A strategy for the implementation of the 'guideline on good pharmacovigilance practices (GVP) for Arab countries' in countries with nascent pharmacovigilance systems: the case of Kuwait

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<tr>
<td>ACF</td>
<td>Advocacy Coalition Framework</td>
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<tr>
<td>ADR</td>
<td>Adverse Drug Reaction</td>
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<tr>
<td>ASEAN</td>
<td>Association of Southeast Asian Nations</td>
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<tr>
<td>CEM</td>
<td>Cohort Event Monitoring</td>
</tr>
<tr>
<td>CIOMS</td>
<td>Council for International Organisations of Medical Sciences</td>
</tr>
<tr>
<td>DGPA&amp;DC</td>
<td>Directorate General of Pharmaceutical Affairs and Drug Control</td>
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<tr>
<td>EC</td>
<td>European Commission</td>
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<tr>
<td>EMA</td>
<td>European Medicines Agency</td>
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<td>EU</td>
<td>European Union</td>
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<tr>
<td>GVP</td>
<td>Good Pharmacovigilance Practice</td>
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<tr>
<td>HCP</td>
<td>Healthcare Professional</td>
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<tr>
<td>ICH</td>
<td>International Conference for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use</td>
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<td>ICSRs</td>
<td>Individual Case Safety Reports</td>
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<tr>
<td>IPAT</td>
<td>Indicator-Based Pharmacovigilance Assessment Tool</td>
</tr>
<tr>
<td>JFDA</td>
<td>Jordan Food and Drug Administration</td>
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<tr>
<td>KDFCA</td>
<td>Kuwait Drug and Food Control Administration</td>
</tr>
<tr>
<td>MAH</td>
<td>Marketing Authorisation Holder</td>
</tr>
<tr>
<td>MBA</td>
<td>Master of Business Administration</td>
</tr>
<tr>
<td>MPPharm</td>
<td>Master of Pharmacy</td>
</tr>
<tr>
<td>MOH</td>
<td>Ministry of Health</td>
</tr>
<tr>
<td>MSc</td>
<td>Master of Science</td>
</tr>
<tr>
<td>MSH</td>
<td>Management Sciences for Health</td>
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<tr>
<td>NCA</td>
<td>National Competent Authority</td>
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<td>NMRA</td>
<td>National Medicines Regulatory Authority</td>
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<tr>
<td>NPVC</td>
<td>National Pharmacovigilance Centre</td>
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<tr>
<td>PASS</td>
<td>Post-Authorisation Safety Studies</td>
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<tr>
<td>PBRER</td>
<td>Periodic Benefit-Risk Evaluation Report</td>
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<tr>
<td>PHP</td>
<td>Public Health Programme</td>
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<tr>
<td>PIDM</td>
<td>Programme for International Drug Monitoring</td>
</tr>
<tr>
<td>PRISMA</td>
<td>Preferred Reporting Items for Systematic Reviews and Meta-Analyses</td>
</tr>
<tr>
<td>PSMF</td>
<td>Pharmacovigilance System Master File</td>
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<tr>
<td>PSUR</td>
<td>Periodic Safety Update Report</td>
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<td>PV</td>
<td>Pharmacovigilance</td>
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<td>QPPV</td>
<td>Qualified Person Responsible for Pharmacovigilance</td>
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<td>RMP</td>
<td>Risk Management Plan</td>
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<tr>
<td>UAE</td>
<td>United Arab Emirates</td>
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<tr>
<td>UK</td>
<td>United Kingdom</td>
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<td>UMC</td>
<td>Uppsala Monitoring Centre</td>
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UREC  University Research Ethics Committee
US    United States
USAID United States Agency for International Development
USD   United States Dollar
USFDA United States Food and Drug Administration
WHO   World Health Organisation
Abstract

Background – Pharmacovigilance (PV) plays a vital role in ensuring medicines’ safety. Differences among countries in the incidence, pattern, and severity of adverse drug reactions (ADRs) mean that it is essential for each country to have a PV system. Although PV is generally well established in developed nations, it remains underdeveloped in a number of countries, including the Arab World and Kuwait in particular. To unify PV practice across the Arab World, the Arab League developed the guideline on good PV practices (GVP) for Arab countries. As Arab countries seek to implement the guideline, understanding what helps and hinders implementation in Arab countries with more or less developed systems can inform improved PV system performance as well as policy development and implementation. This study aimed to explore and identify the key factors impacting PV system performance and policy implementation in Kuwait and other Arab countries with more established PV systems to inform recommendations for strengthening PV in Kuwait.

Method – Three studies were undertaken to address the above aim. Informed by the World Health Organisation (WHO) PV indicators, Study One systematically reviewed literature evaluating PV systems' performance in developing countries. Using the WHO PV indicators as a framework, Study Two employed a mixed-methods approach involving document review, semi-structured interviews, and a survey to explore PV systems' structures, processes, and outcomes, and to offer in-depth understanding of strengths and limitations in Jordan, Oman, and Kuwait. In Study Three, Matland's ambiguity-conflict model of policy implementation served to frame semi-structured interviews exploring the mechanisms of and factors influencing PV policy implementation in Jordan, Oman, and Kuwait.

Results – Study One revealed that overall system performance was poor and varied widely from one country to another. Moreover, it highlighted the scarcity of research providing an in-depth exploration of countries’ PV systems' performance and policy implementation as well as the factors impacting them. In Study Two, system strengths were attributed to the presence of "core" structural indicators including a dedicated and officially recognised PV centre, PV legislation, and a national PV advisory committee, as well as "complementary" structural indicators e.g. a computerised case-report management system. Weaknesses were attributed to the absence of these indicators plus other "core" structural indicators, namely regular financial provision, and adequate staff. Other weaknesses were attributed to low performance in “core” process and outcome indicators including reporting rates, reporter awareness, and signal detection. Study Three found that PV policy ambiguity and conflict were low in Jordan and Oman suggesting an "administrative implementation" pathway. In Kuwait, policy ambiguity was high while sentiments about policy conflict were varied suggesting a mixture between "experimental implementation" and “symbolic implementation”.

Conclusion – This programme of research highlighted the need for applying a holistic and stepwise approach to strengthening PV policy implementation and subsequent system performance that considers countries' resources and infrastructure. Informed by insight gained from the three studies, recommendations for strengthening PV policy implementation and subsequent system performance in Kuwait and other Arab countries with nascent systems were made.
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Dedication

This thesis is dedicated to my parents, Yousuf Garashi and Gloria Mohammad, for their unconditional love as well as their endless support, prayers, and encouragement. I would not be who or where I am today without them.

I would also like to dedicate this thesis to my daughter Layan who I love dearly and who brings me great joy and happiness.
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First and foremost, I would like to express my gratitude to my supervisors Prof Ellen Schafheutle and Dr Douglas Steinke for their continuous support, guidance, patience, and encouragement throughout the entirety of my journey to complete this project. The knowledge and expertise they shared with me as well as their persistent efforts in driving me to excel in my work helped me develop both as a person and as a researcher.

I am grateful to my colleagues with whom I shared an office throughout the time I spent working as a PhD student at the University for providing a warm and friendly environment conducive to carrying out my research. I would also like to acknowledge my fellow PhD students of the Drug Usage and Pharmacy Practice Group whom I will always remember fondly for their friendship. I would also like to extend my thanks to the Division of Pharmacy and Optometry administrative staff, in particular Sarah Bellis and Alyssa Piasecki, who were always there to help me with anything that I required.

My thanks must also be given to the participants from Jordan, Oman, and Kuwait for their willingness to devote their time to take part in this programme of research. Without their valuable contributions, it would not have been possible to complete the research. The assistance provided by members of the national pharmacovigilance centres in Jordan and Oman in establishing contact with members of the pharmaceutical industry in their countries must also be acknowledged.

Outside the scope of my thesis, my thanks are given to my friend and former superintendent at Kuwait Drug and Food Control Administration Ramy Behbehani. Your encouragement has helped me strive to reach greater heights. Finally, I would also like to thank my friends Dr Hussain Hussain and Yaser Sakheer for always keeping in touch regardless of the distance between us or time spent apart.
The author

Hamza Garashi, a Kuwaiti pharmacist, obtained his pharmacy degree (MPharm) from Liverpool John Moores University in 2006. Upon graduation, he returned to Kuwait where he joined Kuwait's Ministry of Health (MOH) as a pharmacist. From the time he joined till the present day he has worked in various positions within different areas of the MOH beginning with Salwa Specialist Health Centre, followed by Al-Adan Hospital, and finally Kuwait Drug and Food Control Administration (KDFCA). During the period between 2009 and 2012, he also worked as a part-time teaching assistant at the Faculty of Pharmacy at Kuwait University. In the year 2010, he obtained his Master of Business Administration (MBA) from the American University of the Middle East, Kuwait. He was granted a scholarship from the Kuwaiti MOH in 2012 which allowed him to obtain a Master of Science (MSc) in Pharmaceutical Services and Medicines Control from the University of Bradford in 2013. His MSc dissertation, which was carried out under the supervision of Professor Brian Clark, was focused on the recommendation of suitable guidelines for the registration of nutraceuticals for Kuwait. Hamza obtained a second scholarship from the Kuwaiti MOH which allowed him to commence his studies (full-time) from September 2017 to obtain his PhD. It is hoped that the recommendations resulting from this programme of work could be used to develop a robust pharmacovigilance system and policy incorporating the guideline on good pharmacovigilance (GVP) practices in the State of Kuwait.
Research dissemination

Peer-reviewed academic journal papers


Peer-reviewed conference presentations

Chapter One: Introduction and background

1.1. Introduction

Since the thalidomide tragedy in the 1960s, adverse drug reactions (ADRs) have garnered increased attention internationally, accompanied by a worrying upward trend in ADRs resulting from prescribed drugs. (1) Of particular relevance is ADRs which are unexpected or severe, leading to increased morbidity, mortality and financial loss, yet are often not recognised or identified before regulatory approval due to the limitations of clinical trials. (2, 3) The steady increase in medicine use worldwide is likely to increase the incidence of ADRs. (1, 3)

To preserve public health and maintain confidence in the healthcare system, governments implement policies in the form of pharmacovigilance (PV) systems to ensure the quality, safety, and effectiveness of approved drugs. (4) The World Health Organisation (WHO) has issued guidelines to support this (5-7). PV systems include mechanisms to monitor and evaluate drug safety throughout a medicine’s entire lifecycle. The PV system serves to collect and analyse reports of drug-related problems including ADRs by employing measures of quality control and assurance as well as disseminating information on potential risks to healthcare professionals (HCPs) and the public. (3)

Given that PV systems in the majority of developing countries (including those of the Arab World) are not well established, worldwide data on ADRs is primarily generated by developed countries where most drugs are developed, tested, and initially marketed. (8, 9) Despite the usefulness of such data to local regulatory bodies in making decisions relating to medications safety. However, the information on adverse effects obtained from developed countries may neither be relevant nor applicable to Arab populations. This is due to the differences in existing local conditions including individuals’ responses to drugs due to ethnicity and genetics, physicians’ prescribing habits, drug regulatory systems in place, and the quality and quantity of available drugs to patients. (6, 10) Therefore, there is a need for every Arab country to establish a PV system to better serve its population's needs.
As part of the Arab League's role in enhancing Arab countries' healthcare systems, an initiative was proposed to establish a guideline on good pharmacovigilance practices (GVP) for Arab countries with the aim of unifying PV activities and procedures among Arab countries. Some Arab countries such as Egypt and Jordan have benefited from implementing the GVP for Arab countries, whereas others lack a system for the establishment of PV activities. In line with these recent policy initiatives, it is important to identify how PV performance and policy implementation can be strengthened in Arab countries where PV is nascent such as in Kuwait which may also benefit other countries at a similar stage. Having introduced the subject matter of the research, the following section provides essential background information.

1.2. Background

1.2.1. Pharmacovigilance

1.2.1.1. Definition and historical background of pharmacovigilance

The WHO defines PV as “the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problems.” The term 'pharmacovigilance' was officially introduced in the 1970s by French researchers to identify the scientific field concerning drug safety. It was coined by combining the Greek word 'pharmakon' meaning drug, and the Latin word 'vigilare', which means “to keep awake or alert, to keep watch”. Although PV is concerned with drug safety during both the pre- and post-marketing phases, it is more prominent in the latter and therefore it is sometimes referred to as post-marketing surveillance.

PV emerged as a response to a series of tragedies that demonstrated the need for continuous monitoring of drug products throughout their entire lifecycle. The origins of PV can be traced back to 1848 in England when the death of a 15-year-old girl from possible ventricular fibrillation was linked to the use of chloroform as an anaesthetic agent. This led to the establishment of a special commission that invited physicians in Britain and its colonies to report anaesthesia-related deaths. Several subsequent events starting from 1937 helped shape the development of PV in its current form. The most significant of these events which acted as a launching point for PV was the thalidomide tragedy which occurred during the
period between the late 1950s and early 1960s. The use of thalidomide, which was marketed as a sedative and anti-emetic that could be used safely during the early stages of pregnancy in over 50 countries between 1956 and 1961, resulted in over 10,000 infants being born with severe defects such as phocomelia. This incident raised policymakers' awareness of the need to implement mechanisms to ensure the accuracy and validity of pharmaceutical companies' safety claims. Furthermore, it emphasised the need to implement mechanisms for the collection, assessment, and communication of information regarding drug safety after regulatory approval for use in clinical practice.

