EVALUATION OF PHARMACOVIGILANCE ACTIVITIES AND ASSESSMENT OF EDUCATIONAL MODULE ON KNOWLEDGE, ATTITUDE AND PRACTICE OF ADR REPORTING AMONG HOSPITAL PHARMACISTS IN UNITED ARAB EMIRATES

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by

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DEDICATION

This thesis is dedicated to the man who will always be with me and mentor me even when he isn't physically there with his words and soul. Your inspiration in this life is the force that never stops pushing me to finish my journey despite all the challenges and obstacles I have encountered. My late father, this work is dedicated to your soul, and although I'm sure you already knew that I did it and that you were proud of me, I still wish you were here with me at this moment. My dear father, may your soul rest in eternal peace.

I am also dedicating this thesis to:

My mom who have raised me to be the person I am today and who has been a wonderful helper when I have been away from home.

My husband and partner of my life Fadi for his boundless support, kindness, merits, and unwavering patience.

My beloved son Waleed whose encouraging words, "Mom, please don't give up," served as a source of inspiration throughout this journey.

My darling sweetie Lara, who has supported me in every way and treated me like her daughter in an effort to help me as much as possible

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Last but not least, I hope that this research work and its outcomes will bring a fruitful contribution to all readers and help to achieve our goals in patient care and the practice of pharmacovigilance in UAE.

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LIST OF ABBREVIATIONS

ADRs	Adverse Drug Reactions
AERS	Adverse Event Reporting System
ASHP	American Society of Health-System Pharmacists
CDC	Center for Disease Control
CDER	Center for Drug and Evaluation and Research
CEM	Cohort Event Monitoring
DHA	Dubai Health Authority
EAC	East African Community
EHR	Electronic health records
EU GVP	European Good Pharmacovigilance Practices
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
GVP	Good Pharmacovigilance Practices
GVP-Arab	Good Pharmacovigilance Practice for Arab Countries
GCC	Gulf Cooperation Council
GHC	Gulf Health Council
HAAD	Health Authority Abu-Dhabi
HCPs	Healthcare Providers
ICSR	Individual Case Safety Report
IQR	Interquartile Range
ICH	International Council for Harmonization
ISoP	International Society of Pharmacovigilance
IPAT	Indicator-Based Pharmacovigilance Assessment Tool
LSR	local safety responsible

KAP	Knowledge, Attitude, And Practice
KAPB	Knowledge, Attitude, Practice And Barriers
MA	Marketing Authorization
MAH	Marketing Authorization Holders
MOHAP	Ministry of Health and Prevention
NMA	National Medicines Authority
NMRAs	National Medicines Regulatory Agencies
NPU	National Pharmacovigilance Unite
PSUR	Periodic Safety Update Report
PV	Pharmacovigilance
PV KPIs	Pharmacovigilance Key Performance Indicators
PVPI	Pharmacovigilance Program of India
PRAC	Pharmacovigilance Risk Assessment Committee
QPPV	Qualified Personnel for Pharmacovigilance
SAV	Safety and Vigilance
SRS	Spontaneous Reporting Systems
SSFFC	Substandard/spurious/falsely labelled/falsified/counterfeit
SPS	Strengthening Pharmaceutical Systems
TSR	Targeted Spontaneous Reporting
UAE	United Arab Emirates
UMC	Uppsala Monitoring Centre
USAID	United States Agency for International Development
USAID	United States Agency for International Development
WHO	World Health Organization
WHO-PIDM	WHO Programme for International Drug Monitoring
WHO-PVI	WHO Pharmacovigilance Indicators

LIST OF APPENDICES

PENILAIAN AKTIVITI FARMAKOVIGILANS DAN PENILAIAN MODUL PENDIDIKAN TERHADAP PENGETAHUAN, SIKAP DAN AMALAN PELAPORAN ADR DALAM KALANGAN AHLI FARMASI HOSPITAL DI EMIRIAH ARAB BERSATU

ABSTRAK

Pelaporan ADR berdiri sebagai asas farmakovigilans, berusaha untuk melindungi keselamatan ubat dan melindungi daripada kejadian buruk. Namun, keberkesanannya bergantung pada penyedia penjagaan kesihatan yang memiliki pengetahuan yang mencukupi, memupuk sikap yang betul, dan mengamalkan amalan yang sesuai terhadap pelaporan ADR. Pada masa ini, di UAE, ahli farmasi hospital memainkan peranan terhad dalam aktiviti farmakovigilans. Kajian ini bertujuan untuk menilai keadaan aktiviti farmakovigilans di UAE, menawarkan intervensi dan menilai kesannya terhadap pelaporan ADR di kalangan ahli farmasi hospital. Kajian semasa menggunakan metodologi berurutan empat fasa di mana mencapai satu matlamat penyelidikan akan membawa kepada yang seterusnya, dan ia menggunakan pendekatan kaedah campuran (kualitatif dan kuantitatif). Dalam Fasa 1, alat IPAT digunakan untuk menilai program PV, melibatkan 5 wakil dari pusat farmakovigilans MOHAP (peringkat kebangsaan) dan 5 ahli farmasi dari 3 hospital yang termasuk dalam kajian. Fasa 2 terdiri daripada kajian kualitatif dengan ahli farmasi terpilih, mencapai ketepuan selepas sepuluh temu bual. Fasa 3 melibatkan tinjauan seluruh negara terhadap 386 ahli farmasi di seluruh negara. Fasa 4 memberi tumpuan kepada pembangunan program pendidikan, dan menilai kesan modul ini terhadap 60 ahli farmasi yang mengambil bahagian. Keputusan menunjukkan bahawa Pusat Farmakovigilans Kebangsaan (NPC) memperoleh jumlah skor 25 daripada 69

berdasarkan item yang diukur manakala jumlah skor lima komponen alat IPAT yang berbeza ialah 59.4% (41/69). NPC juga mencapai (17/26) 65.4% markah daripada petunjuk teras dan (7/17) 41.2% daripada petunjuk tambahan. Dalam fasa 2, keputusan menunjukkan bahawa tidak semua hospital mempunyai sistem PV di institusi mereka dan tidak semua peserta mengetahui proses pelaporan ADR. Fasa 3 menunjukkan majoriti berpengetahuan tentang konsep PV (93.3%; n=319) dan ADR (86.8%; n=297), tetapi mereka tidak mengetahui proses dan sistem pelaporan negara. Skor pengetahuan median (IQR) ialah 5 (3-7)/9. Dari segi sikap, skor median (IQR) ialah 22 (20-24)/30. Mengenai latihan, skor median (IQR) ialah 17.5 (11-21)/24. Berdasarkan fasa 1, 2 dan 3, modul telah dibangunkan dan dilaksanakan dalam fasa 4. Fasa 4 menunjukkan peningkatan yang ketara dalam pengetahuan, sikap dan markah amalan peserta. Laporan ADR meningkat kepada (10, 26) manakala laporan Ralat Ubat (ME) menurun kepada (245, 225) 3- dan 6 bulan selepas campur tangan dalam tempoh tiga bulan. Terdapat juga peningkatan yang ketara dalam kesempurnaan laporan selepas intervensi. Sistem PV negara tidak mematuhi keperluan minimum WHO. Kekurangan pemahaman mendalam ahli farmasi mengenai farmakovigilans dan kepentingannya boleh menjejaskan hasil mana-mana sistem walaupun ia tersedia di institusi. Hasil kajian menekankan keperluan untuk ahli farmasi mendapatkan latihan formal dan disesuaikan tentang farmakovigilans (PV) dan pelaporan reaksi advers ubat (ADR). Akhirnya, intervensi pendidikan meningkatkan Pengetahuan, Sikap, dan Amalan (KAP) mengenai farmakovigilans dalam kalangan ahli farmasi hospital.

