 89 experts had never reported an adverse event to the pharmacovigilance center (Palaian et al., 2011).

According to a study done in Ethiopia, while most healthcare professionals had a positive attitude, they lacked adequate knowledge and experience when it came to reporting adverse medication reactions. The survey comprised 102 healthcare workers, with 61 (59.8%) being nurses, 16 (15.7%) being health officers, and 25 (24.5%) being

pharmacists. Nearly half of the study participants (47%) had insufficient knowledge about reporting adverse medication reactions. The majority of participants (86.3%) had a favorable attitude, whereas more than half of the study participants (51%) did not report any adverse medication reactions. Participants who had not received adverse drug reaction reporting training, as well as health officials and nurse practitioners, exhibited a statistically significant link to a lack of understanding (Seid et al., 2018).

According to Necho Mulatu (2014), the amount of information about ADR reporting is low. ADR reporting is also uncommon among medical practitioners. According to the overall knowledge score, 65.8% of the respondents did not have enough knowledge of the ADR reporting system. Only 16.2 % had ever reported ADR in the course of their professional work. Participating in ADR-related training, being introduced to ADR during college or university education, and having a high level of understanding have all been linked to ADR reporting. A similar study conducted by Gurmesa & Dedefo, (2016) in Nekemte, Ethiopia showed the same results to the above two studies .

According to a study, health care providers in Nekemte town have a low KAP when it comes to reporting spontaneous adverse medication reactions. Only 64 (48.2%), 56 (42.1%), and 13 (9.8%) health care workers properly answered the knowledge, attitude, and practice assessment questions, respectively, of the total respondents. At Felegehiwot Referral Hospital and University of Gondar Teaching Hospital, a hospital-based cross-sectional study on Predictors of nurses reporting practice related to adverse medication reactions was undertaken. Despite the fact that the majority of nurses had experienced an adverse medication reaction, the majority of them did not report it (Adimasu, 2014).

A systematic review of 32 research on KAP ADR and pharmacovigilance among doctors published between 2004 and 2014 found that KAP regarding ADR reporting by doctors was inadequate, implying a pressing need to enhance doctors' pharmacovigilance knowledge, awareness, and practice (Abubakar et al.,2014).

According to a study conducted in Ireland, pharmacists' pharmacovigilance awareness for biological medications needs to be increased, and procedures to support batch traceability need to be improved. In terms of ADR reporting and biological pharmacovigilance, the HCP groups had different mean knowledge scores. Although the majority of HCPs who use biological medications in their practice record them by brand name, various

professions have different practices when it comes to batch number recording (O'Callaghan et al.,2018).

In countries like Ethiopia, where HPs are overworked, the importance of any motivational incentives cannot be overstated. One of the factors contributing to under reporting of ADRs is HPs' lack of interest and desire to report them. Incentives such as delivering a certificate for reporting ADRs or providing pens with a reminder logo as a token of appreciation for participation have been demonstrated to boost ADR monitoring participation (Ermias et al., 2011).

Public understanding and perception of Adverse Drug Reactions

Although pharmacovigilance's primary objective is to identify, evaluate, comprehend, and avoid adverse reactions in order to safeguard the public, patient self-reporting of ADRs has historically been underused. The inclusion of patient reporting was praised in the European Pharmacovigilance Directive, and it was found that consumer reports have numerous differentiating qualities and benefits. They are unaffected by the prescribing physician's judgment and give useful causative information. In contrast to professional reports, many reports openly address the consequences on the person's life, family, and job; they record different medications and types of reactions. They turn patients into active participants, and reporting can help them improve their health literacy; they turn patients into active participants, and reporting can help them improve their health literacy (Herxheimer & Alves, 2010); Avery et al., 2011; Directive 2010/84/EU of the European Parliament and of the Council, 2010). Although several nations, like the United States, Canada, Australia, and New Zealand, have permitted patients to report ADRs directly since the inception of their pharmacovigilance programs, there are still some countries with inadequate or non-existent patient ADR reporting mechanisms.

Numerous research have contrasted unprompted patient reports with reports from experts. In Turkey, a research comparing consumers' spontaneous reporting of adverse drug reactions to those of healthcare professionals found that both consumers and HCPs are reporting more ADRs. Consumers contributed 3141 and HCPs submitted 6009 of the 9150 spontaneous ADR reports that met the minimal reporting criteria that were evaluated.

Consumers contributed 33.3 % of ADRs categorized as serious in this study, while HCPs contributed 52.2 %. Only 10 Designated Medical Event (DME) phrases were utilized by consumers, while HCPs used 35 of the 62 DME terms at least once. Consumers reported the greatest adverse medication reactions to nervous system pharmaceuticals, while HCPs reported the most adverse drug reactions to anti-infective drugs for systemic use. ADRs relating to food were the most commonly reported by consumers (Aydınkarahaliloğlu et al., 2018).

An analysis of 1374 emails containing Yellow Card reports of similar ADRs submitted to the MHRA in the years before the program was used in a study on the negative effects of paroxetine. The authors concluded that the "reports from users and relatives…communicated information that professional reporters can never be expected to provide. They were far richer and described suicidality and withdrawal symptoms much more clearly and intelligibly than the Yellow Card reports" (Medawar & Herxheimer, 2003).

Another study on the advantages and risks of statins was conducted in the Netherlands in 2007, and it got all of the Dutch reports. The TV show resulted in a spike in patient reporting, but not in professional reports. The severity of the ADRs or drug discontinuation were not different between the two groups. Patients reported a higher rate of non-recovery from the ADR than professionals. Nearly 30 patients had stopped taking their medication as a result of the program; many thought they had received insufficient information and that health providers had not effectively addressed their concerns (Van Hunsel et al., 2009).

Direct spontaneous patient reporting can speed up the acquisition of knowledge about adverse effects, which is beneficial to pharmacovigilance. Patient reports are more direct, thorough, and explicit than those obtained through health professionals. Unlike clinical studies, they frequently discuss how unfavorable consequences influence people's lives (Herxheimer et al.,2010).