A consequence of the thalidomide incident was a major change in drug regulations most notably in the United States (US), United Kingdom (UK), and Europe. These changes included the development of legislation requiring drug product marketing authorisation holders (MAH) to provide evidence regarding their products' safety and efficacy prior to obtaining authorisation, as well as spontaneous ADR reporting systems after marketing.

1.2.1.2. Objectives and scope of pharmacovigilance

PV has four main objectives, namely:

a) the identification and quantification of previously unknown drug safety hazards,
b) the elucidation of predisposing factors to drug safety hazards, which if avoided could improve drug safety,
c) obtaining safety evidence on approved drugs to widen their usage, and
d) refuting false-positive ADR signals (a hypothesis of a causal relationship between an ADR and a drug).

These objectives are achieved through carrying out the following activities:

1) collection of medicinal product information relating to the nature, severity, clinical features, and consequences of adverse effects,
2) identification of causative links between medicinal products and adverse effects through documentation and examination of data collected pertaining to adverse effects,
3) taking corrective measures to remove or minimise dangers posed by medicinal products’ adverse effects, and
4) Monitoring the impact of corrective measures taken.
Although PV's origins lie in the focus of drug safety surveillance to monitor and detect adverse drug reactions (ADRs) of medicines holding marketing authorisations, its scope has expanded over the years to include other types of products such as herbal medicines, biologicals, medical devices, and vaccines. This diversity is reflected in the definition of an adverse reaction which is "A response to a medicinal product which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for the modification of physiologic function"(13, p. 40). As such, ADRs can result from the use of the product either within or outside its approved conditions for use (e.g., off-label use, overdose, misuse, abuse, and medication errors) or from occupational exposure.

1.2.1.3. Why is pharmacovigilance needed?

Limitations of clinical trials

Prior to approval by regulatory authorities, drug products are required to undergo extensive testing and rigorous evaluation during clinical trials. However, contrary to the belief that pre-marketing studies have thoroughly covered all relevant drug safety issues when a new drug is introduced into clinical practice, experience of its effects in humans are limited and any drug safety conclusions made are only provisional. One of the reasons for this is the nature of clinical trials' design, which usually involve the enrollment of a limited number of patients (approximately 1,500) and are performed over a relatively short period. Therefore, it is generally only possible to detect commonly occurring ADRs (those with an incidence exceeding 0.1%) and those with short latency. Second, clinical trials do not accurately reflect the real-world conditions that drugs are exposed to once they enter the market and are used by the general population. This is because they often rely on volunteers that are not representative of the general population who may be more at risk of suffering ADRs such as the elderly, patients suffering from multiple conditions, paediatrics, and pregnant women. Furthermore, clinical trials are not able to predict the occurrence of ADRs that are linked to changes in the environment that drugs are used in once they are approved and marketed. These include changes in dosing as well interactions with other medications or food. A third reason relates to the inability during clinical trials to detect ADRs which require the employment of specialised (non-routine) techniques.
Health and economic burden of adverse drug reactions

Despite often being preventable, ADRs pose a significant threat to countries' populations by causing illness and/or disability.(13, 31) In the US, ADRs are believed to be responsible for over 100,000 patient deaths annually, making them the fourth leading cause of death in the country.(31) In comparison, official European Commission (EC) statistics report that an estimated 197,000 deaths occur annually throughout the European Union (EU) due to ADRs.(32, 33) ADRs are also recognised as being responsible for causing a significant number of hospital admissions with data meta-analyses and systematic review data suggesting that the admission rate due to ADRs is 5%.(34-36) ADRs have been deemed responsible for the deaths of between 3% and 18% of all hospital inpatients.(37-40) They prolong hospital stays by approximately three days and place added financial burden on the country's healthcare system.(41, 42) Economically, the healthcare costs associated with ADRs have been estimated to be USD 445 per patient on average which corresponds to USD 21 million per 100,000 adult inhabitants per year.(43, 44) It has been estimated that UK patients with an ADR stay in hospital for approximately eight days, which if extrapolated across the National Health Service (NHS) in England, equates to the occupation of seven 800-bed hospitals at any one time and a total cost of GBP 466 million (USD 622 million).(45) Apart from the direct financial cost, there are also several indirect costs incurred by ADRs, including missed work days and/or morbidity such as anxiety due to the ADR episode.(46)

1.2.1.4. Pharmacovigilance methods

PV involves the use of several methods(27), which can be divided into two main categories, namely passive and active surveillance.(47) Both have their merits and flaws.(48) The primary role of both methods of surveillance is signal generation.(27, 49) Table 1.1. provides a synopsis of some of the research and surveillance methods available for PV, noting the strengths as well as the weaknesses and challenges:

A. Passive surveillance, which is considered to be the most common form of PV, employs no active measures, other than the encouragement of reporters (i.e., HCPs and patients) to report ADRs and other drug-related problems. It is commonly referred to as "spontaneous" or "voluntary" reporting as it is mainly dependent on reporters' initiative and motivation.
<table>
<thead>
<tr>
<th>Method</th>
<th>Pharmacovigilance objective(s)</th>
<th>Strengths</th>
<th>Weaknesses and challenges</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case report</td>
<td>To generate hypotheses of potential ADRs by reporting an event in an individual after exposure to a drug</td>
<td>Low cost and logistically simple Possible to document detailed challenge-rechallenge information</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>No control group Usually inadequate to definitively attribute causation to suspected medicine</td>
<td></td>
</tr>
<tr>
<td>Case series</td>
<td>To generate hypotheses of potential ADRs by reporting an event in a group of patients after exposure to a drug</td>
<td>Low cost and logistically simple Possibility to document detailed challenge-rechallenge information Can describe in some detail a population who received a particular drug</td>
<td>No control group Usually inadequate to definitively attribute causation to suspected medicine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Challenge to select controls (potential for selection bias) Requires initial detection of adverse events/ADRs through other methods Can suffer from confounding Potential for recall bias Cannot determine incidence</td>
<td></td>
</tr>
<tr>
<td>Case-control study</td>
<td>To assess the association between a drug and a particular adverse event by comparing cases with controls</td>
<td>Useful for rare adverse events (small sample sizes are possible) Can assess many exposures Low cost</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Challenge to select controls (potential for selection bias) Requires initial detection of adverse events/ADRs through other methods Can suffer from confounding Potential for recall bias Cannot determine incidence</td>
<td></td>
</tr>
<tr>
<td>Cohort study</td>
<td>To prospectively or retrospectively assess the association between a drug and adverse outcomes by following a group of exposed individuals with or without a control group</td>
<td>Less potential for selection and recall biases if controlled Can assess many outcomes Can determine incidence data</td>
<td></td>
</tr>
<tr>
<td>(single arm or</td>
<td></td>
<td>Needs large sample size if rare adverse events are to be studied Can suffer from information bias Can suffer from confounding (e.g., by indication) Possible high loss to follow-up Can be expensive and logistically</td>
<td></td>
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<tr>
<td>comparative)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Method</td>
<td>Pharmacovigilance objective(s)</td>
<td>Strengths</td>
<td>Weaknesses and challenges</td>
</tr>
<tr>
<td>-----------------------------</td>
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<tr>
<td>Databases:</td>
<td></td>
<td></td>
<td>Difficult (labour intensive)</td>
</tr>
<tr>
<td>- Automated Pooled database (prospective or retrospective, i.e., latter by meta-analyses)</td>
<td>To test (or strengthen) the hypotheses of suspected ADRs post-licence To test (or strengthen) the hypotheses of suspected ADRs pre- or post-licence</td>
<td>Potential for large sample size, therefore good for rare outcomes Can provide denominator data Potential for a large, heterogeneous sample, therefore good for rare outcomes</td>
<td>Unlikely to be suitable in a resource-limited setting owing to population flux, regulatory limitations and a lack of infrastructure Relies on standard (valid) methods across data sources Requires agreement among stakeholders with regard to data ownership and publication Can be expensive and logistically difficult (labour intensive) Data can be too heterogeneous to combine</td>
</tr>
<tr>
<td>Ecological study</td>
<td>To identify/strengthen hypotheses of ADRs by observing trends of populations' exposures to drugs and adverse outcomes</td>
<td>Can use existing data sources (e.g., national statistics) so can be relatively low cost and quick</td>
<td>Data are at the population rather than the individual level Likely to suffer from confounding Relies on accuracy of the source data including exposure data</td>
</tr>
<tr>
<td>Large simple trial</td>
<td>A simplified format of an RCT (see below)</td>
<td>Random allocation of controls for confounding and selection bias Simplified eligibility criteria and follow-up provide more realistic results than a RCT Large sample size gives more opportunity to detect rare events</td>
<td>Can still be expensive and logistically difficult Possible high loss to follow-up Can be ethically challenging</td>
</tr>
<tr>
<td>Method</td>
<td>Pharmacovigilance objective(s)</td>
<td>Strengths</td>
<td>Weaknesses and challenges</td>
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</tbody>
</table>
| Prescription/cohort event monitoring | To detect signals of possible ADRs by collecting all adverse events in a group of individuals prescribed a drug  
To quantify the incidence of adverse events in a population exposed to a drug | Can detect rare signals and other unexpected ADRs  
Prospective data collection  
Can identify risk factors  
Can be "real-world" | Expensive and logistically difficult (labour intensive)  
Requires a large sample size  
Possible high loss to follow-up  
Under-detection may occur in settings with limited diagnostic capacity  
Challenge in attributing cause in the absence of a control group |
| Ecological study            | To identify/strengthen hypotheses of ADRs by observing trends of populations' exposures to drugs and adverse outcomes | Can use existing data sources (e.g., national statistics) so can be relatively low cost and quick | Data are at the population rather than the individual level  
Likely to suffer from confounding  
Relies on accuracy of the source data including exposure data |
| Randomised Control Trial (RCT) | To assess the safety and tolerability of a randomly assigned drug compared with another drug in a particular population | Controls for confounding  
Good for managing bias  
Can assess the frequency of adverse events in active and control groups  
Can identify dose-related ADRs  
Safety assessments should be included in RCTs primarily focused on assessing efficacy | Inadequately powered to identify rare ADRs  
May not detect latent ADRs Not "real-world"  
Expensive and logistically difficult (labour intensive)  
Cannot detect ADRs/drug-related problems allied with irrational use/medication errors  
Can be ethically challenging |
<p>| Registries (e.g., pregnancy registry) | To determine the incidence of an outcome (e.g., birth defects) in a population | Usually prospective: minimizes potential for recall bias | Expensive and logistically difficult (labour intensive) |</p>
<table>
<thead>
<tr>
<th>Method</th>
<th>Pharmacovigilance objective(s)</th>
<th>Strengths</th>
<th>Weaknesses and challenges</th>
</tr>
</thead>
</table>
| Cross-sectional surveys                    | population (e.g., pregnant women) who are intentionally or inadvertently exposed to a drug      | Potential to conduct case control analysis  
Can assess many exposures and outcomes if they are not restricted to a particular disease or drug  
Possibility to include a control group | Potential for high loss to follow-up  
Problems with the accurate recall of medical and drug history can lead to misclassifications  
Potential for missed outcomes in settings with limited diagnostic capacity or inadequate assessment |
| Retail outlet surveys/inspections with laboratory testing | To assess current drug use practices  
To estimate the point prevalence of ADRs in specific institutions | Short duration  
Less expensive and time-consuming than longitudinal studies | Not necessarily reflective of trends  
Not possible to distinguish whether the exposure preceded or followed the event, and thus, cause and effect relationships are not certain |
| Sentinel event surveillance (e.g. mortality audits, hospital record reviews) | To conduct root-cause analysis, which identifies system failures contributing to, and drug-related causes of, morbidity and mortality | Uses existing data sources (e.g., national statistics)  
Educational value to the healthcare providers participating | Challenging in settings with poor record linkage and record keeping  
Can be costly and time-consuming |
B. Active surveillance involves the employment of active (or proactive) measures, which include specific studies and targeted follow-up actions (such as patient feedback collection). Cohort event monitoring (CEM) represents the most comprehensive method. Other methods employed include the use of registers, record linkage and screening of laboratory results in medical laboratories.

1.2.1.5. International organisations involved in pharmacovigilance

Several organisations are involved in the promotion and development of the technical and scientific aspects of PV. These organisations publish various protocols and recommendations concerning the practice of PV and have undertaken several initiatives to guide both national medicines regulatory authorities (NMRAs) and members of the pharmaceutical industry. Collaboration between these organisations is meant to combine their respective areas of expertise to develop solutions to complex problems in the field of PV. These groups include a) the WHO and its collaborating centre for international drug monitoring in Uppsala, Sweden, b) the Council for International Organizations of Medical Sciences (CIOMS), c) the International Conference on Harmonisation (ICH), and d) the European Medicines Agency (EMA). To better understand how these actors fit in the context of PV, their roles are described below:

The World Health Organisation (WHO) and the Uppsala Monitoring Centre

The WHO is the directing and managing power for health within the United Nations' system. “It is responsible for providing leadership on global health matters, shaping the health research agenda, setting norms and standards, articulating evidence-based policy options, providing technical support to countries and monitoring and assessing health trends”(51) The WHO also plays an important role in PV through its establishment of the WHO Programme for International Drug Monitoring (PIDM).(52) The programme is coordinated by the WHO and the Uppsala Monitoring Centre (UMC, i.e. the WHO Collaborating Centre for International Drug Monitoring), which holds the international database of adverse drug events (VigiBase).(52) The UMC also acts as a clearing house for information on drug safety at the service of drug regulatory agencies, the pharmaceutical industry, researchers, and other groups in
need of drug safety information. (53) The goals of the UMC practically translate into activities in the following areas (54):

1) collection of ADR reports on a worldwide scale and maintenance and use of the international database
2) dissemination of information
3) education and advice
4) research and development
5) international harmonisation

The Council for International Organisation of Medical Sciences (CIOMS)
CIOMS was established in 1949 by the WHO and United Nations Educational, Scientific and Cultural Organization (UNESCO) as a non-governmental and non-profit organisation. (55) Its members are mainly representatives from the pharmaceutical industry and NMRAs. Among the key aims of CIOMS is the contribution to "harmonised views of international systems and terminologies used for the safety surveillance of medicinal products and vaccines between stakeholders." (55) Furthermore, their guidance documents have served as a basis for guidelines developed by other international organisations such as the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH).