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ABSTRACT

Adverse drug reaction reporting stands as a cornerstone of pharmacovigilance, striving to safeguard medication safety and shield against adverse events. Yet, its effectiveness hinges on healthcare providers possessing sufficient knowledge, fostering the right attitudes, and adopting appropriate practices toward ADR reporting. Presently, in the UAE, hospital pharmacists play a limited role in pharmacovigilance activities. The study aimed to evaluate the state of pharmacovigilance activities in UAE, offer interventions and assess their impact on ADR reporting among hospital pharmacists. The current study used a sequential methodology of four phases in which achieving one research goal will lead to the next, and it adopted a mixed-method approach (qualitative and quantitative). In Phase 1, the IPAT tool was used to evaluate the PV program, involving 5 representatives from the MOHAP pharmacovigilance center (national level) and 5 pharmacists from the 3 hospitals included in the study (healthcare facilities). Phase 2 consisted of a qualitative study with selected pharmacists, achieving saturation after ten interviews. Phase 3 involved a nationwide survey of 386 pharmacists across the country. Phase 4 focused on the development of an educational program, and assessed the impact of this module on 60 participating pharmacists. The results revealed that the National Pharmacovigilance Center (NPC) earned a total score of 25 out of 69 based on the items being measured while the total score of the five different IPAT tool components was 59.4% (41/69). The NPC also

attained (17/26) 65.4% score of the core indicators and (7/17) 41.2% of supplementary ones. In phase 2, the results showed that not all hospitals have PV system in their institution and not all participants were aware of ADR reporting process. Phase 3 showed that the majority were knowledgeable about the concepts of PV (93.3%; n=319) and ADRs (86.8%; n=297), but they were not aware of reporting process and system of the country. The median (IQR) knowledge score was 5 (3-7)/9. In terms of attitude, the median (IQR) score was 22 (20-24)/30. Regarding practice, the median (IQR) score was 17.5 (11-21)/24. Based on phases 1, 2 and 3, the module was developed and implemented in phase 4. Phase 4 revealed significant enhancements in participants' knowledge, attitude, and practice scores. ADR reports increased to (10, 26) while Medication Errors (ME) reports decreased to (245, 225) 3- and 6-months post intervention respectively within the three months interval. There was also a marked improvement in report completeness post-intervention. Nation PV system does not adhere to the WHO's minimum requirements. The lack of pharmacists' deep understanding of pharmacovigilance and its importance could impact the outcomes of any system even if it is available in the institution. The results emphasize the need for pharmacists to get formal, customized training on PV and ADR reporting. Finally, the educational intervention enhances Knowledge, Attitude, and Practice (KAP) of pharmacovigilance among hospital pharmacists.

CHAPTER 1

INTRODUCTION

1.1 Research Background

1.1.1 Pharmacovigilance and Adverse Drug Reactions

The concept of pharmacovigilance was first established during the 15th century after a series of catastrophic events (Olowofela, 2018). One of these was the thalidomide disaster in 1960, when the use of a drug called thalidomide during pregnancy led to the birth of thousands of children with a birth defect called phocomelia, which involved malformations of the babies' arms and legs (James & Anthony, 2011). This incident demonstrated the need for greater knowledge of drug side effects and the development of drug safety and pharmacovigilance as a separate scientific field (World Health Organization, 2002a), (Najafi, 2018; Fornasier *et al.*, 2018; Beninger, 2018). According to the WHO, the year 1961 marks the official start of pharmacovigilance as a science and practice (Hamid, 2020). The idea of a global cooperative project envisioned for the early detection of potential occurrences similar to the thalidomide tragedy was put forth by the World Health Assembly (Drummond *et al.*, 2019; World Health Organization, 1978; Centre, 2023c). The program was later renamed to WHO Programme for International Drug Monitoring (PIDM) in 1968. The programme was created to act as a comprehensive system for gathering adverse drug reaction (ADR) reports on a global scale and identify drug safety problems as early as possible (Centre, 2023c). Ten years later, in 1978 Uppsala Monitoring Centre (UMC) in Sweden collaborates with WHO to monitor ADRs worldwide. It runs the scientific prospects of the WHO in the world (Centre, 2023c).

The tragedy emphasized the need for systematic methods for gathering, analysing, and disseminating data on ADRs and other unrecognised safety concerns during the widespread administration of medications. It highlighted the need for post marketing surveillance for all medications following the release in the market (World Health Organization, 2002a; Fornasier *et al.,* 2018; Beninger, 2018; Centre, 2023c; Saha, 2014).

Currently, PV includes domains related to ADRs, medication errors, drug-drug interactions, ineffectiveness of medications products, sub-par drugs, and medication abuse (Hamid, 2020; World Health Organization, 2015). In addition to that, PV covers many other products including modern and traditional medicines, vaccines, biosimilars, and devices (Centre, 2023c; World Health Organization, 2015).

Generally, the aim of pharmacovigilance is to "Improve patient care and safety in relation to the use of medicines and all medical and paramedical interventions; Improve public health and safety in relation to the use of medicine; Detect problems related to the use of medicines and communicate the findings in a timely manner; Contribute to the assessment of benefit, harm, effectiveness, and risk of medicines, leading to the prevention of harm and maximization of benefit; Encourage safe, rational, and more effective (including cost-effective) medicines use; and Promote understanding, education, and clinical training in pharmacovigilance and its effective communication to the public" (World Health Organization, 2006).

1.1.2 Pharmacovigilance System Definition

Some studies assumed that ADRs are caused by defects in the design and operation of a system rather than the actions of individual practitioners which suggests that the quality assurance system should be built into the system (Hoonhout *et al.*, 2010).

A pharmacovigilance system is the collection of processes and outcomes that are related to its structures and operations enhance the medication outcomes and minimize medication related problems among the population. It is achieved by effective organizations of different resources in all parts of the health system (SPS, 2009a). The European Economic Community directive defined PV system as "a system that is used to collect information useful in the surveillance of medicinal products, with particular reference to adverse reactions in humans, and to scientifically evaluate such information." (Santoro, *et al*., 2017).