Beyond pharmacovigilance, spontaneous direct reporting has significant advantages in that it encourages and permits greater patient involvement. This is in line with what doctors anticipate from their patients—that they accept and follow medication regimens.

The patient gains knowledge about managing their medications and improving their interactions with medical providers as a result. The effects on people's daily lives are not taken into account in public health estimates of disease burden in populations, as they should.

For these reasons direct patient reporting should be encouraged and routinely incorporated in pharmacovigilance activities (Herxheimer et al., 2010). Blenkinsopp et al. (2006) looked at descriptions of international experience from six nations, as well as seven studies that interviewed or surveyed patients in hospitals or primary care settings. However, none of the studies looked into spontaneous reporting by patients, in which patients choose to report an adverse event that may have been caused by a drug. Patient reports highlighted potential novel ADRs that had not been previously reported by health care providers.

CHAPTER III

Methodology

Data source

The retrospective analysis of the national ADRs data reports patterns for all the marketed drugs submitted to pharmacovigilance database center which is located in Ethiopian drug and food administration and control authority from 2013 to 2018 were analyzed. For this study, only spontaneous ADRs reports reach to PV center and fulfil the minimum criteria for reporting were included. The minimum criteria according to the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E2A criteria used in VigiBase are type of report, qualification of reporter, age and sex of patient, suspected drugs, seriousness of ADR were extracted from data (https://www.ich.org/,1994). The reports that lacked certain details could not be taken into account. Excluded from the analysis were ADR reports obtained from patient support programs, research cases, a case report, and follow-up reports. Additionally, more than one suspected drugs and/or ADR might have been reported in a single document were included.

For each ADR report, information about the patient characteristics (age, sex), qualification of the reporter, suspected medications, ADRs and seriousness of the ADRs was extracted from database. Qualification of reporters of the ADRs were classified as HCPs such as physicians, pharmacists, nurses, health officers, midwifery.

Three age grouping categories was used. Accordingly, patients were divided into the following age groups: pediatric (0–14 years old), adults (15-64 years old), and geriatric (65 and above years old) (https://en.wikipedia.org/wiki/,2016). The Anatomical Therapeutic Chemical (ATC) Classification system was used to classify suspected medicines at level 1 (WHO, 2013)

ADRs were obtained from source data using the Medical Dictionary for Regulatory Activities (MedDRA) and system organ classifications (SOCs) and preferred terms (PTs) (http://www.meddra.org)

Statistical Method

Descriptive statistics were performed based on ADRs as counts and percentages. ADR reports were analyzed based on demographic characteristics (age and gender), geographical area or location from which they were reported, involved body system as defined by the system organ classifications, time of occurrence, health professional who reported cases, drug implicated, and ADR manifestations.

CHAPTER IV

Findings and Discussion

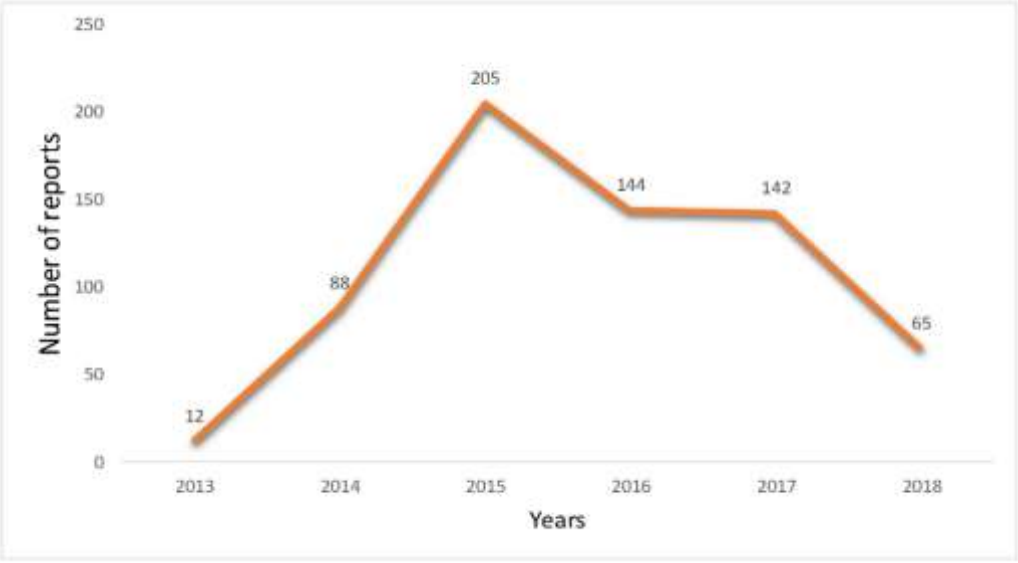
The study examined all of the marketed drugs' spontaneous ADRs reports that were reported to the PV center between 2013 and 2018. During the study period, 657 spontaneous reports met the reporting minimum criteria and were thus included in the analysis.

ADR Reporting trends,

The number of reports began to increase considerably in 2013 (n=12), 2014 (n=89) peaked in 2015 (n=205), and then began to decline between 2016 and 2018 (144, 142 and 65, respectively).

Figure 2.

The Annual Numbers of Spontaneous ADR Reports submitted to PV Center between 2013 And 2018 In Ethiopia.