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)
The ICH represents a unique arrangement that brings together the NMRAs (including those from the EU, the US and Japan) and PI to discuss scientific and technical aspects of drug registration. Since its establishment in 1990, the ICH has strived to "achieve greater harmonisation worldwide to ensure that safe, effective and high-quality medicines are developed and registered and maintained in the most resource-efficient manner whilst meeting high standards." (56) The ICH has published several guidelines focusing on the technical requirements relating to the quality, safety and efficacy of medicinal products, of which the most relevant to PV are the efficacy guidelines E2A–E2F. (57)
The European Medicines Agency (EMA)

The EMA was established in 1995 and is considered a key actor concerning various aspects of the regulation of pharmaceuticals. It plays an important role in maintaining the EU's PV infrastructure by coordinating PV activities conducted by its member states' national competent authorities (NCAs).(58) The EMA is also responsible for developing and updating the Guideline on Good Pharmacovigilance Practices (GVP) in the EU as well as maintaining the internet-based information system EudraVigilance which serves as an electronic database of all reported suspected ADRs within the EU.(58)

1.2.1.6. Pharmacovigilance systems

Generally, a PV system (Figure 1.1) can be described as a system used by an organisation to fulfil its legal tasks and responsibilities in relation to PV and designed to monitor the safety of authorised medicinal products and detect any change to their risk-benefit balance.(59) PV systems are considered an integral part of a country's healthcare policy portfolio. An effective PV system is built upon the shared responsibility of and cooperation between various actors, including regulators, pharmaceutical companies marketing a drug, HCPs, and patients.(60) The functioning of the system is based on effective and timely communication between the different stakeholders, which in turn, allows for its utilisation in making decisions regarding medicines' safety.

![Diagrammatic representation of the pharmacovigilance system. Adapted from Isah et al.](image)

**Figure 1.1.** Diagrammatic representation of the pharmacovigilance system. Adapted from Isah et al.(61)
National governments usually establish a PV system within a network composed of a national centre as well as regional and institutional PV centres. Countries’ national PV systems are, in turn, connected to larger international PV systems such as the WHO’s PIDM. The role the two systems play is further detailed in what follows:

**National pharmacovigilance systems**

The function of the national PV system is the collection and analysis of reports using systems (electronic or manual) that incorporate quality assurance and control measures, in addition to informing stakeholders of the potential risk when signals of new ADRs arise. PV systems are characterised by their structures, resources, processes, tools, outputs, and outcomes. From an operational point of view, the PV system begins with the pooling of safety information from a variety of sources, including clinical trials, spontaneous reports, and literature searches, each with the potential for creating an individual case. These individual cases are monitored regularly for any signals that may arise.

Each case is processed and assessed by staff members within the NPVC and pharmaceutical companies with regards to its relationship (causality) to the product in question and becomes part of the product’s total safety dataset. Furthermore, a systematic analysis of safety issues, as well as an assessment of risk versus benefit, is carried out for aggregate data. Based on the outcome of the investigation carried out, the NMRA decides on the necessary action(s) to be taken which could include any of the following: a) continued passive surveillance, b) active collection of further data, c) addition of a warning to the product information, d) change product information to minimise risk (e.g. restriction in indications), e) suspension of drug licence, f) suspension of marketing and use, f) revocation of licence, g) change in legal status, h) change in legal status or i) application of a specific risk minimisation programme.

Lastly, the PV system communicates information relating to benefit, harm, effectiveness, and risk to practitioners, patients, and the public. In other words, the role of the system is to efficiently collect and analyse the submitted reports and subsequently take the necessary action in dealing with those drugs resulting in ADRs which have been shown to cause serious medical concerns.
The WHO Programme for International Drug Monitoring (PIDM)

The WHO's PIDM can essentially be considered as a PV system covering the entire globe.(66) The PIDM is coordinated by the WHO and the UMC in Uppsala, Sweden, which holds the international database of adverse drug events (VigiBase).(52) The main actors that make up the PIDM include a) the main WHO headquarters, which oversee policy development, b) the UMC, which oversees issues concerning the operational and scientific aspects, and c) member states' national PV centres, which provide data concerning ADRs occurring at the national level to VigiBase.(13) PIDM membership is contingent on a country's NPVC providing evidence of its capacity for PV. At its inception in 1968, the programme comprised of ten member countries (Australia, Canada, Czechoslovakia, Federal Republic of Germany, Ireland, Netherlands, New Zealand, Sweden, the UK, and the US) agreeing to share their reports on adverse reactions to medicines.(67) The programme has since expanded to 149 full members contributing ADR case information and 24 associate members (who do not contribute data to VigiBase) as more countries worldwide have developed national systems for the collection of ADRs reports.(53, 54, 68)

1.2.1.7. Good pharmacovigilance practice (GVP)

After a drug has received regulatory approval, its status changes from experimental to legally established treatment. Similarly, those who use the drug are no longer considered experimental patients who are monitored and protected by the rules of the clinical trial and the provisions of Good Clinical Practice (GCP). However, from a medical standpoint, the product which now holds [a marketing] authorisation is still considered as an experimental treatment for many years as it slowly becomes more established and loses its experimental status.(69, 70) Countries differ in terms of the obligations placed on both MAHs and HCPs to report ADRs. Moreover, differences exist with respect to the public availability of anonymised ADR reporting data.(69, 70)

The above factors taken together with the previously mentioned limitations of pre-registration clinical trials point to effective PV requiring a set of rules, operating procedures, and practices that must be followed to ensure the quality and integrity of the data produced in specific types of research or studies.(71, 72) Therefore, similar to how Good Practice guidance exists for other areas such as
manufacturing, laboratory, and clinical, such guidance exists for PV in the form of good PV practices (GVP). GVP aims to ensure appropriate procedures for the collection, processing, assessment, and distribution of data, in addition to protecting the interests of both public health and individual patients. (70) The objective of GVP is the provision of practical guidance to professionals working in PV in the form of a reference document or medical textbook. (73)

In recent years, various national and regional organisations have announced initiatives concerning the formulation of rules for GVP. Possibly the most prominent example is that of the EMA. In 2008, proposals were published by the EC to amend EU PV legislation. (58) In 2012, the EU’s PV requirements were amended through the implementation of new legislation which both strengthened and consolidated the PV system. (74-76) These amendments came on the heels of a review carried out by the EC of the PV system in the region. Several factors drove the change in legislation, including a desire to strengthen protection of the public through improving existing guidance and practices. Furthermore, the changes aimed to enhance rationalisation and harmonisation of actions taken by the different European member states in response to safety issues, as well as remove effort duplication in relation to reporting, review and assessment activities. (75, 76)

A key outcome of the EC’s amendment of the European PV legislation, which came into effect in 2012, was the development of a guideline on GVP for EU member states. (77) The guideline supports the implementation of the new PV legislation and applies to MAHs, the EMA, and EU member states’ NMRAs. (78) The guideline (which is considered to be among the most robust and widely adopted worldwide) is divided into chapters that fall into two categories: a) modules covering major pharmacovigilance processes, and b) product- or population-specific considerations. GVP modules I to XVI cover major PV mechanisms and procedures (Table 1.2). Annexes provide additional required information: definitions, templates, other guidelines (including policy on access to EudraVigilance as well as ICH topics and guidance. The chapters on product- or population-specific considerations are available for vaccines, biological medicinal products and the paediatric population. (77, 78)
Table 1.2. EMA's good pharmacovigilance practice (GVP) modules. Adapted from Borg et al.(77) and Dollen(79)

<table>
<thead>
<tr>
<th>GVP module title</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Module I – Pharmacovigilance systems and their quality systems</td>
<td>Provides guidance to MAHs, National Competent Authorities (NCAs) and EMA in order for them to establish and maintain pharmacovigilance systems that have been through quality assurance processes.</td>
</tr>
<tr>
<td>Module II – Pharmacovigilance system master file (PSMF)</td>
<td>Contains guidance related to the requirements for the pharmacovigilance system master file, as well as procedures for its maintenance, adaptation of the content and inclusion of subsequent submissions to NCAs.</td>
</tr>
<tr>
<td>Module III – Pharmacovigilance inspections</td>
<td>Provides detailed guidance on the procedures how to plan, conduct, report and perform follow up of pharmacovigilance inspections in the EU. It also provides an outline of the roles of the different parties involved. While general guidance is included in section III.B, section III.C contains the overall operation procedures and processes of pharmacovigilance inspections in the EU.</td>
</tr>
<tr>
<td>Module IV – Pharmacovigilance audits</td>
<td>Contains guidance on how to plan and conduct legally required audits (that can be called ‘internal inspections’). The aim of this module is the facilitation of the performance of pharmacovigilance audits and promotion of a harmonised approach, and encouragement of consistency and simplification of the audit processes. Internationally accepted auditing standards from international auditing standardisation organisations have been used as the basis for the principles of this module.</td>
</tr>
<tr>
<td>Module V – Risk management systems</td>
<td>Provides guidance on risk management systems for medicinal products for human use. However, when considering how to evaluate the benefit/risk balance, risks have to be clarified and understood in the context of benefit and they should be evaluated against it.</td>
</tr>
<tr>
<td>Module VI – Management and reporting of adverse reactions to medicinal products</td>
<td>Contains the legal requirements detailed in Title IX of Directive 2001/83/EC [DIR] and chapter 3 of Regulation (EC) No 726/2004 [REG], which are applicable to NCAs, MAHs and the EMA in relation to the collection, data management and reporting of suspected adverse reactions (serious and non-serious), which are associated with medicinal products for human use authorised in the EU. Reporting of emerging safety issues or of</td>
</tr>
<tr>
<td>GVP module title</td>
<td>Description</td>
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<tr>
<td>Module VII – Periodic safety update report (PSUR)</td>
<td>Contains guidance relevant to the preparation, submission, and assessment of PSURs. PSURs are pharmacovigilance documents intended to provide an evaluation of the benefit–risk balance of a medicinal product submitted by marketing authorization holders covering predefined time periods of the product’s lifecycle during the post-authorisation phase.</td>
</tr>
<tr>
<td>Module VIII – Post-authorisation safety studies (PASS)</td>
<td>Provides guidance for the PASS, which are clinical trials or non-interventional studies. Module VIII does not deal with nonclinical safety studies.</td>
</tr>
<tr>
<td>Module IX – Signal management</td>
<td>Introduces a structured lifecycle for the signal management process, providing detailed guidance for each step.</td>
</tr>
<tr>
<td>Module X – Additional monitoring</td>
<td>Introduces the concept of additional monitoring to collect information as early as possible during the post-authorisation clinical use of a project and to increase awareness about the safe and effective use of certain medicinal products.</td>
</tr>
<tr>
<td>Module XV – Safety communication</td>
<td>Contains guidance to marketing authorisation holders, competent authorities in member states and the EMA on how to communicate and coordinate safety information in the EU.</td>
</tr>
<tr>
<td>Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators</td>
<td>Provides considerations for the selection of risk minimisation activities and how to measure their effectiveness.</td>
</tr>
</tbody>
</table>

**Note:** Module numbers XI, XII, XIII and XIV are void, as their planned topics have been addressed by other guidance documents.(78)
In a similar step to the EU, the 37th regular meeting of Arab Ministers of Health in March 2012 saw the issue of a common decree (number seven) which established “The Higher Technical Committee for Medicines” under the umbrella of the Arab League. The committee comprised of representatives from most Arab countries, and through it came the creation of the guideline on GVP for Arab countries which was published in March 2014 with an effective implementation date of July 1st 2015. The guideline is mainly adapted from the European GVP guideline but modified to take into account social, cultural, and economic specificities of the region. In addition to its aim of harmonising PV practices and regulations, the guideline is seen as a model of best practice. However, it is important to note that the national competent authorities are afforded the discretion to adopt additional or different measures for their respective countries. The guideline aims to impact the practice of PV in each country, thereby increasing activities such as ADR reporting and signal detection. Furthermore, it aims to help in the development of “Regulatory Pharmacovigilance” in some Arab countries.

1.2.1.8. Pharmacovigilance in the Arab World

The Arab World (Figure 1.2) is made up of 22 countries covering a total area of approximately 13.6 million km² beginning in North Africa and ending in West Asia. The population of the Arab World equates to approximately 436 million people, who share a common language (Arabic) and religion (Islam). The 22 countries (Algeria, Bahrain, Comoros, Djibouti, Egypt, Iraq, Jordan, Kuwait, Lebanon, Libya, Mauritania, Morocco, Oman, Palestine, Qatar, Saudi Arabia, Somalia, Sudan, Syria, Tunisia, the United Arab Emirates (UAE), and Yemen) are all members of the Arab League.