The country's pharmacovigilance system should make use of all resources at the national health care authorities, pharmaceutical industries, and international levels to ensure the safety of the nation's medications. Figure 1.1 shows the stakeholders, the organizations and the duties needed to establish efficient pharmacovigilance framework (Potter, 2004). In order to establish a robust system for resolving pharmaceutical safety issues, this approach highlights the need to build capacity to implement both passive and active techniques to close gaps linked to health structure, systems, and roles; staff and infrastructure; skills; and tools. The most important capacity-building requirements for achieving a fully operational and long-lasting pharmacovigilance system are shown for each tier in Figure 1.2. Building structural and system capacity necessitates creating a workable regulatory and organizational

structure as well as standards for monitoring medications safety. It is necessary to clearly define the duties of different individuals like advisory committees, government institutions, hospitals and healthcare providers, the pharmaceutical companies, and patients. Providing adequate staffing and infrastructure, ensuring new staff expertise and constructing appropriate tools to improve the collection of data, analysis, and reporting build upon these foundational capacities (Potter, 2004).

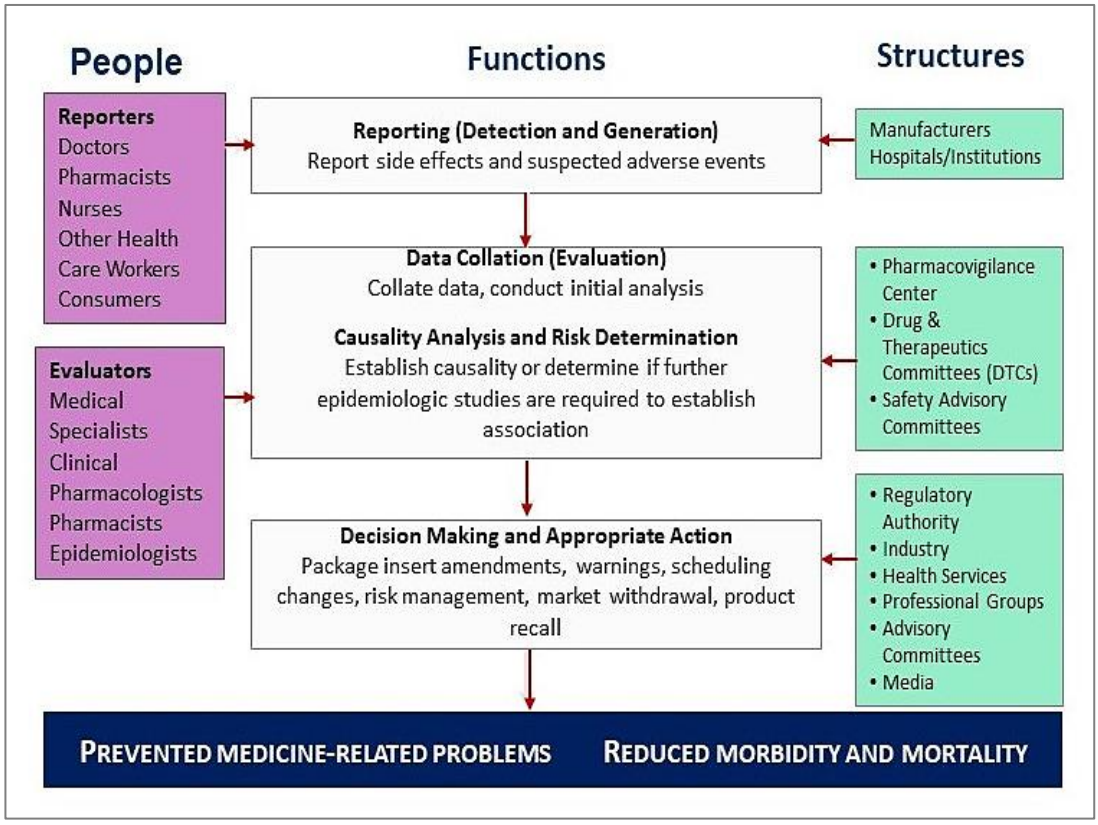

Figure 1.1 Pharmacovigilance Framework Components.

Adopted from Supporting Pharmacovigilance in Developing Countries, The Systems Perspective (Potter C. Systemic capacity building: a hierarchy of needs. Health Policy and Planning [Internet]. 2004 Sep 1 [cited 2023 Jul 17];19(5):336–45. Available from: https://academic.oup.com/heapol/article-lookup/doi/10.1093/heapol/czh038)

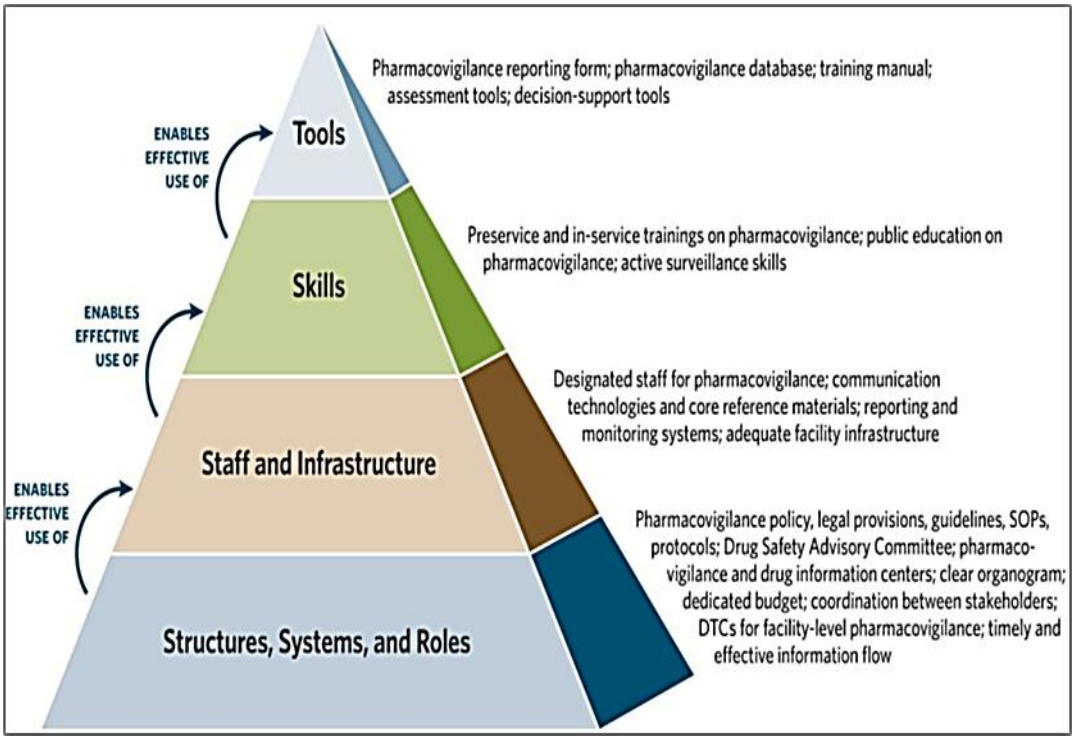

Figure 1.2 Pharmacovigilance Building Blocks

Adopted from Supporting Pharmacovigilance in Developing Countries, The Systems Perspective ((Potter C. Systemic capacity building: a hierarchy of needs. Health Policy and Planning [Internet]. 2004 Sep 1 [cited 2023 Jul 17];19(5):336–45. Available from: https://academic.oup.com/heapol/article-lookup/doi/10.1093/heapol/czh038)