ADRs by sex

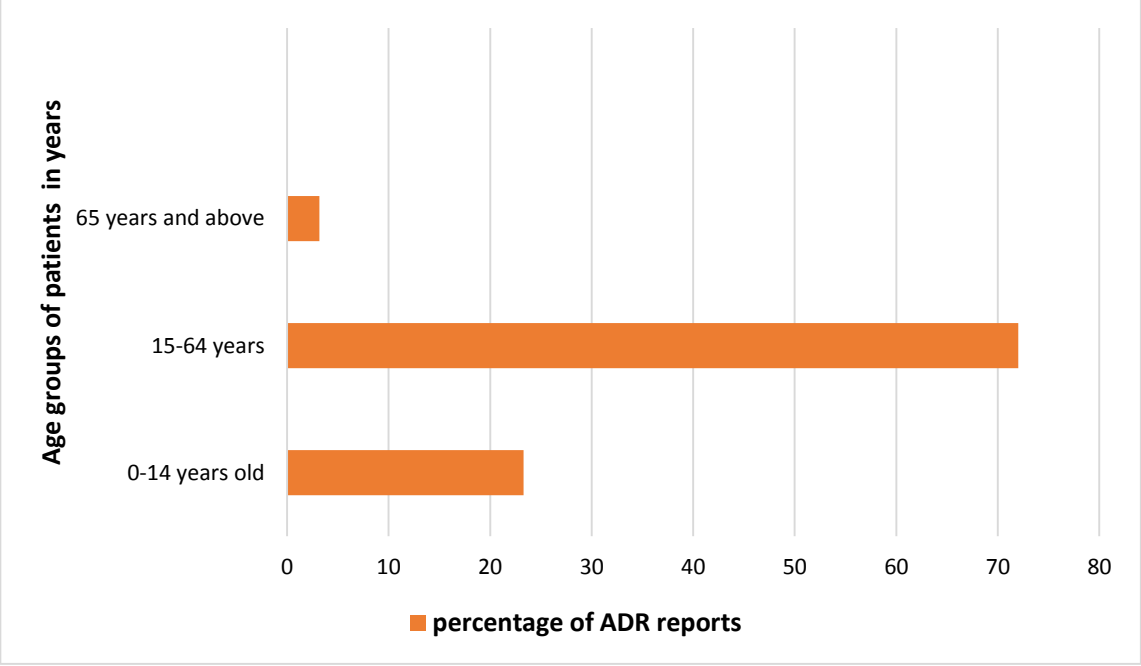
In terms of patient gender, females were reported in 370 (56.3%) of reports, while men were reported in 287 (43.7%) of reports. Females reported a higher percentage of incidents than males.

ADRs by age

To observe the trend of reporting with respect to age groupings, ADRs by age were estimated in three categorical age groups. The age group 15-64 years had the highest number of ADRs (475, 72.3 %), followed by 0-14 years (154, 23.4 %), and 65 years and above (21, 3.2 %). Only a small minority of reports (7.1%) failed to mention the age group.

Figure 3

Distribution of ADR Reports by Different Patient Age Groups in 2013-2018



Qualification of reporters

During 2013 and 2018, pharmacists reported the majority of ADRs (81.7 %), followed by health officers (7.2%), nurses (5.8%), and physicians (5.2%), nurses (5.8%). Midwifery (0.2%) reported a small proportion of reports (Table 2).

Table 2.

The Pattern Of Spontaneous ADR Reporting By Health Care Professionals In Ethiopia From 2013-2018.

Qualification of reporters	**2013**	**2014**	**2015**	**2016**	**2017**	**2018**	**Total**
Pharmacist	10 (83.3)	69 (78.4)	168 (82.3)	114 (79.2)	119 (83.8)	57 (87.7)	537 (81.7)
Physician	1 (8.3)	9 (10.2)	8 (3.9)	5 (3.4)	10 (7.1)	1 (1.5)	34 (5.2)
Nurse	1 (8.3)	6 (6.8)	16 (7.8)	5 (3.4)	7 (4.9)	3 (4.6)	38 (5.8)
Health officer	0*	5 (5.6)	12 (5.8)	20 (13.9)	6 (4.2)	4 (6.1)	47 (7.2)
Midwifery	0	0	1 (0.5)	0	0	0	1 (0.2)
Total	12 (100)	89 (100)	205 (100)	144 (100)	142 (100)	65 (100)	657 (100)

*0 indicates no report

ADRs for different therapeutic groups

The first ATC code levels were used to analyze suspected drugs mentioned in ADRs reports. The ATC level classes "anti-infective for systemic use" (78.6%), "antiparasitic products, insecticides, and repellants" (4.8%), "alimentary tract and metabolism" (3.6%), and "nervous system" (3.6%) are the most commonly reported ATC classes of drugs. These ATC classes were the most commonly reported drug groups throughout all years studied (figure 2). "Antibacterial for systemic use" and "antivirals for systemic use" are the two main product groups implicated in "ant infective for systemic use."

Trimethoprim and sulfamethoxazole have the highest number of ADRs (14.1 %), followed by amoxicillin (10.5%), zidovudine, lamivudine, and nevirapine (6.6%), and finally ciprofloxacin (5.5%) (Table 2).

Figure 4.

Percentage distribution of ADR reports by anatomical therapeutic chemical (ATC) class (first level) of suspected drugs from 2013 to 2018.

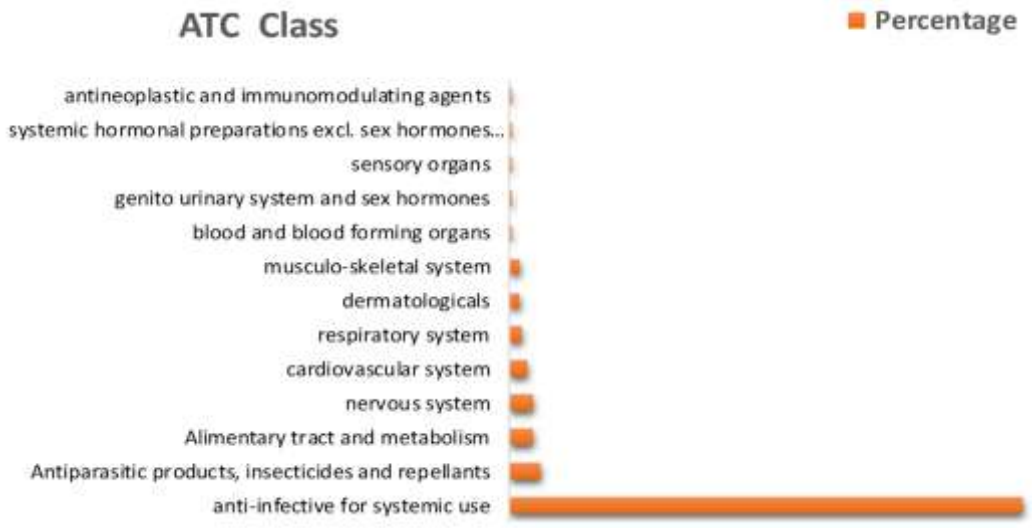


Table 3. Top 10 drug lists and their respective therapeutic classes related to the ADR rreports by health care professionals from 2013 to2018.