PV is relatively new to the Arab region and many of the systems in place are still in their infancy as the majority (86%) of countries in the Arab World established their PV systems after the year 2000. Arab countries’ PV systems vary widely in terms of their level of development as well as in their implementation and practice of PV activities. An examination of the systems in place in the Arab World, published in 2014, reveals that Egypt, Jordan and Saudi Arabia have strong regulations in PV based in their drug regulatory authorities. In addition, Morocco receives support from WHO, wherein the WHO Collaborating Centre for Strengthening PV Practices was established to assist the WHO through capacity-
building in Eastern Mediterranean, Francophone, and Arab countries. In contrast, countries such as Kuwait, Djibouti, Lebanon, Palestine, and Qatar have either weak or non-existent PV systems. (82, 86, 88, 91)

Compared to the general level of structural and organisational development of countries within the Arab World along with their level of investment in healthcare and pharmaceutical expenditures, most of these countries' PV systems are currently underdeveloped. A 2015 study found that only six (Jordan, Egypt, Morocco, Saudi Arabia, Sudan, Tunisia) out of the 24 Arab and Eastern Mediterranean countries studied met the requirements for a minimally functional PV system. (89)

To ensure that global data are as up to date as possible in the WHO-UMC database (VigiBase), member countries are required to send individual case safety reports (ICSRs) to the WHO-UMC at least every quarter. Because only member countries transmit ICSRs, a full picture of drug safety in all Arab countries is not easily obtained. The combined representation of the Arab countries in the WHO drug monitoring system VigiBase amounts to only 0.6% of the total number of submitted cases. This figure is very low considering that the total population of the Arab World amounts to approximately 5.6% of the world's population according to the World Bank. (84, 93)

Figure 1.2. Map of the countries of the Arab World. (94)
Over the past two decades, there has been an increase in Arab countries’ interest in PV and recognition of its importance as part of the healthcare system. Recognising the importance of PV as a part of public health, the Arab League developed the “Guideline on Good Pharmacovigilance Practices (GVP) for Arab Countries” in 2014 (which are based on the EU GVP guideline) to harmonise practices in the region (12, 80, 90). However, effective implementation of these guidelines requires improvement in the existing PV systems in these countries. Implementation of the guideline among Arab countries thus far has differed across the Arab World with some countries such as Egypt and Jordan implementing all aspects of the guideline, others such as Algeria and Saudi Arabia have developed and implemented their own guidelines, and some countries such as Bahrain and Djibouti lacking PV systems altogether.(87)

1.2.1.9. Pharmacovigilance in Kuwait

The State of Kuwait (Figure 1.3) is a small country within the Arab World with a total area of 17,818 km² and a population of approximately 4.7 million people.(95) Geographically, it is nestled at the top of the Persian Gulf where it is strategically flanked by large and powerful neighbours Saudi Arabia, Iraq, and Iran. Its location and large oil reserves make it one of the richest countries in the world.

Figure 1.3. Map of Kuwait.(96)
Research evidence investigating PV in Kuwait is limited, and Kuwait's PV system is, like PV systems in most other Arab countries, underdeveloped. (86-88, 91) Despite Kuwait's NMRA taking positive steps in recent years to develop PV in the country such as establishing ADR reporting requirements for MAHs and providing an online reporting form for HCPs and patients, it does not have a formal PV system in place. (86) Furthermore, despite the availability of the online reporting form, very few reports have been received by the NPVC. Evidence on PV in Kuwait focusing on the knowledge, attitudes, and practices of HCPs regarding PV and ADR reporting has shown that they lack awareness. (97-99)

At present, most of the world's drug safety data originate from the developed world. (8, 9) However, differences in local factors including drugs' effects on patients, prescribing patterns, regulation methods, quality, and availability mean that data used in assessing ADRs may have limited validity or relevance for patients living outside these countries. (10, 88) Hence, countries outside the developed world must implement policies aimed at building and/or strengthening existing national PV systems. (100) To ensure patient safety and enhance efforts aimed at supporting the development and strengthening of PV systems in Kuwait and other Arab countries, it is imperative to gain a deep understanding of the existing conditions within the individual countries.

Moreover, from what has been previously presented, it becomes apparent that PV plays an important role as a part of national governments' public health policy developed as a means of ensuring that the medicines available and used by patients are safe and effective. Therefore, to achieve the research aim, it is also necessary to understand the process of policy implementation.

1.2.2. Policy implementation

After the development of a policy, the attention is then turned towards the implementation process, with the literal meaning of implementation being carrying out, accomplishing, fulfilling, producing or completing a given task. (101) van Meter and van Horn define policy implementation as:
"Those actions by public and private individuals (or groups) that are directed at the achievement of objectives set forth in prior policy decisions. This includes both one-time efforts to transform decisions into operational terms, as well as continuing efforts to achieve the large and small changes mandated by policy decisions." (102, p 447)

The importance of understanding policy implementation arises from the fact that it is an essential aspect of the policy process. Learning from the obstacles encountered during the implementation process promotes learning about how to better structure policies to ensure that they result in the effects desired by those who designed them. Moreover, studies on implementation can provide advice to policy makers on how to best structure programmes to increase the probability of successful implementation. (103) The understanding of the actors, the mechanisms, and the reasons for policy being put into effect can be grouped under the term policy implementation research. Policy implementation research is defined as “how governments put policies into effect.” (104, p 2) The literature identifies three main eras (generations) of policy implementation research referred to as first, second and third-generation. (104, 105) In what follows the main features in addition to the strengths and weaknesses of the three generations of policy implementation research are described through summarising the views of authors who have previously reviewed the literature relating to the subject.

1.2.2.1. First-generation policy implementation research
Mounting concerns over the effectiveness of wide-ranging reform programmes gave rise to the first-generation of implementation studies in the United States, which dominated much of the 1970s. (103) The focus of these studies was on how a single authoritative decision was carried out at either a single or multiple locations. (106) Pülzl and Treib (107) cite studies carried out by Derthick (108), Pressman and Wildavsky (109), and Bardach (110) as the most popular of this era. Overall, studies of this period can be described as pioneering and contributed to raising awareness of the issue among the scientific community as well as the general public. (106, 107) Furthermore, this generation drew attention to the outcome of policy. (111) The focus of this generation of research was to understand the reasons behind the failure of particular policies in reaching their goals. (103, 111)
Studies of this generation of research can be characterised as being explorative focusing mainly on placing policy implementation as part of a policy cycle divided into several stages e.g. agenda setting, policy formulation, implementation and evaluation. (104, 105) A top-down approach was used to describe implementation failure through the identification of factors to explain what central policy makers see as an implementation gap, for example, flawed or unclear policy, resource insufficiency, implementers’ poor compliance, policy community opposition, and unfavourable socioeconomic conditions. (104, 111)

Some of the criticisms directed at the research carried out in this era include characterising it as pessimistic due to its focus on case studies which served as examples of implementation failure. (106) Furthermore, due to its focus on individual case studies, it failed to create more generalizable and predictive theories which could be applied to and tested with other cases. (101, 103, 111) Additionally, “in its attempt to identify the implementation process, the research of this era assumed that policy formation and implementation was a rational, linear process.” (111, p 249)

Lastly, in a reflection of the predominant concept of politics/administration separation of the time was the recognition that policy implementation and formation were different and separate from each other. (111)

1.2.2.2. Second-generation policy implementation research

The focus of second-generation implementation studies was on explaining the relationships between policy and practice. (101) In contrast to first-generation studies, scholars of the second-generation proposed several theoretical frameworks and hypotheses. (107) In addition, rather than focusing on a single or a few cases, it pursued the creation of theories of policy that could be generalised to numerous cases. (103) A defining characteristic of this generation of research was the debate between scholars belonging to two schools of thought known as the top-down and bottom-up approaches to implementation research. (105)

Top-down approach

According to several authors (101, 103, 107, 112), some of the most prominent researchers of this school of thought are van Meter and van Horn (102), as well as Mazmanian and Sabatier (113). Birkland defines this approach as “a way of studying policy design and implementation that considers the goals of the highest-level policy designers, and traces the design and implementation of the policy through the
lowest-level implementers.” (103, p 334) The top-down approach views implementation from a control perspective in that it tries to prescribe advice on the method(s) of structuring implementation from the top in order for legislation to achieve its desired goal while reducing the number of decision points that could be vetoed. (105) In other words, the main emphasis is on decision makers’ ability to construct explicit policy objectives and on controlling the implementation stage. (107) A prime example of this approach as cited by Pülzl and Treib (107) as well as Cerna (112) is the work of Sabatier and Mazmanian (114), which lists six criteria for effective implementation: 1) clear and consistent policy objectives, 2) causal theory forms the basis of the program, 3) adequate structure of implementation process, 4) commitment to the program’s goals by implementation officials, 5) support of interest groups as well as legislative and executive sovereigns, and 6) no detrimental changes in the socioeconomic framework conditions.

The top-down perspective is based on the assumption that implementation begins with a decision made at the top, e.g. central government. (103, 107, 111) A single authoritative decision or statement of policy often characterises this approach (103) and the policy implementation process follows this in a linear fashion. (111) Furthermore, it is assumed that there is a “direct causal link between policies and observed outcomes.” (107, p 91) Other assumptions of this approach are highlighted by Birkland (103) as follows:

1. The policy’s goal is clearly defined and can be used to measure its performance.
2. The policy tools contained within a policy for the accomplishment of its goals are clearly defined.
3. Implementers’ capacity and commitment to a policy are well understood by policy designers. Capacity includes resource (human and financial) availability, legal authority and autonomy, as well as the required knowledge for effective policy implementation. Commitment, on the other hand, refers to the level of desire to accomplish the goals of policy designers at the top by implementers; high commitment levels indicate shared goals and values between policy designers and lower-level implementers.
In this approach, these features’ presence is assumed by implementers or that it is possible to overcome any problems put forward by these assumptions. (103) Hence, “the top-town perspective emphasises formal steering of problems and factors, which are easy to manipulate and lead to centralisation and control.” (101, p 40)

On the one hand, the main strength of this approach is its attempt to develop policy advice that can be generalised as well as create behavioural patterns across different policy areas which are consistent. (115) On the other hand, one of the criticisms of this approach is its failure to consider the importance of actions taken in the policy-making process prior to implementation due to its focus on statutory language as its starting point. (101, 112) Moreover, the approach has been accused of considering the implementation as a purely administrative process and ignoring or eliminating political aspects. (101, 111, 112) Another point of criticism is the emphasis on policy decision framers as key actors, therefore ignoring the impact of local actors. (101, 103, 112) Further criticism comes from the top-down model’s rational approach, which is unachievable in practice due to the chaotic nature of policy making, behavioural complexity, goal ambiguity and contradiction. (101, 111) Additional criticism of this approach stems from the role Lipsky’s (116) “street-level bureaucrats” (local actors) play in policy implementation. Top-down theorists view them as obstacles to successful implementation, thus acting as deviants within the system and whose behaviour needs to be controlled. (101, 116) It is argued that the level of street bureaucrats’ discretion is so great that the expectation of policy designers’ ability to control the actions of these agents is unrealistic. (101, 103) Table 1.3 summarises the key features of the top-down and bottom-up policy implementation perspectives.