Developing a robust pharmacovigilance system entails more than just collecting data on adverse drug reactions (ADRs). It should encompass mechanisms for identifying, evaluating, and minimizing risks, as well as facilitating communication. The process of risk identification involves not only spontaneous ADR reporting but also early warning systems for medicine safety. Active surveillance plays a crucial role in evaluating risks. Risk minimization and communication, integral to pharmacovigilance, involve implementing strategies to mitigate known risks, disseminating drug safety information, and promoting rational medicine usage. However, in numerous countries such as Indonesia, Cambodia and other Asian countries, pharmacovigilance efforts remain disjointed and often fail to address all aspects of a comprehensive medicine safety system (Nwokike *et al*., 2014).

The spontaneous reporting system serves as the foundation of global pharmacovigilance (World Health Organization, 2015). It involves systematically gathering, compiling, and analyzing reports of suspected adverse drug reactions (ADRs) to identify signals, communicate them, and manage risks. An example of such a reporting form is the Individual Case Safety Report (ICSR), which is utilized worldwide to collect and document cases of ADRs (Baldo *et al*., 2018).

The PIDM network comprises several key actors: a) the WHO headquarters in Geneva, focusing on policy matters; b) the Uppsala Monitoring Centre (UMC) in Sweden, responsible for operational and scientific oversight; and c) member country national pharmacovigilance (PV) centers, tasked with reporting national data to the international database (VigiBase) (World Health Organization, 2002a; World Health Organization, 2015). Figure 1.3 of the WHO represents the PV system. The process initiates locally, with patients, healthcare professionals (HCPs), and pharmaceutical companies submitting reports of suspected ADRs to regional or national centers for compilation, analysis, and evaluation. Subsequently, this information is forwarded to the WHO Individual Case Safety Report (ICSR) database – VigiBase. UMC then provides feedback to national pharmacovigilance centers to take appropriate action (World Health Organization, 2015). The sophistication of operations varies, ranging from basic infrastructure in low- and middle-income countries to advanced technology in resource-rich nations.

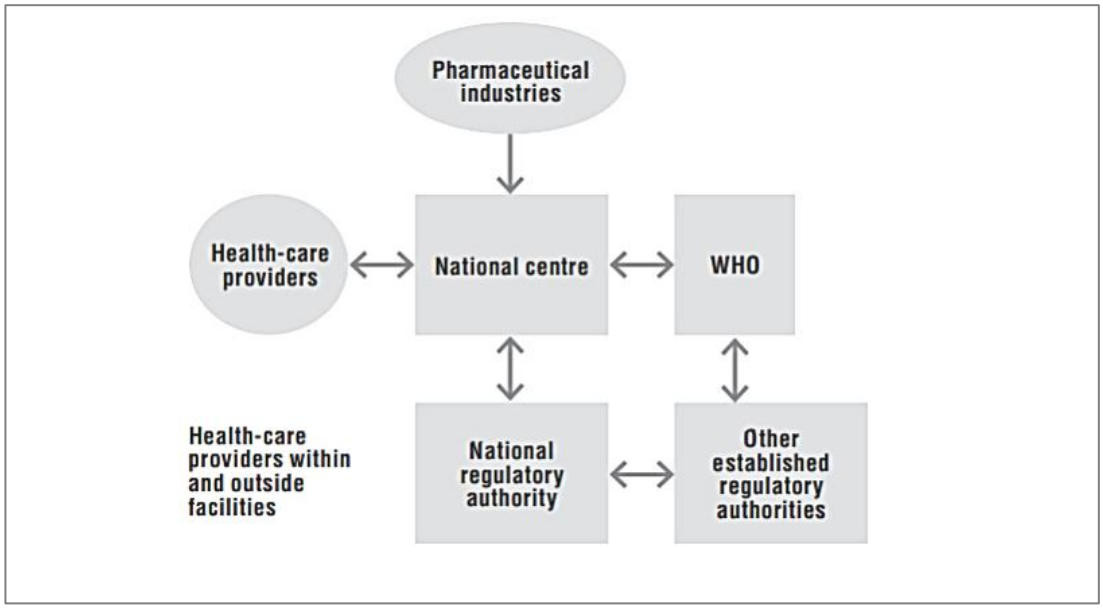

Figure 1.3 Diagrammatic representation of the pharmacovigilance system

Adopted from WHO Pharmacovigilance Indicators: A Practical Manual for The Assessment of Pharmacovigilance Systems (Quality Assurance and Safety of Medicines Team (2006) The safety of medicines in public health programmes: pharmacovigilance, an essential tool. World Health Organization. Available at: https://apps.who.int/iris/handle/10665/43384 (Accessed: 16 July 2023).

The WHO and UMC fulfil multiple roles in coordinating and evaluating adverse drug reactions (ADRs) and communicating potential risks. They also guide the establishment of national pharmacovigilance systems (World Health Organization, 2007). The collective efforts of various member countries have bolstered the number of ADRs archived in the WHO database (Vigibase™). Initially, countries gained admission to the PIDM by submitting reports. However, the quality of their systems and the organization of their pharmacovigilance teams can vary. As of now, there are 176 countries (155 full, 21 associates) in the WHO monitoring program (Centre, 2023a).

Effective pharmacovigilance programs can help identify risks as quickly as possible, minimizing or preventing harm (Said & Hussain, 2017). The foundation for solid and thorough post marketing surveillance drug studies is a proper spontaneous

ADR reporting system (Moore, 1998). Because premarketing clinical trials have so many restrictions, these studies make up for any incomplete information on drug safety (Saha, 2014; Moore, 1998).

1.1.3 Minimum Requirements of the WHO for the PV System

The WHO minimal requirements for PV system were established as the initial benchmark in 2010 for those nations looking to develop their PV systems (Maigetter *et al.,* 2015; Jha *et al.,* 2021; PV, 2010). These set of requirements were utilized as the measuring criterion for their systems including communication strategies, spontaneous reporting system, PV center, national database, ADR or PV advisory committee, and ADR reporting forms. These specifications guarantee that a PV system is present and capable of functioning at the lowest allowable quality level (PV, 2010).