No	Suspected drug(s)	Therapeutic classes (ATC code)	Reports [(n, (%)]
1	Trimethoprim and sulfamethoxazole	Anti-infective for systemic use (J)	93 (14.1)
2	Amoxicillin	Anti-infective for systemic use (J)	69 (10.5)
3	Zidovudine, lamivudine and nevirapine	Anti-infective for systemic use (J)	44 (6.6)
4	Ciprofloxacin	Anti-infective for systemic use (J)	36 (5.5)
5	Zidovudine	Anti-infective for systemic use (J)	25 (3.8)
6	Praziquantel	Antiparasitic products, insecticides and repellents (P)	21 (3.2)
7	Rifampicin, isoniazid, pyrazinamide, ethambutol	Anti-infective for systemic use (J)	15 (2.2)
8	Efavirenz	Anti-infective for systemic use (J)	12 (1.8)
9	Nevirapine	Anti-infective for systemic use (J)	10 (1.5)
10	Lamivudine, tenofovir disoproxil and efavirenz	Anti-infective for systemic use (J)	9 (1.4)

ADRs by system organ classifications

Figure 4 shows the percentage distribution of the most frequently reported system organ classes for ADRs when categorized by *system organ classification*. The most commonly reported ADR *system organ classification* in the database are skin and subcutaneous tissue disorders 437 (66.5%), Gastrointestinal disorders 47 (7.2%), blood and lymphatic system problems 40 (6.1%), and nervous system illness 28 (4.3%). Figure 5 depicts the most often reported terms during the study period. Rashes 220 (33.5%), itching 76, (11.56%), anemia

51(7.7%), allergy 47(7.2%), and vomiting 30(4.6%) were the most commonly reported phrases by healthcare professionals.

Figure 5.

Percentage distribution of system organ classes for ADRs reports by health care professionals to pharmacovigilance database from 2013 to 2018.

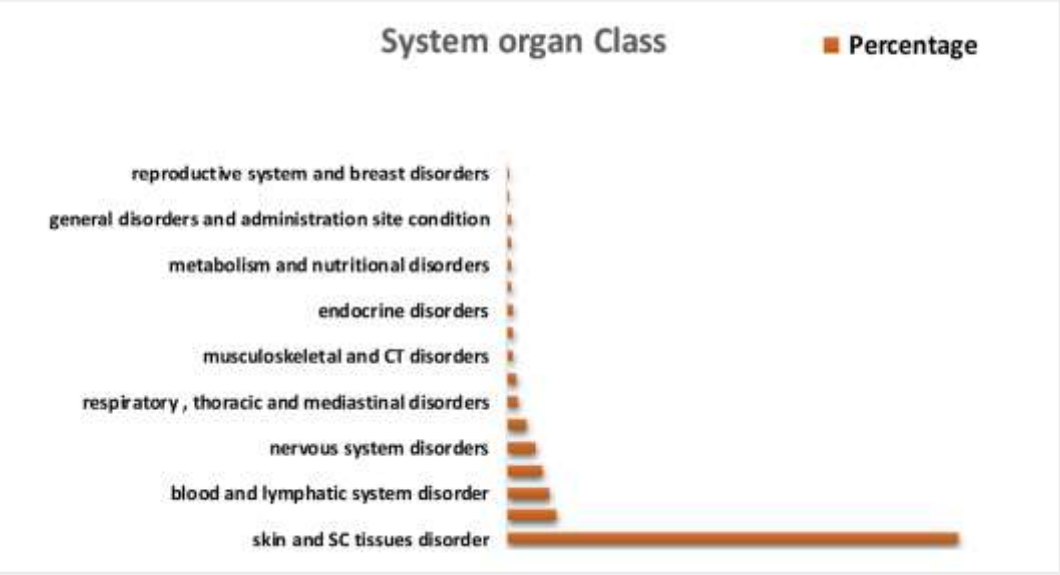
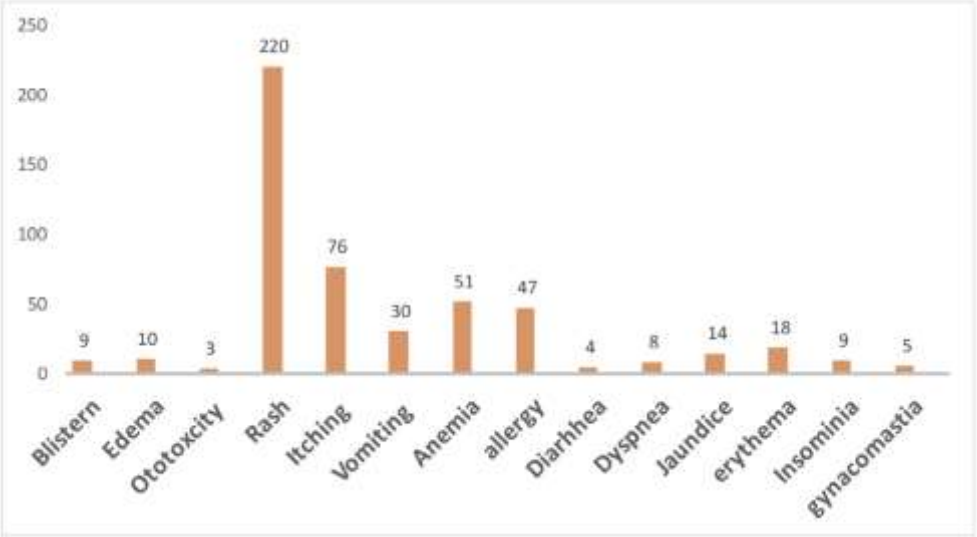


Figure 6.

The most frequent preferred terms by healthcare professionals.