**Table 1.3.** Comparison of top-down and bottom-up implementation perspectives. (101, p 40)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Top-down perspective</th>
<th>Bottom-up perspective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Policy decision maker</td>
<td>Policy makers</td>
<td>Street-level bureaucrats</td>
</tr>
<tr>
<td>Starting point</td>
<td>Statutory language</td>
<td>Social problems</td>
</tr>
<tr>
<td>Structure</td>
<td>Formal</td>
<td>Both formal and informal</td>
</tr>
<tr>
<td>Process</td>
<td>Purely administrative</td>
<td>Networking, including administrative</td>
</tr>
<tr>
<td>Authority</td>
<td>Centralisation</td>
<td>Decentralisation</td>
</tr>
<tr>
<td>Output/Outcomes</td>
<td>Prescriptive</td>
<td>Descriptive</td>
</tr>
<tr>
<td>Discretion</td>
<td>Top-level bureaucrats</td>
<td>Bottom-level bureaucrats</td>
</tr>
</tbody>
</table>
**Bottom-up approach**

The late 1970s and early 1980s saw the emergence of bottom-up theories as a critical response to the overly structured top-down theories explaining policy implementation. This stemmed from the dissatisfaction with the top-down approach’s inability to explain several unsuccessful outcomes. (103, 107) Birkland defines the bottom-up approach as: “a way of studying policy design and implementation that considers the abilities and motivations of the lowest-level implementers, and tracks policy design from that level to the highest levels of government.” (103, p 337) According to Pülzl and Treib (107), some of the most influential bottom-up researchers are: the American researchers Lipsky (116) and Elmore (117), as well as the Swedish scholar Hjern (118) who also worked in collaboration with other authors such as Porter (119) and Hull (120). Pülzl and Treib (107), as well as Cerna (112), cite the work of Hjern et al. (118-121) as a prime example of the bottom-up approach to policy implementation. This theory’s strategy involves studying a policy problem, identifying the network of actors involved in service delivery in either a single or multiple local areas and enquiring about their goals, strategies, activities, and contacts. The contacts are then used as a means of mapping a network and identifying the relevant implementation structure (planning, financing, and execution) for relevant governmental and non-governmental policies at the local, regional, and national levels. According to Sabatier (122) “this provides a mechanism for moving from street-level bureaucrats (the 'bottom') up to the 'top' policymakers in both the public and private sector.” (122, p 32)

The aim of the bottom-up approach is “to give an accurate empirical description and explanation of the interactions and problem-solving strategies of actors involved in policy delivery.” (107, p 94) The starting point of this perspective is a problem in society. (101) This approach recognises the ambiguity of goals and their potential for conflicting with both other goals in the same policy area, and the norms and motivations of those known as “street-level bureaucrats”. (103) Lipsky (116) uses this term to refer to front-line public service employees, who interact directly with citizens and capable of applying discretion. Scholars of this approach reject the idea of policy definition occurring at the central level and the requirement of implementers’ compliance as neatly as possible with its objectives. (103, 107) Thus, the focus of this approach is on individuals and their
behaviour, and as such street-level bureaucrats are considered as a central component in the political process. (101, 116) Street-level bureaucrats are believed to possess a better understanding of clients’ needs given their direct contact with the public. (101, 107) It is argued that employing organisations provide street-level bureaucrats with significant autonomous power which stems from the considerable amount of discretion at their disposal. (101, 107) The bottom-up approach scholars also argue that policy formulation and implementation cannot be separated and that policy making is a continuous process that occurs throughout the policy cycle. (103, 107) Both Schofield (111) and Paudel (101) point to the work of Berman (123), another prominent bottom-up scholar, which theorises that policy implementation takes place at the macro (central policy) and micro (institutions, the public, the problem itself) levels as an example of this approach. Berman (123) argues that policy implementation occurs as a result of interaction between the two levels. At the macro implementation level, a government programme is devised by centrally located actors, whereas local organisations at the micro level react to macro-level plans by developing and implementing their own programmes. (123)

One of the positive aspects of this approach to policy implementation according to Cerna is “its focus on centrally located actors who devise and implement government programmes, thus contextual factors within the implementing environment are important. Actors and their goals, strategies and activities need to be understood in order to comprehend implementation.” (112, p 18) Another advantage of this approach is its view of implementation as working through a network of actors rather than through an inflexible specified process which neglects the depth of the policy-making environment. (103, 112) One of the criticisms of the bottom-up approach is its overemphasis of street-level bureaucrats’ ability to frustrate the goals of top policy makers. (103, 115) This criticism is two-factored: First, standard democratic theory dictates that actors whose powers are derived from their accountability to sovereign voters through their elected representatives exercise policy control, which makes the bottom-up approach’s rejection of policy makers’ authority questionable. (115) The authority of local service deliverers, however, is not derived from this power base. (115) Second is the overemphasis of the level of local autonomy and discretion. (115, 122) Another criticism is the approach’s failure to take into account target groups’ power differences. Paudel (101) and Birkland (103)
cite the works of Winter (124) as well as Schneider and Ingram (125) respectively as demonstrating that more positively constructed populations have greater power and thus a greater degree of influence on the impact of policies that affect them. This stems from the fact that the choice of tools is made at the top, based on the desired behavioural change and the nature of the population itself.(103)

1.2.2.3. Third-generation policy implementation research (hybrid/synthesising approach)

The top-down and bottom-up approaches draw attention to the implementation process. However, the two approaches conflict with one another by ignoring the portion of implementation reality explained by the other.(101, 107) Several authors (103, 107, 112) point to the work of researchers such as Elmore (126), Sabatier (122), Goggin et al. (106), Ripley and Franklin (127), as well as Winter (124) as attempts at synthesising the strengths of the two approaches into a single approach to address the structuring of policy from the top as well as the likelihood of its alteration or subversion at the point of implementation.

Matland(115) and Sabatier(122) cite the work carried out by Elmore(126) as an early attempt at synthesising the top-down and bottom-up approaches. The synthesis sought to combine Elmore’s previous work on “backward mapping” (117) (a bottom-up approach), with a concept he termed as “forward mapping” (a top-down approach).(115, 122) Backward mapping entails taking into consideration the ultimate target’s incentive structure.(122) This is achieved by “stating precisely the behaviour to be changed at the lowest level, describing a set of operations that can ensure the change and repeating the procedure upwards by steps until the central level is reached”(115, p 151) On the other hand, forward mapping entails taking into consideration the policy instruments and other resources at one’s disposal.(122) This is achieved by “stating the precise policy objectives, elaborating detailed means-ends schemes, and specifying explicit outcome criteria by which to judge policy at each stage.”(115, p 151) The argument here is that the success of a programme is dependent on both elements given their intertwinement.(122)

Sabatier(122) proposed a different theoretical approach to the study of policy implementation known as the Advocacy Coalition Framework (ACF). The framework starts at the bottom and proceeds to look at “a whole variety of public and private actors involved with a policy problem as well as their concerns with
understanding the perspectives and strategies of all major categories of actors (not simply programme proponents).”(122, p 39) The provision of a simplified, abstract model of a complex system and recognising the importance of structural features of policy means that elements of the top-down perspective are also incorporated.(103) The ACF reflects the concept that implementation is contained within a policy subsystem rather than in one-to-one relationships between the different actors in the process, i.e. designers, implementers, and targets.(103)

Goggin et al.(106) attempted to bridge the gap between the top-down and bottom-up approaches by developing a model based on communicative theory perspective of intergovernmental implementation.(101, 103, 107) It is indicated in the theory that states’ implementation is influenced by a combination of incentives and restrictions “from the federal, state and local level; by a state’s decisional outcomes; and by a state’s capacity to act.”(101, p 44) The interaction of these elements of the theory determines how implementation proceeds in specific policy areas.(101) According to Birkland(103) two key propositions sum up this theory:

1. implementation success occurs as a result of credible officials sending clear messages to receptive implementers who either possess or are allocated sufficient resources to implement policies that are supported by affected groups.
2. the delay of policy implementation on the part of states through strategic delay can lead to improved policy implementation through innovation, policy learning, bargaining, and the like.

Matland’s(115) synthesis of the top-down and bottom-up approaches known as the “ambiguity-conflict model”, which rather than try to combine the two approaches simultaneously, explains when the two approaches are most appropriate. The model hypothesises that the levels of ambiguity and conflict of a policy’s goals and means involved determine the value of each approach. Four policy implementation paradigms are identified: administrative, political, symbolic; and experimental. As an example of how this model works, political implementation which involves a top-down approach would likely be more suited to instances when there is a high degree of conflict surrounding the goal allied with a high degree of certainty (low ambiguity) on how it might be implemented such as in the case a specific industry sector’s taxation.(112)
The theories put forward by this generation attempt to overcome the conceptual weaknesses of the top-down and bottom-up approaches to policy implementation. This is achieved through focusing on “empirical arguments about the proper conceptualisation of the implementation process”(107, p 97) and combining both sides’ extreme arguments into models that encompass both central steering and local autonomy. Furthermore, a number of these models highlight important factors that had previously received little attention.(107)

1.3. Conclusion

The purpose of this chapter was to provide essential background information which contextualises and informed this programme of research. The chapter revealed that PV, which is concerned with drug safety, is the science dealing with the detection, assessment, monitoring, and prevention of adverse effects of a wide range of medicinal products.(25, 26) Furthermore, PV is considered to be an important tool for ensuring patient safety considering the limitations of clinical trials performed on drugs in the pre-marketing stage.(3, 28-30) The significant morbidity and mortality(13, 31-36), as well as the associated financial costs(41-45) resulting from the ADRs arising with the use of drugs, gives PV added importance.

PV in the Arab World is a relatively new concept with most of the countries in the region instituting PV systems within the past two decades as the importance of having a strong PV system in place has gained increased attention.(80, 86, 87) However, significant variations exist among Arab countries in terms of their PV systems' level of development and the practices carried out.(86, 88, 91) These differences are influenced by local contextual factors (e.g. healthcare expenditure, disease types and prevalence, and political climate) which can lead to variability in medicine use and the profile of ADRs suffered by patients.(10, 128) Therefore, it is important that every country establish its own PV system. Recognising the importance of PV as a part of public health, the Arab League developed the "Guideline on GVP for Arab Countries" to both improve and harmonise practices in the region.(12, 80, 90) However, effective implementation of these guidelines requires improvement in the existing PV systems in these countries.(81)

Efforts have been made in recent years to improve PV in Kuwait including the development of an electronic reporting form and, more recently (April 2021),
obtaining full membership in the WHO PIDM. However, Kuwait is still considered behind other countries in the region in terms of its PV system’s maturity as it still does not possess a formal PV programme. Furthermore, it is faced with the challenge of under-reporting of ADRs among HCPs due to lack of awareness. These factors put it at a disadvantage in terms of its ability to adequately detect problems and subsequently make decisions regarding the use of drugs that are relevant to the local population. In this context, strengthening Kuwait’s and other Arab countries' PV systems is considered a key issue.

An important function of policymakers involves maintaining oversight over implemented policies to ensure their efficiency and effectiveness. Moreover, the WHO recommends that PV systems incorporate evaluation and assessment mechanisms with specific performance criteria. Despite the growth in PV development and practice among Arab countries, a gap remains in efforts to assess, evaluate, and monitor their systems' and activities' status, growth, and impact. To ensure patient safety and enhance efforts aimed at supporting the development and strengthening of PV systems in Arab countries, it is important to understand existing conditions within the individual countries. Moreover, as Arab countries seek to implement the Arab GVP guideline, and given PV's importance as part of a country's public health policies' portfolio, understanding the mechanism(s) of policy implementation and the factors influencing it can inform best practice in nascent systems in the region. International experience has demonstrated that adopted policies are not always implemented as expected and do not necessarily achieve their intended results. In addition, policymakers frequently focus on outputs or outcomes while ignoring the implementation process which could reveal the barriers to effective implementation. Policy analysts and policymakers have long held an interest in cross-country comparisons of health systems and policies as understanding systems, processes, and developments in one group of countries can help inform policy learning and implementation in another. Furthermore, learning about the implementation process can assist in gaining a better understanding of the factors impacting policies' success or failure. As such, gaining an intimate understanding of the workings of the PV systems domestically and abroad along with the best approach to policy implementation will be
instrumental in successfully advancing the existing PV system in countries with nascent systems.
Chapter Two: Overview of programme of research

2.1. Introduction
Chapter One served to describe existing research and the gaps in current understanding around the importance of PV, the state of PV systems in the Arab World, and the need to better understand performance of existing PV systems, their strengths and weaknesses, and also what contributes to effective implementation of PV policies. This chapter provides the aim and objectives of this programme of research alongside an overview of its components, or in other words, how these aims and objectives were addressed.

2.2. Aim
The programme of research aimed to employ an evidence- and theory-informed approach to better understand the key factors impacting PV performance and policy implementation in developing countries, to inform recommendations for the implementation of good PV practice in countries with nascent PV systems.

2.3. Objectives
1- To identify and synthesise the recent published peer-reviewed evidence pertaining to the evaluation of the characteristics, performance, and/or effectiveness of PV systems in developing countries.
2- To describe implemented PV system performance (structures, processes, and outcomes) in three Arab countries at varying levels of PV performance (including Kuwait), and to explore underpinning reasons for strengths and limitations in these countries.
3- To explore the mechanism and factors acting as impediments or facilitators to the implementation of PV policy in these three Arab countries.
4- Informed by insight gained through addressing the preceding objectives, formulate recommendations for strengthening PV policy implementation and subsequent system performance in Kuwait (and other Arab countries with nascent PV systems).
2.4. Overview of programme of work

The programme of research started with a narrative literature review (Study One – Chapter Four) which aimed to synthesise published peer-reviewed studies concerned with the assessment of developing countries' PV systems' performance based on a set of pre-determined key performance indicators. This served to address the first objective of this programme of research.

To address the second and third objectives of this programme of research, the next step involved carrying out a mixed-methods study employing qualitative and quantitative methods (Study Two – Chapter Five). Qualitative interviews were conducted with key stakeholders in select Arab countries with varying levels of PV maturity/performance (Jordan, Oman, and Kuwait) to explore the structures and practices, as well as the strengths and challenges facing their implemented PV systems. Questionnaires distributed to the PV leadership in the select Arab countries were used to evaluate the performance of the PV systems implemented in two of the three selected Arab countries (Oman and Kuwait) based on an analysis of the figures pertaining to their PV systems' processes and outcomes. The "WHO PV indicators"(7) were used to frame study design, data collection and analysis.

Study Three (Chapter Six) explored the processes of and the perceived factors impacting PV policy implementation in select Arab countries with varying levels of PV maturity/performance (Jordan, Oman, and Kuwait). Qualitative interviews were conducted with key stakeholders in the selected Arab countries to address the programme of research's fourth objective. Matland's(115) ambiguity-conflict model of policy implementation was used to frame study design, data collection and analysis.