As outlined in the practical manual for the assessment of pharmacovigilance systems (World Health Organization, 2015), the minimum standards set by WHO and its partners for any country with a pharmacovigilance system include:

i) Establishment of a national pharmacovigilance center collaborating with the WHO Program for International Drug Monitoring, staffed with dedicated personnel (at least one full-time), consistent basic funding, defined missions, and well-defined structures and responsibilities.

ii) Implementation of a nationwide database or system for collecting and managing adverse drug reaction (ADR) reports.

iii) Adoption of a national spontaneous reporting system featuring a national individual case safety report (ICSR) form, facilitating ADR reporting.

iv) Formation of a national ADR or pharmacovigilance advisory committee capable of providing technical support for case investigation, risk assessment, risk management, causality assessment, and crisis management, including crisis communication.

v) Development of a clear communication strategy for both routine communication and communication during crises.

1.1.4 Global Standards for Pharmacovigilance System

There was no single comprehensive document or organization that established a specific set of Global Standards for Pharmacovigilance, instead, various regulatory authorities and organizations around the world are involved in pharmacovigilance (Marie, 2015; Singh, 2015). Some of the main organizations are:

i) WHO: It provides guidance on pharmacovigilance practices and encourages collaboration among member countries to improve drug safety monitoring. WHO pharmacovigilance activities are coordinated by the Safety and Vigilance (SAV) team which forms a sub-unit of the Essential Medicines and Health Products Department at WHO Headquarters in Geneva.

ii) The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH): The ICH develops guidelines for pharmacovigilance, among other aspects of drug development and regulation. These guidelines are widely recognized and followed by regulatory agencies worldwide.

iii) The U.S. Food and Drug Administration (FDA): The FDA sets pharmacovigilance regulations and requirements in the United States and works with pharmaceutical companies to ensure drug safety.

iv) The European Medicines Agency (EMA): The EMA is responsible for the evaluation and supervision of medicinal products in the European Union. It sets pharmacovigilance guidelines and requirements for pharmaceutical companies operating in the EU.

v) The International Society of Pharmacovigilance (ISoP): ISoP is a global organization focused on promoting pharmacovigilance practices and research. It organizes conferences and publishes journals related to drug safety.

The guidelines and recommendations issued by organizations such as the WHO serve as the foundation for establishing safety protocols in countries, with pharmaceutical companies mandated to adhere to these guidelines (Singh, 2015). Standardization and harmonization of these guidelines offer numerous benefits, including preventing duplication of efforts, facilitating information sharing, minimizing risks to public health, and streamlining the time and resources required for medicine development.

The WHO SAV collaborates with six Collaborating Centers to advance global pharmacovigilance activities. These centers, established in the following order, include the WHO Collaborating Centre for International Drug Monitoring in Uppsala, Sweden; Advocacy and Training in Pharmacovigilance in Accra, Ghana; Pharmacovigilance in Rabat, Morocco; Pharmacovigilance in Education and Patient Reporting in Lareb, the Netherlands; the WHO Collaborating Centre for Drug

Statistics Methodology located in the Norwegian Institute of Public Health in Oslo, Norway; and the Pharmacovigilance Program of India (PVPI) in New Delhi, India. These centers play pivotal roles in scientific advancement, capacity building, and offering technical assistance to nations (Centre, 2023c; Marie, 2015).

1.1.5 Pharmacovigilance Systems at the Global Level

In developed countries like USA, the safety profiles of medications available to the American public are being regularly evaluated by the FDA Center for Drug and Evaluation and Research (CDER) via diverse tools during drug development process, and at the marketing stage as well (Marcus *et al.,* 2012). CDER works on assessing a wide range of pre-market information required before the products' approval. Such information includes the in-vitro data, chemistry of the drug, clinical pharmacology, microbiological and toxicological studies as well as research conducted in animal models and human clinical trials (Marcus *et al.,* 2012).

Additionally, post-marketing safety apprehensions are evaluated via systematic pharmacoepidemiologic approaches and pharmacovigilance activities which contribute to the early detection of medication errors while capturing the potential safety signals simultaneously (Marcus *et al.,* 2012). In order to tackle the safety issues, the pharmacovigilance regulations are designed to include 3 main steps: signal generation, signal refinement, and signal management. Moreover, numerous pharmacoepidemiologic studies are being conducted in developed countries for the purpose of offering supplemental data that would quantify the safety concerns that are correlated with the exposed populations (Wise, 2011). When it comes to analyzing the risk-benefit ratio, a multidisciplinary teams are assigned to evaluate the epidemiologic information of each medication as well as the premarket and postmarket data available

in order to write up recommendations and updates regarding the safety of drugs (Marcus *et al.,* 2012). The Adverse Event Reporting System (AERS) of the FDA has acted as a computerized database for medication errors and as a reservoir for ADRs reports for all medications including biologic drugs marketed in US since 1997 (Research, 2019). Recently, around six million records registered in AERS includes therapeutic biological drugs as well as all prescription and over-the-counter medications on a domestic and foreign level. The spontaneous ADR reports are submitted through portals like MedWatch, or through the FDA's safety and adverse event reporting system, or it can be submitted directly to the AERS via pharmaceutical manufactures by computerized gateways Commissioner (2022). In Europe, which is also considered a well-developed region with advanced PV systems, the company which is responsible for marketing authorization of medications owns the legal responsibility of operating PV systems. Those responsibilities include collecting safety data of drugs contentiously, submitting ADRs reports within the given timeframes, and notify regulatory authorities immediately with any changes that may occur in the risk-benefit ratio (Marcus *et al.,* 2012).

On the other hand, there is undesired situations observed in developing countries which are represented in the numerous limitations present in the healthcare systems including the problem of shortages in essential resources like the availability of well-qualified HCPs and equipment (Elshafie *et al.,* 2018). Not to mention that since developing countries hold the majority of worldwide disease burden, their healthcare systems are often overwhelmed with just offering a cure to their diseased patients rather than thinking thoroughly about the safety of such used cures (Isah, 2012). The lack of proper tracking of exposures and outcomes of drugs used in developing countries highlights the need for further investigations concerning drug safety in these

countries (Elshafie *et al.*, 2018). However, in the past two decades, a noticeable growth in the awareness regarding the topic of promoting the safe use of medications has been established in the developing countries (Elmontsri *et al*., 2018). This includes paying more attention towards enhancing the quality of PV practices via developing national PV programs. The good news is that many developing countries have actually managed to become associate members or even full members of the WHO-PIDM Program (Centre, 2023a; Abbas *et al.*, 2023; Ampadu *et al.*, 2016; Olsson *et al.*, 2015; Thomas & Zachariah, 2018; Palaian, 2018). In addition, there is a recent considerable growth in the ADRs reporting to Vigibase in developing countries anticipated as the percentage rose from 6.7% to 12.5% during six years' timeframe between 2011 and 2017 (Palaian, 2018). However, the majority of studies reveal that in most scenarios developing countries still fail to implement a fully functioning and successful PV system within their healthcare system (Beninger, 2018; Hazell & Shakir, 2006; World Health Organization, 2006; Clarke *et al.*, 2006). The struggle of developing countries in establishing PV polices is evidently reflected by the small number of ADR reports submitted to the UMC by developing notions compared to those submitted by developed countries (Palaian, 2018).