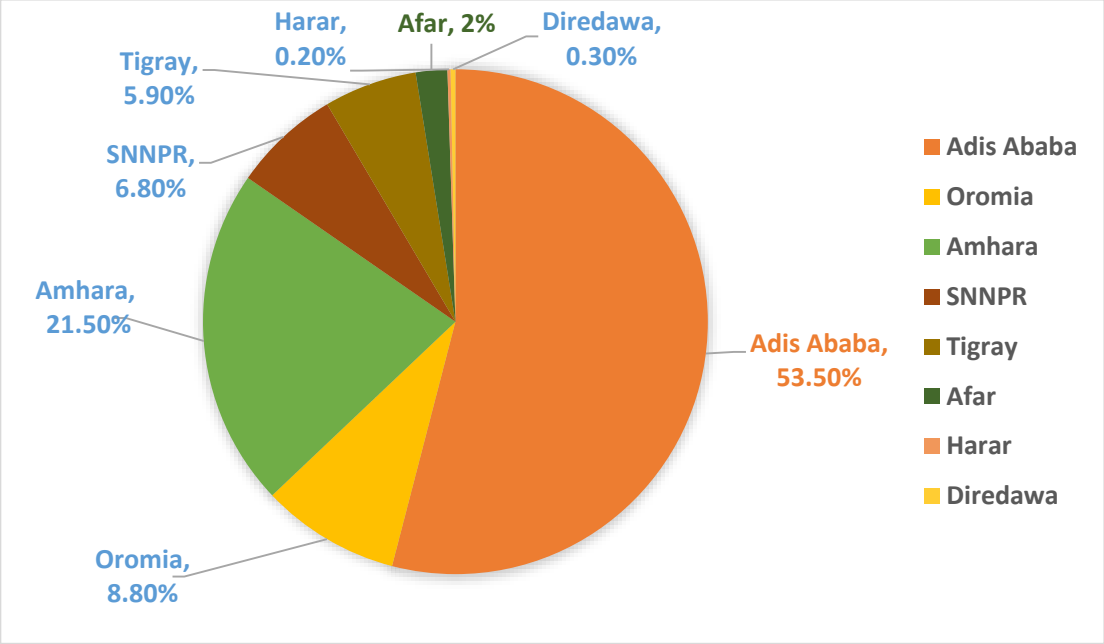


ADR report by location

The capital Addis Ababa reported 353 (53.7%) of the ADR reports, followed by the Amhara area 142 (21.6%), Oromia 59 (9%), SNNPR 46 (7%), Tigray 40 (6.1%), and Afar 14(2.1%). During the data collection period for this study, no reports were recorded in the remaining regions.

Figure 7: -

The percentage of ADRs reports from different regions in Ethiopia 2013 to 2018.



ADR out-come at the time of reporting

At the time of reporting, the majority of patients 430 (65.4%) had recovered without sequalae. However, (18, 2.7%) were found with sequalae, 58 (8.8%) had not yet been recovered, and 8 (1.2%) died, drug may be contributory and 128 (19.5%) were unknown outcome. In 15 (2.3%) of reports ADR outcome at the time of reporting not recorded.

CHAPTER V

Discussion

The purpose of this research was to look into the patterns of spontaneous ADR reporting in Ethiopia's national PV database. During the study period, the ADRs profile in the country revealed a fluctuating pattern. Between 2013 and 2015, there was the greatest increase, however, between 2016 and 2018, there was a considerable reduction. Despite the fact that the number of ADRs reported in Ethiopia was low and fluctuating in comparison to that in industrialized countries, it nevertheless shows an increased tendency, indicating that the health care professionals are becoming more aware of PV system in Ethiopia which was established under Food, Medicines and Healthcare Administration and Control Authority in 2002.In 2008, Ethiopia became an official member of the World Health Organization program for international drug monitoring (Ampadu et al., 2016) and voluntary reporting has been effective as in 2010 (Hailu & Mohammed, 2020). Since the establishment of the PV system, the number of ADR reports received from health care professionals is limited in numbers(Adimasu, 2014). The low level of ADRs reporting in this study can be linked to a variety of reasons, including insufficient HCP training, a lack of reporting tools, limited utilization and poor feedback on ADRs surveillance reports, and low coverage/poor integration at health facilities(Ermias et al., 2011).

During 2013 and 2018, ADRs reported in female patients (56.3%) were substantially higher than those reported in male patients (43.7%). This is in line with earlier research that have found that females are more likely than males to develop ADRs (Adimasu, 2014; Ampadu et al., 2016; Hailu & Mohammed, 2020). Males, on the other hand, had a higher risk of ADR than females, according to studies by Sriram et al., 2011 and Richa et al., 2015. The higher prevalence of reporting among females could be due to a variety of factors. ADR occurrence is affected by a variety of factors such as patient age, gender, number of drugs taken, length of hospital stay, genetic factors, ethnicity, dietary, and environmental factors (Sriram et al., 2011). Female patients may have a higher frequency

of ADRs, and they may also consult health care practitioners about ADRs more frequently (Richa et al., 2015).

The number of ADRs reported was higher in the 15-64 year old age group (72.3%) which was much higher than those for the other age groups of pediatric and geriatric populations. Multi-drug therapy or other disorders such as hypertension, diabetes, asthma, or other chronic diseases may be the cause of excessive morbidity in the adult population. Our findings are similar with the finding of (Adimasu, 2014; Saxena et al., 2017).

Only a few (3.2%) reports were received from those aged 65 and above. This is supported by other studies. Geriatric ADR was reported at a rate of 4.3% in a study by (Amin, Shah, Desai, Shah, Maheriya, et al., 2018) also, similar results indicated by Sriram et al., 2011. Despite the fact that patients in the geriatric age group are particularly prone to adverse drug reactions, the minimal number of ADRs reports received indicates that this group has gotten inadequate attention (Patidar et al., 2013).

For the years 2013-2018, it was observed that pharmacists reported more ADRs than physicians, health officers, and nurses. This rise in ADR reports among pharmacists could be explained by Ethiopia's recent shift in pharmacy practice from product-oriented to patient-focused clinical pharmacy practice (Morimoto et al., 2011).