Finally, the thesis concludes with a discussion of the key findings of the programme of study by integrating findings from all three studies and highlighting implications for policy and practice (Chapter Seven). In addition, the programme of research's fourth objective (recommendations for strengthening PV system performance and policy implementation) will be addressed. Figure 2.1 provides a visual representation of the overall workflow of the programme of research. Chapter Three will present the research philosophy, theoretical framework, and methodology used in carrying out this programme of research.
Figure 2.1. Flow chart demonstrating the structure of the programme of research.
Chapter Three: Research philosophy, theoretical framework, and methodology

3.1. Introduction
This chapter presents the theoretical concepts and methodological approaches underpinning this programme of research by discussing the methods employed in each of the three studies (Chapters Four, Five, and Six respectively) undertaken including the justifications for choosing them as well as the ethical approvals required to conduct them.

3.2. Research philosophy
The decision as to which methods are used to answer a research question is predominantly informed by an overarching research strategy or a set of decisions about the research design and choices about the appropriate tools and methods for collecting and analysing data. Furthermore, the choice of methods employed to carry out the research is based on different ontological or epistemological approaches. Briefly, ontology's concern lies with the question: 'What is the nature of the social world?'(134) It is often presented in research as a binary distinction between whether the phenomena being studied are composed of our ideas of things (idealism), or of the things in themselves, unmediated by ideas (realism).(135) Alternatively, epistemology relates to the set of rules determining how we can learn about the phenomena being studied, and what counts as valid evidence about these phenomena.(134)

Different ontological and epistemological positions tend to be associated with different paradigms, which provide researchers with a set of unified principles and rules for conducting research. Quantitative research tends towards the realist end of the spectrum of ontology in that it adopts a more objective approach to epistemology, whereas qualitative research falls more towards the idealist end and adopts a more subjective approach.(134, 135) Quantitative research is guided by a positivist paradigm, whereas qualitative research is guided by an interpretivist paradigm.(134, 135) The basic assumption of positivism is that the goal of science
and research is to "develop the most objective methods possible to get the closest approximation of reality." (136, p. 19) Positivist approaches to research are typically predicated on deductive testing of hypotheses or proposed explanations and are associated with the use of quantitative methods. (134) This aligns with quantitative research's emphasis on structure including a consistent operational definition, precisely worded questions, and statistical analysis. (136) Quantitative research aims to determine what works best or which variables best explain a result using methods involving structured data collection and controlled measurements such as surveys, clinical trials, rating scales and structured observation. (136, 137) The majority of qualitative research, on the other hand, is derived from an interpretivist perspective, which views the world as "constructed, interpreted, and experienced by people in their interactions with one another and wider social systems." (136, p. 23) Qualitative methodology seeks to gain insights into a phenomenon experienced by participants by enabling them to speak freely to understand peoples' interpretation of the world by attempting to understand the meaning and significance of the world from the perspective of those who live in it. (136) Qualitative research aims to thoroughly explore day-to-day interactions, how events transpire, and the individual meanings of these events for those involved using methods such as interviews, focus group discussions, participant observations, and documentary analysis. (136, 137) Mixed methods research represents the third research paradigm which aims to bridge the gap between quantitative and qualitative research by combining or associating both qualitative and quantitative forms. (138, 139) This research paradigm adopts the philosophical position of pragmatism (140) which is not committed to any one system or reality and does not see the world as an absolute unity. (139) In the pragmatist position, "knowledge of the world can be obtained by observation, experience and experimentation." (139-144)

3.2.1. Paradigm choice and rationale for the chosen research method

Based on what has been discussed above, it can be inferred that each of the three paradigms differ in terms of the approach employed to address the research's aims and objectives. The choice of research paradigm will dictate the choice of method(s) and hence how it addresses the research aim and context. For the purpose of this research, a mixed-methods approach, benefitting from the depth of detail and
exploration of new concepts and phenomena associated with the use of qualitative methods(145), combined with a more standardised, quantitative, component was considered to be the best option. The combined use of quantitative and qualitative methods can increase the overall strength of a study compared to either method alone.(144) In the case of this research, the use of a mixed-methods approach acknowledges the constructivist nature of individuals’ experiences whilst also attempting to obtain a more objective, standardised view. Hence, the research adopts an almost dual philosophical stance (i.e. pragmatism).(146)

Historically, researchers avoided combining qualitative and quantitative methods due to differences in their philosophical underpinnings which impact how they are designed, conducted and interpreted.(139, 147) However, time has given rise to the argument that the philosophical differences between qualitative and quantitative approaches should not render them incompatible nor determine the choice of methods researchers use.(141, 143) Mixed methods research involves the combined use of quantitative and qualitative approaches in a single study or series of related studies.(142) The pragmatist perspective which forms the basis for mixed methods research views neither approach as being superior to the other with each approach possessing its own set of strengths and weaknesses.(139, 143) Proponents of this perspective have advocated for capitalising on the respective strengths of each approach and overcoming their shortcomings by combining them.(139, 141-144) Quantitative approaches often employ large sample sizes, therefore, yielding more generalisable conclusions. However, quantitative approaches' use of objective facts, statistics and numerical data to test theories results in generalisations that lack context thus failing to explain the phenomenon in question.(143, 148) Contrastingly, reliance on a qualitative approach results in rich descriptive data thus allowing the researcher to carry out an in-depth examination of issues and to discover new concepts.(134) However, the employment of small sample sizes with this approach means that it lacks generalisability.(143, 149) Hence, the adoption of a mixed-methods approach allows the researcher to overcome the limitations that arise when employing a single methodological approach.(146) Moreover, it offers a means of triangulating data from different sources thus uniting quantitative and qualitative findings.(150)
Mixed methods research is made up of different design categories, namely convergent design, explanatory sequential design, and exploratory sequential design. Each of the three categories possesses criteria for selecting one of them based on timing, weight, mixing, and the use of theory. The choice of the most appropriate category of mixed methods approach to employ depends on the aim of the study and the question it seeks to answer. The first category (i.e. convergent) of mixed methods research involves the researcher bringing together the results of the quantitative and the qualitative data analysis so they can be compared or combined. The intent here is to compare the two sets of data with the objective of "obtaining a more complete understanding of a problem, to validate one set of findings with the other, or to determine if participants respond similarly if they check quantitative predetermined scales and if they are asked open-ended qualitative questions." On the other hand, the latter two categories (i.e. explanatory sequential design and exploratory sequential) follow a sequential approach involving two phases. A single method is employed for both data collection and analysis in the first phase; subsequently a different method is employed for these processes in the second phase. In the explanatory sequential design, the first phase employs a quantitative approach which is followed in the second phase by a qualitative one to explain or expand on the results of the first phase. In comparison, the exploratory sequential involves the qualitative approach occurring in the first phase and the quantitative approach being based on the qualitative results. The quantitative results build on the initial qualitative results or provide a clearer understanding of the initial qualitative perspectives of participants.

Given the nature of this programme of research, a convergent mixed-methods design was chosen to broadly explore and understand PV systems' performance and PV policy implementation. A qualitative approach was used to explore the strengths and weaknesses of the PV systems performance and the mechanisms of and factors influencing PV policy implementation in three Arab countries possessing PV systems at different levels of maturity. Qualitative research aims to answer specific humanistic ‘why and how’ questions using rich, insightful data (of experiences, views or perceptions presented as text or images) obtained from a small group of participants in their natural settings. A quantitative approach was also employed to assess the processes and outcomes/impact of the PV systems in select
Arab countries. Quantitative research is concerned with the systematic and statistical measurement of the relationships between variables.(152) This offered a means of triangulating data sources that can unite quantitative and qualitative findings.

3.3. **Theoretical frameworks underpinning the research**

Theories can be applied in different ways and at different stages to guide research and ensure robustness and rigour in the research development process.(153) Given the programme of research's dual focus of PV system performance and policy implementation, two theoretical frameworks were employed to underpin the empirical work, namely the WHO PV indicators(7) and Matland's ambiguity-conflict model of policy implementation(115). In what follows, a description of these two theoretical frameworks and their location in the programme of research they were used will be provided.

**3.3.1. WHO pharmacovigilance indicators**

The WHO PV indicators were originally developed as a means of providing a baseline allowing the “assessment or quantification of the growth and performance of PV, which will enable comparison within and between countries, regions and facilities.”(7, p 1) Furthermore, they are designed to be simple and can be understood by any worker in PV without formal training in monitoring and evaluation.(7)

An alternative framework for assessing PV system performance, namely the Indicator-Based PV Assessment Tool (IPAT) developed by Management Sciences for Health (MSH) under a United States Agency for International Development (USAID) programme, was considered for use in this programme of research, but was dismissed due to its lack of sensitivity and specificity as a measurement tool.(154)

The WHO PV indicators measure, monitor and assess PV systems’ effectiveness which includes estimating their societal impact.(7) According to the WHO, the PV indicators are “measures of inputs, processes, outputs, outcomes, and impacts of development projects, programmes or policies related to health systems and services. They provide information for measuring how well a PV programme is achieving its objectives.”(7, p 4) The main objective of the indicators is the provision of measures enabling the assessment of the status of PV, the activities and their impact, globally at all levels of the healthcare system, to ensure patient safety.(7)
The WHO PV indicators are made up of 63 indicators in total, with an additional nine indicators designated for public health programmes (PHPs). The 63 indicators are classified into "core" (n=27) and "complementary" indicators (n=36). Core indicators are considered as highly relevant, important and useful in characterising PV; complementary indicators are additional measurements considered as relevant and useful, which serve to further characterise the PV situation. The 63 indicators are classified into three main categories as follows(7):

1- Structural indicators (10 core, 11 complementary): Assess the existence of key PV structures, systems and mechanisms.

2- Process indicators (9 core, 13 complementary): Assess the extent of PV activities, i.e. the extent to which the system is operating.

3- Outcome/impact indicators (8 core, 12 complementary): Measure the effects (results and changes) of PV activities, i.e. the extent of realization of PV objectives.

The WHO PV indicators(7) were employed as a framework in this research programme as a means of facilitating data extraction as part of the review of published peer-reviewed research that evaluated the characteristics, performance, and/or effectiveness of PV systems in developing countries (Chapter Four, Study One). In addition, they were used to examine the structures, processes, and outcomes of the PV systems to gain insights into the implementation and factors affecting PV system performance in Kuwait and select Arab countries with more mature systems (Chapter Five, Study Two).

3.3.2. Matland's ambiguity-conflict model of policy implementation

Matland's model(115) was deemed to be the most suitable for this project given its parsimonious synthesis of many of the main findings of the literature on policy implementation. The model has been widely used in policy implementation analysis, the description and analysis of the relationships between policy and practice, implementation success or failure, and has produced valuable insights regarding policy implementation.(101) In addition, it is considered both relevant and attractive due to its simplicity.(155-157) The model serves as a tool to determine or predict how the implementation process will develop, and which factors are most likely to contribute to successful implementation along with the challenges to be expected and the possible solutions to overcoming them. Hence, it not only assists in
analysing the implementation process, but also can inform recommendations for strengthening it.

Other policy implementation models considered for use to inform the programme of research included Sabatier's (122) Advocacy Coalition Framework (ACF), Elmore's (126) forward and backward mapping model. The ACF was excluded due to the difficulty in determining the beliefs of the main actors, mapping the advocacy coalition, and establishing all the internal and external factors which can affect the policy sub-system. (112) In comparison, the forward and backward mapping model was excluded due to its reputation as being useful as a tool for discussion, however, it lacks the explanatory power as a theory. (115)

The ambiguity-conflict model synthesises the traditional top-down and bottom-up approaches of policy implementation. Matland's (115) policy implementation analysis framework hypothesises that two key factors underlie the policy implementation process: the degree of ambiguity in the formulation of a policy means and ends, and the degree of conflict triggered by the policy per se. Furthermore, it is these factors that explain how different implementation approaches emerge in different contexts.

Policy conflict occurs when the actors involved in the implementation process have incompatible views concerning the policy’s goals, the means to reach those goals, and/or conflicting value systems. Policy ambiguity, on the other hand, occurs when policy goals are unclear and/or there is uncertainty in terms of the means to achieve them. The extent of policy conflict is a determinant of the difficulty of successful implementation, whereas the extent of ambiguity in the policy’s goals and/or means affects its perception by policy implementers, thereby increasing the importance of local conditions for successful implementation. The model combines these two dimensions into a four-cell matrix, with each cell representing a different approach to implementation (Figure 3.1). Despite the model’s presentation of ambiguity and conflict as dichotomous, Matland (115) stresses that the theoretical constructs are continuous and that there is no tipping point causing radical shifts from one implementation type to another.

In administrative implementation, both ambiguity and conflict are low. Given that both the policy goals and the means for achieving them are clear, implementation is
similar to that observed in the top-down approach. The most important factor in determining successful implementation, in this case, is the provision of implementation actors with the necessary support in terms of resources. In political implementation there is low ambiguity and high conflict concerning the policy as although the goals are understood, they are the subject of dispute. Policy success in this case is determined by the power of policymakers to impose its implementation on subordinates. Thus, the implementation process here also follows a top-down approach.

![Conflict Matrix](image)

**Figure 3.1.** Ambiguity-Conflict matrix: Policy implementation processes. (115, p. 160)

With experimental implementation, the policy is characterised as having high policy ambiguity and low policy conflict. In such a case, successful implementation is dependent on contextual (circumstantial) factors present in the implementing environment such as the existence of policy solutions and the presence of certain actors at a time and place. Therefore, broad variations in outcomes are likely to be observed from one location to another. Implementation here is better described by the bottom-up approach rather than that of the top-down approach. Finally, in the case of symbolic implementation, both ambiguity and conflict are high. This situation is depicted by Matland(115) as one in which despite the policy receiving substantial coverage at the adoption stage, it ultimately has little effect. Policy success is determined by “the coalition of actors at the local level who control the available resources.” (115, p. 168) Hence, the bottom-up approach is the most appropriate in describing the implementation process in this scenario. Table 3.1 summarises the key features of the model's four implementation approaches.
Matland's model(115) was employed as a framework in this research programme to underpin Study Three's (Chapter Six) exploration of the PV policy implementation process and the facilitators and barriers impacting it in three select Arab countries at different levels of PV system maturity.