The growth in the number of countries with dedicated pharmacovigilance (PV) programs is promising, rising from ten in 1970 to 136 in 2019 and further to 176 in 2022, reflecting a strengthened commitment to therapeutic product safety surveillance (Centre, 2023a). As more national PV centers join the global PV community, it becomes essential to assess the functionality and performance of these systems to ensure their positive and effective contributions to global PV data and practices (World Health Organization, 2015; Edwards & Lindquist, 2016; Schurer *et al.*, 2017).

1.1.6 Pharmacovigilance in the Arab Countries

The recent implementation of new regulations has brought increased attention to the scope of pharmacovigilance in Arab countries, shaping the concepts and activities of pharmacovigilance systems within each nation. Given that half of the Asian Arab countries are members of the Gulf Cooperation Council (GCC), they can often adopt similar approaches to various healthcare system activities, including pharmacovigilance, providing them with an advantage over African counterparts. Some Arab nations, such as Morocco, Jordan, and Egypt, have well-established pharmacovigilance systems with notable achievements in this field (Bham, 2015). Morocco, in particular, has been acknowledged as an exemplary role model for other Arab nations seeking to strengthen their pharmacovigilance capacity and activities. Furthermore, Morocco actively contributes to the global pharmacovigilance system as one of the WHO's collaborating centers (Alshammari *et al*., 2019).

Arab countries have embraced the "Good Pharmacovigilance Practice for Arab Countries" (GVP-Arab), developed in 2015 by the Higher Technical Committee for Medicine under The Arab League, drawing inspiration from the European Good Pharmacovigilance Practices (EU GVP) utilized in developed European nations (GVP. Arab., 2015; Silander & Wallace, 2015). Although rooted in the EU GVP, this guideline respects the right of national medicines authorities (NMAs) in Arab countries to impose additional or altered requirements (GVP. Arab., 2015).

The primary aim of the GVP-Arab is to provide guidance to Marketing Authorization Holders (MAHs) of pharmaceuticals for human use in Arab countries regarding standards, procedures, and roles in human pharmacovigilance. Ultimately, the goal is to enhance efforts to ensure that all patients in Arab countries have access

to safe, effective, and high-quality medicines by ensuring that MAHs fulfill their key role in monitoring the safety of their medical products for human use (GVP. Arab., 2015).

While recognizing the diversity in healthcare and regulatory systems among Arab countries, the main objective of GVP-Arab is to harmonize pharmacovigilance practices and regulations across these nations (GVP. Arab., 2015). This recommendation should be viewed as an "ideal model" for each national medical authority in an Arab nation to strive toward implementing, either presently or in the future, at the national level.

Among the members of the WHO UMC, 14 Arab countries hold full membership status, while three hold associate membership. Associate members do not contribute data to VigiBase (Centre, 2023a; Centre, 2023c).

1.2 Research Focus

1.2.1 Importance of establishing a Pharmacovigilance System

The existence of a pharmacovigilance system aids in assessing the scope and severity of ADRs and help in preventing recurrence. If the system doesn’t exist, ADRs still occur and nobody can be aware of them before they actually happen. Aside from the effects of ADRs on morbidity, mortality and the associated costs to health systems, ADRs also have additional costs related to the decline in public trust in the healthcare system, financial loss to the pharmaceutical industry, nonadherence to treatment, and the emergence of drug resistance (Lebega *et al*., 2012).

In the absence of a pharmacovigilance system, avoidable ADRs may occur and healthcare costs may rise. Over 70% of ADRs that required hospitalisation could be

prevented and thus saving the treatment expenses (Pirmohamed *et al.*, 2004). Patients with ADRs spent an additional 16,000 to 24,000 US dollars in hospital stays, which was an average of 8 to 12 days longer than patients without ADRs (Kass-Bartelmes, 2005). Additionally, the PV system can help in the proper use of medications. According to WHO, more than half of all medicines are prescribed, dispensed, or sold incorrectly worldwide, and half of all patients fail to take their medications correctly (World Health Organization, 2002a). Furthermore, PV system improve patient safety by raising the quality of pharmaceutical industry products. The absence of PV system has a negative impact on treatment, such as increased therapeutic switching, the need for more expensive regimens, drug resistance, increased patient drop-out rates, and nonadherence (Lebega *et al*., 2012).

1.2.2 Pharmacovigilance System Assessment

Pharmacovigilance System Assessment refer to evaluations conducted to assess the effectiveness, efficiency, and compliance of a pharmacovigilance system. It aims to ensure that pharmaceutical companies, regulatory authorities, health care facilities, and other stakeholders have robust systems in place to monitor and manage the safety of medicinal products throughout their lifecycle. These assessments help identify areas of improvement, ensure compliance with regulatory requirements, and enhance patient safety. The Assessments may be conducted by regulatory authorities, independent audit organizations, or internal teams within the PV center or the pharmaceutical companies or any healthcare facilities. During the assessment process of a pharmacovigilance (PV) system, various aspects are evaluated, including its structure, processes, and outcomes. This evaluation entails the use of validated Pharmacovigilance Key Performance Indicators (PV KPIs) to address each assessment

objective. PV KPIs, developed by international professional bodies such as the WHO and the Strengthening Pharmaceutical Systems (SPS) Program, enable the formulation of strategic and operational recommendations and aid in identifying system limitations based on structure, process, and outcome criteria (World Health Organization, 2015) (SPS. 2009b). These measurable indicators serve as benchmarks to gauge the performance of a pharmacovigilance system and its ongoing improvement efforts.

Various tools are utilized to assess pharmacovigilance (PV) systems, including the WHO Pharmacovigilance Indicators (WHO-PVI) and the Indicator-Based Pharmacovigilance Assessment Tool (IPAT), among others. These tools categorize indicators into core and supplementary categories, each encompassing structural, process, and outcome or impact indicators. The data for structural indicators is primarily qualitative, whereas process and outcome or impact indicators rely on quantitative data (World Health Organization, 2015; SPS. 2009b). The quality of a context-based system evaluation heavily relies on the perspectives of national PV stakeholders and is closely linked to the prevailing PV challenges in the country. This data aids in resolving PV issues and evaluating national PV processes as needed (World Health Organization, 2015; Edwards & Lindquist, 2016).

WHO-PVI comprises 63 indicators, with 27 core and 36 complementary indicators, while the IPAT tool includes 43 indicators, with 26 core and 17 supplementary indicators addressing various components of pharmacovigilance and medicine safety systems (World Health Organization, 2015; SPS. 2009b). IPAT is a comprehensive performance metric tool that encompasses both regulatory and medication safety indicators, focusing on critical issues related to health systems that are fundamental to the overall capacity and sustainability of a medicine safety system.