Gurmesa & Dedefo, 2016 compared health care professionals' understanding of ADR reporting, finding that physicians and pharmacists were more aware of ADR than health care officers and nurses. Another study found that nurses, health care officials, and physicians were 93.1% less likely than pharmacy professionals to have adequate knowledge of ADR reporting.

Skin and subcutaneous tissue diseases (66.1%), gastrointestinal disorders (7.2%), blood and lymphatic system disorders (5.2%), and nervous system disorders (4.2%) were the most frequently reported ADRs among SOCs for ADRs. This pattern differs from the global pattern of ADRs from 2000 to 2009, when the most often reported SOCs for ADRs were general disorders and administrative site problems, skin and subcutaneous tissue disorders, and GIT disorders (Amin, Shah, Desai, Shah, Maheriya, et al., 2018). On the other hand this study is consistent with other studies by (Santos & Coelho, 2006),(Tripathy

et al., 2021) and (Patidar et al., 2013) but it differs from reports of (Asiamah et al., 2022) where gastrointestinal manifestations had the highest rate, which was second highest in our study (7.2%).

Suspect drugs mentioned in ADR reports were investigated at the ATC level 1. The drugs suspected of being linked to an ADR most frequently reported by health care professionals belong to the classes "anti-infective for systemic use" (78.6%), "antiphrastic products, insecticides and repellants" (4.8%), "aalimentary tract and metabolism" (3.6%), and "nervous system" (3.6%) at the first ATC level. This is similar to the patterns of ADRs observed by (Aagaard et al., 2012) in upper middle-income countries, where drugs from the ATC class of anti-infective for systemic (24.5%) showed high rates of reporting. However, antineoplastic and immune modulating medicines accounted for 26.5% of all ATC drugs reported in Turkey (Richa et al., 2015) although it was the eight most common ATC groups in the upper middle-income countries (Amin, Shah, Desai, Shah, Maheriya, et al., 2018). "Antibacterial for systemic use" and "antivirals for systemic use (dominated by antiretroviral)" are the main therapy groups implicated in "anti-infective for systemic use" in this study. The dominance of antiretroviral medicines in African ADRs is probably unsurprising given the continent's high HIV/AIDS burden. Because healthcare staff in these programs are typically trained in PV systems, it is projected that there will be more ADRs on these products with well-funded programs giving access to antiretrovirals. Indeed, the majority of published PV studies from Africa focus on antiretroviral drug safety (Gurmesa & Dedefo, 2016).

Drugs from the "anti-infective for systemic use", "gastrointestinal tract and metabolism", and "nervous system" classes are among the most widely used in Ethiopia, therefore it's no surprise that they were among the most commonly reported drugs at the first ATC level. Our findings resemble another study on this topic by (Aagaard et al., 2012).

Trimethoprim plus sulfamethoxazole (14.1%) is the most prevalent drug that causes ADR, followed by amoxicillin (10.5%) and zidovudine, lamivudine, and nevirapine (6.6%). It's possible that the high reporting rate for these therapeutic groups is due to higher drug consumption. Furthermore, most of these agents cause immediate and easily observable reactions that are classified as skin and subcutaneous tissue disorders, general disorders,

and administration site conditions, for which causality between the drug and the reaction can be established quickly. This result is inconsistent with other studies in Turkey where adalimumab where the most commonly reported active substances by Fattinger et al., 2000, and Rivaroxaban by van Graan et al., 2018 respectively.

This study examined only at spontaneous reports received to a national database between 2013 and 2018, which is similar to study by Aagaard et al., 2012 who analyzed spontaneous reports submitted to VigiBase from 2000 to 2009. Antiretroviral and antibiotics are the main product classes implicated in ADRs, according to Ampadu et al., 2016, who examined spontaneous ADRs characteristics between Africa and the rest of the world using Vigibase data.

The drug classes associated in ADRs from Africa differ from those from the rest of the globe. Disparities in disease patterns and prescriptions, variances in PV systems and ADR reporting, and differences in health systems and health literacy, to name a few, could all have a role (Gurmesa & Dedefo, 2016). (Anita Conforti, Sibilla Opri1, Paola D'Incau, Laura Sottosanti, Ugo Moretti, 2017; Desai et al., 2011; Sriram et al., 2011), reported that antibiotics are the most common classes causing ADRs which is similar in our study patients on anti-infective for systemic use had maximum ADRs. Trimethoprim and sulfamethoxazole were the most common drugs to cause ADRs (14.5%), followed by amoxicillin (10.5%), zidovudine, lamivudine, and nevirapine (3.8%), and ciprofloxacin (5.5%). It is because of increased consumption of anti-infective for systemic use for long duration as compared to other classes of drugs.

CHAPTER VI

Conclusion and Recommendation

Even though the number of ADRs reported in Ethiopia was low and irregular compared to those in industrialized countries, the data nevertheless showed an increase in ADR reports, which suggests that healthcare professionals are getting more knowledgeable about PV systems. This study showed that more effective pharmacovigilance methods and public policies must be established in order to improve the number of spontaneous reports. In conclusion, raising the quantity of spontaneous reports and enhancing the caliber of notifications, encouraging active surveillance in hospitals, and performing training for healthcare professionals are all crucial.

Limitation of This Study

Data limitations in this study need to be addressed in the future to allow for more rigorous analysis and findings. Many ADR reports collected were excluded due to incomplete information. Nonetheless, our findings could help researchers develop hypotheses for future drug-event interactions research.