Table 3.1. Ambiguity-Conflict matrix: Policy implementation processes. Adapted from Hudson, B.(158 p. 230)

<table>
<thead>
<tr>
<th>Low Conflict</th>
<th>High Conflict</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low Ambiguity</strong></td>
<td><strong>High Ambiguity</strong></td>
</tr>
<tr>
<td>Administrative Implementation</td>
<td>Political Implementation</td>
</tr>
<tr>
<td>• Goals are given and a means for problem-solving is known</td>
<td>• There is conflict over both goals and means</td>
</tr>
<tr>
<td>• A central authority has the information, resources, and sanction capability to enact the desired policy</td>
<td>• The implementation process is a key arena for conflict</td>
</tr>
<tr>
<td>• Implementation is hierarchically ordered with each link receiving orders from the level above</td>
<td>• Implementation outcomes are determined by the distribution of power</td>
</tr>
<tr>
<td>• The policy is spelt out explicitly at each level and there is agreement on responsibilities and tasks</td>
<td>• Compliance is not automatically forthcoming</td>
</tr>
<tr>
<td>• Relatively uniform outcomes at the micro-level across many sites</td>
<td>• Low ambiguity ensures that monitoring of compliance is relatively easy</td>
</tr>
<tr>
<td><strong>Experimental Implementation</strong></td>
<td><strong>Symbolic Implementation</strong></td>
</tr>
<tr>
<td>• Outcomes depend largely on which actors are involved</td>
<td>• Ostensibly implausible combination</td>
</tr>
<tr>
<td>• Variation in outcomes from site to site</td>
<td>• Salient symbols can produce high levels of conflict even when the policy is vague</td>
</tr>
<tr>
<td>• Outcomes are hard to predict</td>
<td>• Outcomes will vary across sites</td>
</tr>
<tr>
<td>• Opportunities for local entrepreneurs to create local policies</td>
<td>• Outcomes will depend upon the balance of local coalition strength</td>
</tr>
<tr>
<td>• Compliance monitoring mechanisms are of limited relevance</td>
<td>• Policy ambiguity makes it difficult to monitor activities</td>
</tr>
<tr>
<td>• The policy may become a low priority</td>
<td></td>
</tr>
</tbody>
</table>

3.4. Methods

Methodological details of the qualitative and quantitative approaches used for each of the studies in this programme of research are provided in the following sections.
3.4.1. Study One

Study One (Chapter Four) consisted of a narrative literature review, which is defined as “a scholarly summary along with interpretation and critique.” (159) A narrative review describes and discusses the state of the science of a specific topic from a theoretical and contextual point of view. (160) The narrative literature review carried out as part of this programme of research aimed to synthesise current peer-reviewed published research that evaluates the characteristics, performance, and/or effectiveness of PV systems in developing countries.

Given that narrative literature reviews do not necessarily state or follow rules about the search for evidence, it was performed systematically for the purpose of this programme of research. The rationale for this stemmed from the fact that systematic reviews along with randomised controlled trials, and meta-analysis are considered the "gold standard" with respect to providing research-based evidence. (161) As such, they serve as a rigorous means of identifying research gaps and informing a research programme's approach. The review's development and reporting involved the following steps: defining the research question; writing a plan for the systematic review and having it reviewed; constructing and implementing a search strategy; screening the references identified, assessing studies against the inclusion/exclusion criteria; extracting data; critically appraising studies included in the review; synthesising findings; considering bias introduced by studies; writing the report; interpreting findings and drawing conclusions for a wider audience. (162) A more detailed description of the literature search strategy from Study One including; the literature search and identification strategy used; the electronic databases and additional means of identifying literature; the inclusion and exclusion criteria; and the appraisal used is presented in Chapter Four.

3.4.2. Studies Two and Three

Study Two (Chapter Five) was a mixed-methods study exploring PV system structures, processes, and outcomes along with strengths and weaknesses within three Arab countries with systems at different levels of maturity using the WHO PV indicators. Qualitative methods including document review and interviews and quantitative methods in the form of a survey were used to address the aims of this study.
Study Three (Chapter Six) was a qualitative study exploring the mechanisms of and factors influencing PV policy implementation in three Arab countries with PV systems at different levels of performance. Qualitative interviews were used to achieve the aims of this study.

3.4.2.1. Methods justification

Multiple methods were considered for the qualitative data collection including observations, document review, focus groups, and qualitative interviews. Participant observation was excluded due to the risk of altering the observed participants’ behaviour as well as the risk of the introduction of bias due to the observer developing relationships with the participants. Focus groups were also discounted as a method because it meant sacrificing the amount of detail obtained from the individuals' experiences. Additionally, there is the possibility one of the participants in the focus group dominating the discussion at the expense of the other participants. Moreover, focus groups pose logistical challenges in terms of organising a time that would suit all the participants and absences tend to occur. Therefore, a mixture of qualitative methods including document review/analysis and qualitative interviews were chosen as methods for the qualitative data collection.

Document analysis is a systematic procedure for reviewing or evaluating both printed and electronic documents (computer-based and Internet-transmitted) material. Use of this method was seen as important in developing an understanding of the PV system and policy implemented in the study countries. It was chosen as a data collection method for Study Two because it provides contextual data, it helps in raising questions that need to be asked, and it helps provide supplementary data.

Interviews are one of the most common methods used in health-related qualitative research. The aim of conducting interviews is “to go below the surface of the topic being discussed, explore what people say in as much detail as possible, and uncover new areas or ideas that were not anticipated at the outset of the research.” The use of interviews in qualitative research allows the researcher to better understand individuals’ perspectives thereby collecting data that is rich. Such data is collected from a relatively small number of cases and serves to develop a greater understanding of the issues being considered. Given the exploratory nature of
the aim of this phase of the study, the use of interviews as a data collection method was deemed to be the most appropriate means of achieving the aims of studies Two and Three (Chapters Four and Five respectively).

Semi-structured interviews were used for studies Two and Three (Chapters Four and Five respectively) due to the flexibility they provide both the interviewer and interviewee allowing either side to deviate to pursue an idea or response in more detail. (166, 168) Interviews for these two studies were conducted as a single set of interviews covering subjects related to both studies. Unstructured interviews were considered but were discounted due to their time-consuming nature, the requirement of a skilled interviewer, and their production of large amounts of text which is difficult to analyse. (166) The researcher also had previous experience conducting semi-structured interviews with members of the NMRA and the pharmaceutical industry as part of the research programme he carried out to obtain his MSc.

A cross-sectional survey was employed in Study Two as a method for quantitative data collection. A cross-sectional survey is described as a research method that “collects data to make inferences about a population of interest at a specific point in time.” (169) Cross-sectional survey research designs are efficient approaches for collecting data and information about the characteristics, behaviours and attitudes from a sample of a defined population. (170) The use of an experimental design in this programme of work was not considered as an option at the onset of the research design process because insights from the narrative literature review suggested a paucity of published literature on the factors impacting PV system performance and policy implementation.

3.5. Ethics

Ethical approval was not required for Study One (Chapter Four) as it only involved secondary data analysis from published literature. Ethical approval for studies Two and Three (Chapters Five and Six respectively) were obtained from the University of Manchester Research Ethics Committee (UREC) (reference number 2018–3990-7300, dated 22/10/2018, Appendix I). UREC approval was granted for subsequent amendments made to the programme of research including widening the participant inclusion criteria (reference number 2019-3990-9911, dated 27/3/2019, Appendix II) and collecting additional empirical data (reference number 2021-3990-20131, dated
20/7/2021, Appendix III) to support the inference made from the interview data that the differences identified between the PV systems in Jordan, Oman, and Kuwait (in relation to the WHO PV indicators and Matland's model) reflect differences in the actual performance of these systems.

The senior management of the NMRAs in the three countries granted permission to conduct the study based on their standard protocol. Copies of the letters sent to, and approvals issued by, the NMRAs in these countries were submitted to UREC as part of the ethics application (Appendices IV to IX).

3.6. Chapter summary
This chapter provided a description of and justification for the methodological approach that was employed in this programme of research. The next three chapters (Chapters Four to Six) provide a more detailed description of the studies carried out and how the key results obtained helped to address the overall aim and objectives.

The programme of research commenced with a review of the literature to provide up to date evidence on the status of developing countries’ PV systems and inform the approach for the empirical work conducted thereafter. The narrative literature review, which was performed systematically, synthesised recently published peer-reviewed evidence concerning the evaluation of developing countries’ PV systems performance (Study One, Chapter Four).

This was followed by a mixed-methods study involving documentary review, interviews, and a survey to explore the structures, processes, and outcomes of three Arab countries with differing levels of PV system performance (namely, Jordan, Oman, and Kuwait) to identify their areas of strength and weakness (Study Two, Chapter Five).

The final study was a qualitative study that employed interviews to explore the mechanisms of and factors influencing PV policy implementation in the three Arab countries of Jordan, Oman, and Kuwait (Study Three, Chapter Six).
Chapter Four: Study One – A narrative literature review of pharmacovigilance systems in developing countries using the WHO pharmacovigilance indicators

4.1. Introduction

Most developed countries started PV activities after the thalidomide disaster in the 1960s by establishing PV systems and joining the WHO PIDM.(8, 171, 172) Developing countries did not join the PIDM until the 1990s or later, but since then the number of developing countries implementing PV and joining WHO PIDM has steadily increased. (8, 171, 172) As mentioned in Chapter One, differences in developing countries' PV systems are influenced by local contextual factors such as healthcare expenditure, disease types and prevalence, and political climate.(173) These differences can lead to variability in medicine use and the profile of adverse effects suffered by patients which makes it essential that every country establish its own PV system.(6)

Over the past few decades, international organisations (e.g. CIOMS and ICH) and NMRAs have published a considerable amount of legislation and guidance to provide countries with a legal foundation and practice guidelines for national PV systems.(174) A prominent example is the EMA's GVP guideline which many developing countries wishing to align their new and evolving national PV frameworks with international standards use as a reference for setting up their national PV systems.(174, 175)

The WHO recommends that PV systems incorporate evaluation and assessment mechanisms with specific performance criteria.(71) Despite the growth in PV development and practice among developing countries, a gap remains in efforts to assess, evaluate, and monitor their systems' and activities' status, growth, and impact.(61) To promote patient safety and enhance efforts aimed at strengthening PV systems in developing countries with nascent PV systems, it is imperative to assess existing conditions.(4, 7) Such assessment can help define the elements of a
sustainable PV strategy and areas for improvements as the basis to plan for improved public health and safety of medicines.(4, 61, 176)

This chapter presents the first study carried out as part of the wider programme of work which involved reviewing and synthesising published peer-reviewed literature on evaluating developing countries' PV systems' performance. The aim of the review and the approach taken to find relevant literature are initially presented, followed by the review's findings that aided in informing the approach for the empirical work.

A version of this chapter is a paper entitled “A systematic review of pharmacovigilance systems in developing countries using the WHO pharmacovigilance indicators” which has been published (open access) in Therapeutic Innovation and Regulatory Science. 2022; Volume 56, Issue 5, Page 717-743. Digital object identifier (DOI): https://doi.org/10.1007/s43441-022-00415-y.(177)

4.2. Aim

This narrative literature review aims to systematically identify and synthesise published peer-reviewed research that evaluates the characteristics, performance, and/or effectiveness of PV systems in developing countries.

4.3. Methods

This narrative literature review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.(178)

4.3.1. Theoretical framework

The WHO PV indicators(7) were applied as a theoretical framework to inform the data extraction and analysis of this study. Further details pertaining to the individual indicators can be found in the preceding chapter (Chapter Three, section 3.3.1) as well as in the WHO PV indicators manual.

4.3.2. Information sources and search strategy

As part of conducting the narrative literature review, the researcher had to make judgements concerning its scope. The first of these judgements involved deciding on the timeframe of the search. Given the global trend towards following the most
recent versions of best practice guidelines and the need to obtain the most up-to-date
data as possible, it was deemed appropriate that the literature search begin from 2012
onwards since that is the date when the EU guidelines on GVP were due for
implementation. The second judgement concerned the choice of countries to be
included in the study. Given the vast number of countries worldwide and the focus of
the overall programme of research being on Kuwait, which is considered a
developing country despite its high-income status, the review's inclusion criteria
were limited to developing countries. This was done to limit the reviewed studies to
those conducted within a similar context. However, literature on PV systems in
developed countries was acknowledged through comparing findings with those
obtained by the review as part of the discussion. Finally, a judgement was made
regarding the type of products the PV systems were set up to monitor. The choice
was made to focus the search on PV systems set up to monitor ADRs associated with
the use of pharmaceuticals given the fact that other types of products such as herbal
medicines, vaccines, medical devices, etc. most often fall under different sets of
regulations than those for pharmaceuticals.