Additionally, IPAT serves as a quality improvement tool, encouraging users to monitor progress over time.

1.2.3 Pharmacovigilance System in UAE

1.2.3(a) Brief about UAE

The United Arab Emirates (UAE) is a Western Asian country. It shares borders with Saudi Arabia and Oman, and it has maritime borders with Iran and Qatar. It is also known for its oil and gas activities. Its capital, Abu Dhabi, is the country's most prominent city. On the other hand, Dubai, the second-largest city, is regarded as an international hub. The UAE was founded from a union of seven emirates in 1971, including the capital Abu Dhabi, Dubai, Sharjah, Ajman, Ras Al Khaimah, Fujairah, and Umm Al Quwain (Dhabi, 2016) (Figure 1.4) (Koornneef *et al*., 2017). The official language spoken in the UAE is Arabic, and the official religion is Islam. As of 2023, the current population of UAE is 10,246,132 (UAE, 2023).

Figure 1.4 Map of UAE showing the seven emirates

(Koornneef, E., Robben, P. and Blair, I. (2017) 'Progress and outcomes of health systems reform in the United Arab Emirates: a systematic review', *BMC Health Services Research*, 17(1), p. 672. Available at: https://doi.org/10.1186/s12913-017-2597-1)

1.2.3(b) Healthcare System in UAE

The country's healthcare system is governed by three health regulatory bodies: The Ministry of Health and Prevention (MOHAP), which is known as the Ministry of Health, is in charge of implementing government policy pertaining to the provision of healthcare for all UAE nationals and residents (Koornneef *et al*., 2017; UAE, 2021). The Ministry also responsible for providing healthcare to UAE citizens, developing training, prevention, and health programs, coordinating the practice of healthcare professions, and establishing, running, and supervising healthcare facilities (UAE, 2021). Practically speaking, MOHAP oversees regulatory compliance in the northern emirates as well as healthcare services (Northern Emirates: Sharjah, Ajman, Umm Al Quwain, Ras Al Khaimah and Fujairah). Additionally, it issues licenses and regulates drugs and medical equipment prices on a national level (UAE, 2021). The second healthcare authority in the country is Health Authority Abu-Dhabi (HAAD), which oversees Abu Dhabi's healthcare sector. It establishes the health system's strategy and tracks and evaluates the population's health as well as the effectiveness of the system in the city (UAE, 2021; HRA, 2024). Dubai Health Authority (DHA) is the third healthcare organization in the country. It regulates all healthcare services provided in Dubai by granting licenses to healthcare providers and facilities and conducting facility inspections (UAE, 2021; HRA, 2024).

Table1.1 displays healthcare and related indicators in the UAE. According to World meter elaboration of the most recent United Nations data, the country's current population is 10,246,132 as of June 2023. It equates to 0.13% of the global population. Healthcare facilities include both public and private hospitals, as well as public and private clinics. The number of healthcare facilities increased year after year. More details in Table 1.1.

Table 1.1 Healthcare and Related Indicators in the UAE

Parameters	Number
Population	10,246,132 (2023)
Number of hospitals	157 hospitals and 5369 health centres (2023)
Healthcare workers	113 thousand (in 2017) 26151 Physicians (2020)
Pharmaceutical market size	US$342.80m (2023)
Number of drugs approved	2000 (DOH) (2023)
Per head capita income	$41,770 (2020)
Healthcare expenditure (per head)	$2,041.3 (2022)
Ratio of Physicians-to-population	2.9 doctors for every 1,000 residents

1.2.3(c) Pharmacovigilance System and ADRs reporting policies in UAE:

In 2008, the UAE initiated its PV program in the capital Abu Dhabi by launching the National Pharmacovigilance Unite (NPU), which is aimed at preventing medication errors and the suspected ADRs (Alebrahem *et al.*, 2014). This program was carried out through the establishment of a centralized database that allows healthcare providers and patients to report suspected ADRs and medication errors. The data collected will then be used to issue safety warnings, provide professional education and training, conduct drug regulatory activities, and develop national drug therapeutic guidelines (Fahmy, 2008). By 2013 UAE became a full member of the WHO UMC in Sweden (Alshammari *et al.*, 2019) (Figure 1.5). The program's implementation was made possible through the participation of various groups such as the public, healthcare providers and pharmaceutical companies.

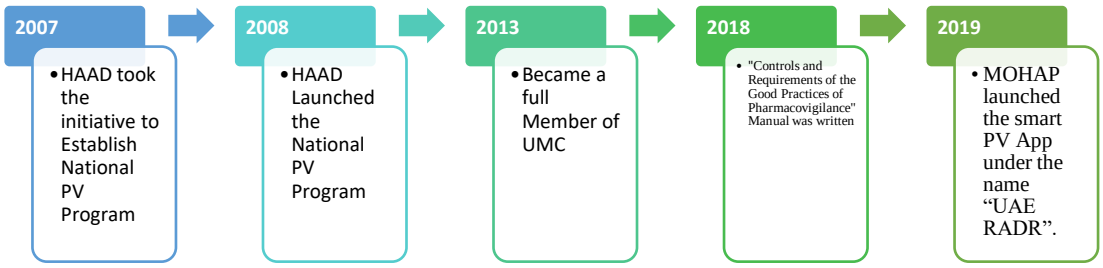

Figure 1.5 Historical events of PV development in UAE

The UAE, like other Arab countries, has incorporated the GVP-Arab guidelines into its pharmacovigilance system. The policy is known as "UAE MOH Guidelines in Good Vigilance Practice (GVP) For Marketing Authorization Holders / Pharmaceutical Manufacturers in UAE." (UAE. MOH. GVP, 2018). The Marketing Authorization Holders (MAH) should ensure that all information relevant to a medicinal product's risk-benefit balance is reported to the PV section/ Drug Department/ UAE MOHAP in accordance with these guidelines (UAE. MOH. GVP, 2018).

Moreover, the MOHAP mandates that every MAH should have a pharmacovigilance system in place as well as qualified personnel for pharmacovigilance (QPPV) whom are residing in the UAE (UAE. MOH. GVP, 2018). International pharmaceutical corporations that own local agents will not require having QPPV; yet local safety responsible (LSR) personnel based in UAE would be still necessary (Alshammari *et al*, 2019). Similar to the Good Pharmacovigilance Practices (GVP) for Arab nations, the guideline specifies that the QPPV/LSR should be a pharmacist or physician who is accessible around-the-clock (Alshammari *et al*, 2019; UAE. MOH. GVP., 2018).

MOHAP and other healthcare authorities in the UAE is committed to maintaining a high level of medication safety. Reporting ADRs of medicines and medical products can be done through different methods to make it easier for any healthcare professionals, consumers or MAH to report; these methods are: 1. Straightforward paper based reporting forms, reporting to PV @moh.gov.ae; 2. Online reporting system, 3. Smart phone application (UAE. MOH. GVP., 2018).