CHAPTER VII

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APPENDICES

Appendices **I**

የመረጃ ደህንነት የስምምነት ውል

Data security agreement

ቀን: 09/01/2012 EC

Date:20/09/2019

ለጥናትና ምርምር ተግባር የሚውሉ መረጃዎችና ሪፖርቶችን ሚስጥራዊነታቸውንና ደህንነታቸውን ለመጠበቅ የተደረገ የውል ስምምነት

This data collection agreement was made between data owner and investigator to safeguard the security and confidentiality of the data's used for academic research purpose

ውል ሰጭ: የኢትዮጵያ የምግብ መድሃኒትና ጤና ክብካቤ አስተዳደር ቁጥጥር ባለስልጣን

Data Owner: Ethiopian Food, Medicines and Health Administration and Control Authority (FMHACA)

ውል ተቀባይ: ዘላለም ገ/ግዲ አኔቦ

Investigator: Zelalem Gebretsadik Anebo

የኢፌድሬ ሳይንስና ከፍተኛ ትምህርት ሚኒስቴር

Federal Ministry of Science and Higher education

አድራሻ: ሳይንስና ከፍተኛ ትምህርት ሚኒስቴር

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ይህ የውል ስምምነት ውል ሰጭ/የኢ/ም/መ/ጤ/ክ/አ/ቁ/ባ/ የሚረዱ የተለያዩ መረጃዎችንና ሪፖርቶችን ሊያቀርብላቸው ውል ተቀባዩ ደግሞ እነዚህን መረጃዎችና ሪፖርቶች ደህንነታቸውንና ሚስጥራዊነታቸውን ለመጠበቅ ለሚያከናውኑት ጥናትና ምርምር ግብዓትነት ለመጠቀም እንዲረዳ የተደረገ ነው::

This data collection agreement is made to facilitate the data collection process of the investigator and also to safeguard the security of the data's and reports provided by FMHACA (data owner) for academic research purpose.

1

ውል ሰጭ/የኢ/ም/ሙ/ጤ/ክ/ኢ/ቁ/ባ/ በፈደራል ደረጃ በምግብ፣ መድሃኒት፣ ጤና ተቋማትና ጤና ባለሙያዎችን የማስተዳደርና መቆጣጠር ስልጣንና ተግባር በእዋጅ፣ ደንብና መመሪያዎች የተሰጠው መንግስታዊ መ/ቤት ሲሆን ለውል ተቀባይ ለሚያስፈልጉት መረጃዎችና ሪፖርቶች ላይ ሙሉ በሙሉ የባለቤትነት መብት ያለው ሲሆን የኢፌዴሪ የሲያንስና ከፍተኛ ትምህርት ሚኒስቴር በደብዳቤ ቁጥር ሳከት/ኢ.ኢ.ሳ/ 1.16/1554/11 በቀን፡ 06/10/2011 ዓ/ም ለጥናትና ምርምሩ የሚረዳ መረጃ በመሰጠት እንዲተባበር በመጠየቁ መረጃዎችንና ሪፖርቶችን ሚስጥራዊነትንና ደህንነታቸው በጠበቀ መልኩ ለተፈለገው ጥናትና ምርምር እንዲውል ፈቅዷል።

The data owner (FMHACA) have the mandate to regulate food, medicines, health care personnel and health institutions at federal level. The Authority has a full ownership on the data provided to the investigator. The authority provided the data to the investigator based on the letter issued by Federal Ministry of Health on the date July 6/2018 and Ref. No: ሳከት/ ኢ.ኢ.ሳ/ 1.16/ 1554 /11 to facilitate the data collection process for his PhD research work of the investigator.

ውል ተቀባይ በቱርክ ሀገር የሲሚን ቆጵሮስ ሃገር በሚገኘው ኒር ኢስት ዩኒቨርስቲ ባገኙት የስነተኛ ዲግሪ የትምህርት እድል "*Analysis Adverse Drug reactions (ADRs) Reporting Pattern and Knowledge, Attitude and Practice among Health Care Professionals (HCPs) Towards Pharmacovigilance in Turkey and Ethiopia: A Comparative Study*" በሚል ርዕስ ለሚያከናውኑት ጥናትና ምርምር ግብዓትነት የሚውል የተሰያዩ መረጃዎችና ሪፖርቶችን ከውል ሰጭ የኢ/ም/ሙ/ጤ/ክ/ኢ/ቁ/ባ/ የሚቀርብለት ይሆናል።

The investigator is a PhD student of Near East University, faculty of Pharmacy, Department of pharmacology Turkish Republic of Northern Cyprus (TRNC) will conduct his PhD study on the topic of "*Analysis Adverse Drug reactions (ADRs) Reporting Pattern and Knowledge, Attitude and Practice Among Health Care Professionals (HCPs) Towards Pharmacovigilance in Turkey and Ethiopia: A Comparative Study* and FMHACA agreed to provide the required data and reports for the purpose of this study.

የውል ሰጭ ግዴታ/ the role and responsibilities of the data owner (FMHACA):

1) የ5 (2013-2018 እ.ኤ.አ) አመት የጤና ተጽዕኖት/Adverse Drug Reactions (ADRs)/ ሪፖርቶችን ለውል ተቀባይ ያቀርባል

1) FMHACA will provide 5(2013-2018 G.C) year health facility Adverse Drug Reaction (ADR) data

2) ከዚህ ውል ስምምነት ጋር አባሪ የተደረገ በተለያዩ ክፍሎች የሚውሉ መጠይቆች/መረጃዎች በተቻለ ፍጥነትና ብዛት እንዲሞሉ ድጋፍ ያደርጋል

2) The different department of FMHACA will fill the questionnaire prepared by the investigator

የውል ተቀባይ ግዴታ/ the role and responsibilities of the investigator:

1) ከውል ሰጭ የሚረከባቸውን /Adverse Drug Reactions (ADRs)/ ሪፖርቶችና መረጃዎች ርዕሱ ከላይ ለተጠቀሰው ጥናትና ምርምር ብቻ የሚውል ግዴታ አለበት

1) The investigator must use the Adverse Drug Reaction (ADR) reports and data's collected from FMHACA for "*Analysis Adverse Drug reactions (ADRs) Reporting Pattern and Knowledge, Attitude and Practice Among Health Care Professionals (HCPs) Towards Pharmacovigilance in Turkey and Ethiopia: A Comparative Study* " academic study only

2) እነዚህን ሪፖርቶችና መረጃዎችን ደህንነታቸውን የመጠበቅ እና በጥንቃቄ የመያዝ ግዴታ አለበት

2) The investigator must safeguard the security of the data's and reports not to be abused and used for other than the intended purpose

3) የሪፖርቶቹንና መረጃዎቹን ሙሉ ሚስጥራዊነት የመጠበቅ ግዴታ አለበት

3) The investigator must fully safeguard the security of the data's

4) የሪፖርቶቹንና መረጃዎቹን በተመለከተ ያለ ውል ሰጭ የፅሁፍ ፈቃድ ለሶስተኛ ወገን በሙሉ ወይም በከፊል እንዲሁም በማንኛውም መንገድ አሳልፎ መስጠት ወይም መሸጥ አይችልም

4) The investigator will not be able to transfer or sold the data by any means in full or in part to a third party without the consent of the data owner

5) የጥናትና ምርምሩ ተግባር ሲጠናቀቅ ለውል ሰጭ ማሳወቅ አለበት

5) The investigator will report the result of the study to the data owner

6) የጥናትና ምርምሩ በተመለከተ ውል ተቀባይ ጥቅም ላይ ለማዋል በጠየቀ በ30 ቀን ውስጥ ውል ሰጭ አረጋግጦ ምላሽ መስጠት አለበት

6) The data owner should respond within 30 day for the request of the investigator to use the study

7) ጥናትና ምርምር ውል ከተፈረመ ቀን ጀምሮ እስከ 2014 ዓ/ም ድረስ መጠናቀቅ አለበት

7) The study will be completed up to September 2020 (Pagume 2013 EC) since the date of this agreement signed by the two parties

ከላይ በውል ተቀባይ ግዴታነት የተዘረዘሩ ድርጊቶችን ውል ተቀባይ በመተላለፍ ሲገኝ በኢትዮጵያ የወንጀል ህግ ተጠያቂነት ከማስከተሉም በተጨማሪ ውል ሰጭ ለደረሰበት ጉዳት በኢትዮጵያ የፍትሃ ብሄር ህግ መሰረት የመጠየቅ መብት ይኖረዋል::

The investigator will be liable to penalty according to the Ethiopian criminal code if the investigator not able to perform under this agreement and also the data owner

request the investigator by Ethiopian civil code for any damage/loss occurred as a result of this study

ይህ የውል ስምምነት በሚራ ቀኖ ሙሉ ፈቃድ ያለ ምንም ተዕፅኖና ማስገደድ ውል የተፈፀመ በመሆኑ በኢትዮጵያ የፍትሃ ብሄር ህግ አንቀፅ 1731፡2005 (1) መሰረት ተዋዋዮቸን የሚያስገድድ በህግ ፊትም ተቀባይነትና ተፈፃሚነት የሚኖረው ነው።

This agreement executed between the two partics freely and voluntarily and the agreement will be legal under the Ethiopian civil code article 1731፡2005 (1) based on this the two article the two agreed parties are enforced by law.

እኛ 1) [illegible] 13/01/12 2) [illegible] 13/01/2012

We 1) _____ 2) _____

ውል ሰጭና ተቀባይ ይህንን የውል ስምምነት ሲያደርጉ በምስክርነት ተገኝተን በመሉ ፈቃድና ስምማነት ሲዋዋሉ አይተናል ሰምተናል

We, witness that the two agreed parties entered in to agreement freely and voluntarily.

ውል ሰጭ (Data Owner)	ውል ተቀባይ (Investigator)
ስም፡-የኢ/ም/መ/ጤ/ኪ/እ/ቁ/ባ/	ዘላለም ገ/ጻዲቅ አንቦ
Data Owner (FMHACA)	Zelalem Gebretsadik Ancbo
ፊርማ (Signature)	ፊርማ (Signature)

ኪሩቤል ዘሙዴ
የሰው ሀብት ሥራ አመራር
ዳይሬክተሬት ዳይሬክተር

CURRICULUM VITAE

Appendices II

Name	**Zelalem Gebretsadik**	**Surname**	**Anebo**
Place Of Birth	Wolayta Soddo	Date Of Birth	November 26, 1985
Nationality	Ethiopia	E-Mail	zelalemga@gmail.com
Address-Mobile	+251912387870		zelalemga@gmail.com

Educational background	**Names Of Educational Institutions**	**Graduation Year**	**Awarded**
Pharmacology	Near East University, Nicosia, Turkish Republic of North Cyprus	2022	Ph.D.
Pharmacology	Addis Ababa University , Addis Ababa, Ethiopia	2011	M.Sc.
Veterinary Medicine	Jimma University, Jimma, Ethiopia	2008	DVM
High School	Soddo comprehensive high and preparatory School	2004	Certificate

Employment History	Name of Organization	From	Up to
academic rank of lecturer and Assistant Professor	Wollega University	2008	2013
Director for Veterinary drug quality standard, Registration and certification directorate	Ethiopian Veterinary drug and feed administration and control authority	2014	2017

Training attended	Name of organization	Year	Award
appropriate inspection standards for local veterinary vaccine manufacturers	AU-PANVAC at Debrezeit, Ethiopia prepared in collaboration of GALVmed	2014	Certificate
Good manufacturing practice (GMP) of Drugs	USAID/USP	2014	Certificate
Higher English Diploma Program	Wollega University, Institute of Teachers Education	2012-2013	Certificate
Balanced Score Card (BSC) training	Ethiopian management Institute (EMI)	2014	Certificate
Developing Execution skills of change army	Ethiopian management Institute (EMI)	2014	Certificate
Dossier Assessment for veterinary immunological products e	Jacaranda Hotel, Jacaranda Hotel, Nairobi, Kenya.	2015	Certificate

"Advanced Analytical Techniques: Basic Principles and Application for quality assessment of drugs and pharmaceuticals"	NIPER Sector 67, S.A.S. Nagar, Punjab, India	2016	Certificate
Strategic planning and management for business sector	Ethiopian management Institute (EMI	2016	Certificate

Language	Listening	Speaking	Writing	Reading
Amharic	Native	Native	Native	Native
English	Excellent	Excellent	Excellent	Excellent
Turkish	Fairly	Fairly	Fairly	Fairly
French	Fairly	Fairly	Fairly	Fairly

PLAGIARISM RPORT

Appendices III