At the local level in the UAE, healthcare providers, patients, and pharmaceutical companies submit reports of suspected adverse drug reactions (ADRs) to the Pharmacovigilance (PV) section or Drug Department of the UAE Ministry of Health and Prevention (MOHAP) for collation, analysis, and evaluation. This information undergoes further processing and is then forwarded to the WHO Individual Case Safety Report (ICSR) database – VigiBase. The PV section receives feedback on findings, which are then communicated to the Uppsala Monitoring Centre (UMC) for appropriate action (Figure 1.6) (UAE. MOH. GVP, 2018; RSE.MOH., 2021).

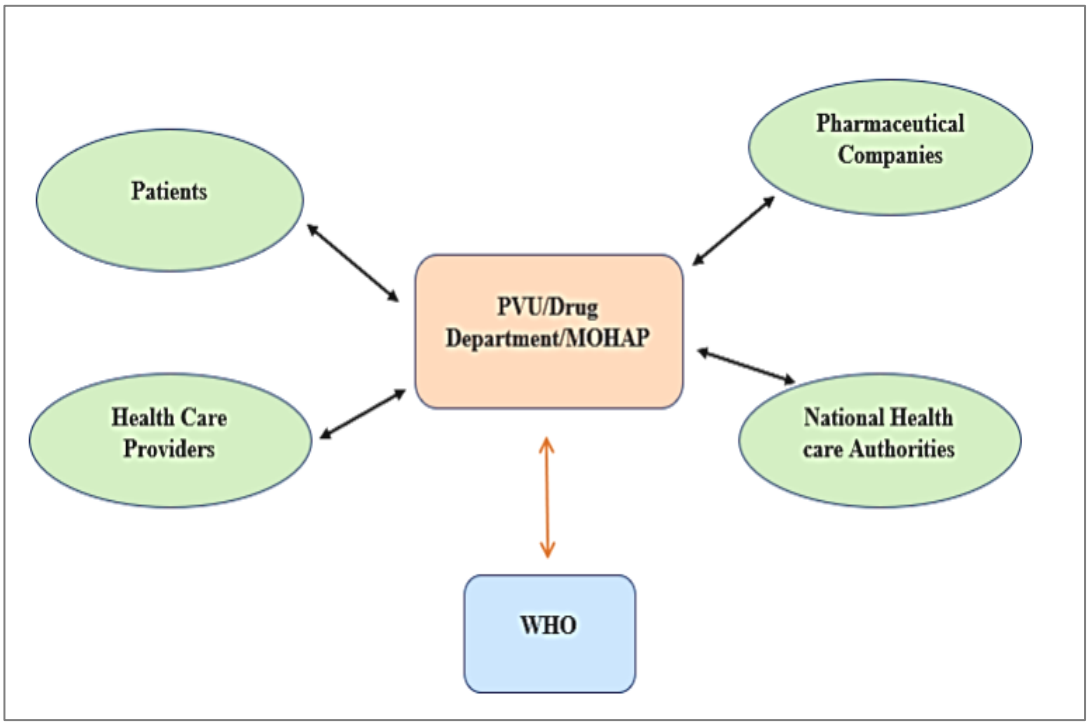

Figure 1.6 Diagrammatic representation of the PV system in the UAE

UAE like other countries, depends on the spontaneous reporting system (SPS) to collect information about ADRs (Elkalmi, 010). SRS is one of the most widely used methods in pharmacovigilance, involving the voluntary reporting of ADRs by healthcare providers, pharmaceutical companies, and, in some cases, patients and a

specific form is used to collect the data of ADRs (Hazell & Shakir, 2006). The amount of ADR reports collected by last year was 4436 reports, which is far below the WHO's optimal level of reporting requirements (200 per million/year) (PVMR., 2010; World Health Organization, 2006).

1.2.3(d) Pharmacists Role in Pharmacovigilance Reporting in UAE

The role of pharmacists has evolved significantly over time. Initially, their responsibilities were focused on the chemical composition and raw materials of drugs, drug production, and dispensing. However, in recent years, pharmacists have taken on a more consultative role, providing physicians with advice on drug therapy (Arabyat et al., 2020; Yan et al., 2022). They play a critical role in reducing the incidence of ADRs and drug-drug interactions, as well as offering information and training on proper drug use (Hohl et al., 2015; Yan et al., 2022). In addition, pharmacists make significant contributions to pharmacovigilance as they are often the first to report adverse medication reactions. They are instrumental in the development, maintenance, and ongoing evaluation of ADR programs and are responsible for educating healthcare professionals about potential ADRs. Furthermore, pharmacists play a vital role in conducting post-surveillance safety and efficacy studies (Said & Hussain, 2017).

In the UAE, the role of hospital pharmacists is predominantly centered around medication supply and dispensing, with limited involvement in comprehensive patient care services. While they have the potential to extend their services to various hospital areas, such as ambulatory care clinics, their activities primarily revolve around medication procurement, inventory management, and dispensing. Clinical assessment of patient needs for pharmaceutical care receives minimal attention, if any, due to factors such as insufficient clinical training and a shortage of pharmacists in hospital

settings (Dameh, 2015). According to a study by Dameh conducted in 2009, these factors contribute to the challenges faced by hospital pharmacists in providing effective and efficient services (Dameh, 2015).

1.3 Research Rationale

Adverse drug reactions (ADRs) significantly contribute to global morbidity and mortality rates (Ahmad *et al*., 2013). Studies have highlighted the diverse consequences of ADRs, ranging from socioeconomic to health-related issues, and in severe cases, even death (Formica *et al.* 2018; Wolfe *et al*., 2018; Qing-ping *et al*., 2014; Pedrós *et al.,* 2014; Oshikoya *et al.,* 2011). ADRs are a major cause of hospitalization, accounting for 5-13% of cases overall and rising to 24% in elderly patients (Bénard-Laribière *et al*., 2015). The economic burden of avoidable ADRs in Western nations is substantial, ranging from €2,851 to €9,015 for inpatient care and €174 to €8,515 for outpatient care (Formica *et al.*, 2018). Moreover, ADRs have been associated with longer hospital stays, potentially costing up to €706 million annually in the UK alone (Pirmohamed *et al.,* 2004). Hence, addressing medication safety concerns and ADRs is crucial for reducing healthcare system costs and mitigating morbidity and mortality associated with drug use (World Health Organization, 2002a; Ahmad *et al*., 2013; Garashi *et al.*, 2022).

ADR reporting is a key pharmacovigilance (PV) method aimed at ensuring medication safety and mitigating harmful events (Ahmad *et al*., 2013). It plays a critical role in the early detection of serious and rare ADRs, guiding causality hypotheses, investigation priorities, and regulatory measures (Najafi 2018; Melo *et al*., 2020). However, effective ADR reporting depends on the knowledge, attitude, and