Four key databases (EMBASE, MEDLINE, CINAHL Plus, and Web of Science)
were searched for international peer-reviewed research evidence from January 2012
to July 2021 using a variety of keywords including words with the same meaning,
alternative spelling, and plural forms. The search was initiated using the keyword
'pharmacovigilance' and its synonyms in combination with other groups of keywords
that covered ‘evaluation’. Additional relevant material was identified through
scanning the included studies' reference lists. The search terms employed in the
study are provided in Table 4.1 (see Appendix X for search strategy details).

**Table 4.1. Keywords used for the search**

<table>
<thead>
<tr>
<th>Keyword</th>
<th>Search terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacovigilance</td>
<td>Pharmacovigilance OR Drug Surveillance Program OR Drug Safety OR Adverse Drug Reactions Reporting Systems OR Postmarketing Surveillance</td>
</tr>
<tr>
<td>Evaluation</td>
<td>Evaluat* OR Monitor* OR Assess* OR Benchmark*</td>
</tr>
</tbody>
</table>
4.3.3. Data screening

The screening and paper selection process was performed according to the Preferred Reporting Items for Systematic Reviews (PRISMA) guidelines(178) thus providing transparency to the process. This also means that the study can be easily repeated and allows for reproduction of the study data at a later date. Upon completion of the database search, all duplicate titles were removed. This was followed by a screening process of the abstracts followed by the full texts by the researcher against the inclusion/exclusion criteria (Table 4.2). For all papers which appeared relevant, the full-text paper was retrieved, and the criteria were applied.

4.3.4. Data extraction, synthesis, and quality assessment

A data extraction tool based on the WHO PV indicators checklist(7) was used to collect data from each of the studies included in the review at two levels: overall study and studied country/countries. For each of the included studies data was extracted based on which of the WHO PV indicators the study provided information on and mapped against the individual indicators. For the individual countries assessed in the studies, data (qualitative and quantitative) relating to each indicator were extracted. Each of the individual indicators was scored separately, then a final score was calculated for each study and each country based on the 63 indicators. If an indicator provided the information required, a score of 1 was given, whereas a score of 0 was given where data were not provided, missing, not applicable, or not clear. In cases where information for a particular country was provided by more than one study, the data from the latest study was used. In cases where country data were available for more than one system level (e.g. national level and institutional level), the information from the higher level was used. The final scores were used to benchmark national PV performance and compare countries both within and across regions.
Table 4.2. Inclusion and exclusion criteria

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Setting</strong></td>
<td>Developing countries</td>
</tr>
<tr>
<td><strong>Species</strong></td>
<td>Human</td>
</tr>
<tr>
<td><strong>Location</strong></td>
<td>International</td>
</tr>
<tr>
<td><strong>Language</strong></td>
<td>English</td>
</tr>
<tr>
<td><strong>Design/Study type</strong></td>
<td>Qualitative and quantitative studies. Randomised control trials (RCTs) with a primary component related to the evaluation or assessment of pharmacovigilance systems or activities.</td>
</tr>
<tr>
<td><strong>Publication type</strong></td>
<td>Full-text peer-reviewed journal papers based on empirical research or with a clear empirical base</td>
</tr>
<tr>
<td><strong>Publication date</strong></td>
<td>2012 – 2021</td>
</tr>
</tbody>
</table>

**Focus of study**

Studies about the characteristics, performance metrics, or effectiveness of pharmacovigilance system(s) at some level e.g. PV centre (national or peripheral), healthcare facilities (hospitals or clinics), Public Healthcare Programmes (PHP), or pharmaceutical companies within a developing country.

- Studies focusing on non-medication related adverse events (e.g. surgical adverse events), allergies, medication errors, abuse or misuse, medical devices, veterinary products, traditional or complementary medicines, vaccines, food supplements.
- ADR reporting systems based on computerised physician order entry systems, electronic medical records, and registries specific to one drug or disease.
- Studies of pharmacodynamic, pharmacokinetic, and pharmacogenetic measures.

The quality of included papers was evaluated using Hawker et al.'s (179) nine-item checklist for appraising studies employing different methodological approaches. The checklist allows scoring of individual parameters thereby providing a total score that allows comparison of strengths and weaknesses within and across studies. Total scores could range from 9 to 36, and papers were rated as “Good” (4), “Fair” (3), “Poor” (2), “Very poor” (1) for each of the nine checklist items (title, introduction and aims, method and data, sampling, data analysis, ethics and bias, results,
transferability or generalisability, implications and usefulness). Hawker et al. (179) do not suggest any limits for categorising the sum quality ranking of studies, therefore, cut-offs suggested by researchers who previously used this checklist were adopted. (180, 181) As such, studies were grouped as follows: high (30–36 points), medium (24–29 points) and low quality (9–23 points). The data extracted from the studies were placed into Microsoft Excel and NVivo. Extracted data were analysed by the researcher to aid study and country comparisons.

4.4. Results

Following the removal of duplicates (n=2,175), 8,482 studies were screened, and 8,462 studies were excluded following title, abstract, and full-text review. A manual search of reference lists of the remaining studies (n=20) led to identifying one additional study, bringing the total to 21 studies. Figure 4.1 presents a PRISMA flowchart demonstrating this process.

4.4.1. Study characteristics

The 21 included studies (Table 4.3) altogether evaluated PV systems in 51 countries across single or multiple countries’ National PV Centres (NPVCs), Public Health Programmes (PHPs), healthcare facilities (e.g., hospitals), or pharmaceutical companies. Most of the studies (n=13) had been published since 2016. Eleven studies focused on African countries (182-192) with one of these papers also including India(187). Four studies involved Middle Eastern and/or Eastern Mediterranean countries(86, 88, 89, 193), and four covered East or Southeast Asian countries(194-197). One study dealt with countries in the Asia-Pacific region(198) and one study focussed on a country in South America(199).

Ten of the included studies employed self-completion questionnaires as a method of data collection (86, 88, 89, 190, 193-195, 197-199), while nine employed a mixed-methods approach (182-186, 188, 189, 191, 192) including interviewer-administered questionnaires alongside documentary review. Only two studies (187, 196) employed only qualitative methods including interviews and literature or documentary review. Sixteen studies (89, 182-192, 195-199) evaluated or assessed PV practice or performance. The remaining five studies(86, 88, 193, 194, 198) surveyed or provided an overview of countries’ PV situation and offered insights into the maturity of PV systems.
Figure 4.1. Flow diagram of studies included/excluded in the narrative literature review.
Eight studies (86, 88, 184, 189, 194-196, 198) focussed on the national PV centre(s), while three studies (182, 183, 186) took more of a system-wide approach by also including other levels, i.e. healthcare facilities and PHPs. Three studies (188, 191, 193) focused on PV at the regional level within a country. Five studies (185, 190, 192, 197, 199) focused on PV in stakeholder institutions including pharmaceutical companies/manufacturers, PHPs, drugstores, and medical institutions.

Thirteen studies (89, 182-189, 191, 192, 195, 198) employed an analytical approach that relied on the use of a framework. The most frequently used frameworks (n=3) were the IPAT (182, 183, 186) and the WHO PV indicators (191, 192, 198). Two studies used the East African Community (EAC) harmonised PV indicators tool (184, 185) and two employed the WHO minimum requirements for a functional PV system (187, 195). Two studies (188, 189) employed the Centers for Disease Control and Prevention (CDC) updated guidelines for evaluating public health surveillance systems (200) alongside the WHO PV indicators (7). One study employed a framework that combined indicators from the IPAT and the WHO PV indicators (89).

4.4.2. Study quality

Using Hawker et al.'s (179) nine-item checklist, the overall quality of included studies was deemed as medium (n = 7 studies) or high (n = 14 studies). The detailed scoring of the included studies' quality assessment is supplied in Appendix XI. The lowest scoring parameter was "ethics and bias" (1.9 ± 0.6); the highest-scoring parameter was "abstract and title" (3.9 ± 0.3). The methods used were considered appropriate for all included studies, however, seven did not provide sufficient detail on the data collection and recording process. (88, 183, 189, 190, 193, 194, 199) Clear sample justification and approaches were only described in three studies (188, 189, 191). Only three studies (88, 190, 199) rated poorly or very poorly with respect to data analysis due to limited or no detail. Apart from one study (193), studies provided clear descriptions of findings. Only three studies (186-188) detailed ethical issues such as confidentiality, sensitivity and consent. No studies described or acknowledged researcher bias/reflexivity. Study transferability or generalisability were affected by the use of small sample sizes (182, 186), survey non-response (86, 88, 89, 190, 198), focus on the national PV centre (195), the institutional level rather than the individual (HCP or patient) level, the exclusion of some types of institutions (197), and non-testing of questionnaire reliability (194). Only four
studies(186, 194-196) achieved a score of 4 for the "implications and usefulness" parameter by suggesting ideas for future research and implications for policy and/or practice.

The main limitation described by the reviewed studies related to information validity and completeness. Eight studies (86, 88, 184, 185, 187, 188, 194, 197) cited limitations that included pertinent data being missing, reliance on the accuracy of information provided by study participants, or inability to verify or validate information obtained. The second limitation in terms of prominence was that related to the collected data's currency. Four studies(86, 88, 184, 197) reported that the data collected might not fully reflect the current state of PV in the studied countries as some of the findings may have changed since the time the assessment was carried out. Finally, there were limitations related to the evaluation tools used to conduct the evaluation of PV performance which were reported by two studies (186, 191). Kabore et al. (186) highlighted four limitations inherent to the IPAT including 1- Its sensitivity and specificity had not been established, 2- Possible imprecision in the quantification of responses in the scoring process, 3- The assessments' reliance on respondents' assessments' declarations, and 4- The necessity of local adaptation due to the tool's limited testing and validation. Two studies (191, 192) pointed out that lack of trained personnel, poor documentation, and the need for in-depth surveys which nascent systems are unable to execute hindered the provision of results for the process and outcome indicators. Furthermore, it was indicated that, as a tool, the WHO PV indicators lacked a scoring system that could quantify the indices thereby highlighting system deficiencies numerically.(191)
### Table 4.3. Summary of details of included studies and quality assessment scores

<table>
<thead>
<tr>
<th>Author(s), publication year</th>
<th>Study aim</th>
<th>Study design</th>
<th>Study setting</th>
<th>PV system level</th>
<th>Sample size</th>
<th>Methods</th>
<th>Evaluation Tool(s)</th>
<th>Aspects evaluated by study</th>
<th>Quality Score (of 36)</th>
<th>Study limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abiri, O. T. &amp; Johnson, W. C. N. (2019)(182)</td>
<td>To evaluate current status of PV in Sierra Leone through comprehensive and system-based approach that covered the Pharmacy Board of Sierra Leone, healthcare facilities and Public Health Programmes.</td>
<td>Descriptive cross-sectional study</td>
<td>Sierra Leone</td>
<td>NMRA, health facilities, and Public Health Programmes (PHPs)</td>
<td>14 participants</td>
<td>Structured interviews with key informants from Pharmacy Board of Sierra Leone (PBSL), 6 hospitals, 6 Public Health Programmes (PHPs), and documentary review</td>
<td>Indicator-Based PV Assessment Tool (IPAT)</td>
<td>1- Policy, law and regulation; 2- Systems, structures and stakeholder coordination; 3- Signal generation and data management; 4- Risk assessment and evaluation; 5- Risk management and communication.</td>
<td>30</td>
<td>Small sample size recruited through convenience sampling. Use of score of 60% as threshold for overall functionality of PV system despite no evidence from IPAT</td>
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<tr>
<td>Allabi, A. C. and Nwokike, J. (2014)(183)</td>
<td>To draw up a portrait of policy documents and practical actions in the areas of PV, quality control of Artemisinin-based Combination</td>
<td>Not reported</td>
<td>Republic of Benin</td>
<td>PV systems in drug regulation system (DPM), National malaria control programme (NMCP), known as &quot;Programme</td>
<td>68 physicians, 45 pharmacists and 43 pharmaceutica l company representative s, key informants from the National Laboratory of</td>
<td>Interviewer administered semi-structured questionnaire with physicians, pharmacists, and pharmaceutica l company representative</td>
<td>Semi-structured questionnaire based on ADR reporting and reasons for non-reporting; no framework reported for focus groups; structured interviews &amp;</td>
<td>Semi-structured questionnaire: knowledge, attitude &amp; practice relating to spontaneous reporting of ADRs, specific questions</td>
<td>28</td>
<td>Not reported</td>
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<tr>
<th>Author(s), publication year</th>
<th>Study aim</th>
<th>Study design</th>
<th>Study setting</th>
<th>PV system level</th>
<th>Sample size</th>
<th>Methods</th>
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<th>Aspects evaluated by study</th>
<th>Study limitations</th>
<th>Quality Score (of 36)</th>
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<tr>
<td>Therapies (ACTs) and monitoring of resistance of ACT in Republic of Benin (situational analysis), identification of the main barriers which prevent their implementation and the discussion focus on the recommendations for towards the establishment of an effective and functional PV system in Benin.</td>
<td>National de Lutte Contre le Paludisme&quot; (PNLP) in Benin, quality control of drugs centre (LNCQ) and the biggest teaching hospital (CNHU)</td>
<td>Drugs Control Quality (LNCQ), Directorate of Pharmacy and Drug Regulations (DPM), National Malaria Control Programme (NMCP) and the Director of the teaching hospital in Cotonou: Centre National Hospitalier Universitaire (CNHU).</td>
<td>documentary review based on Indicator-Based PV Assessment Tool (IPAT); SWOT analysis</td>
<td>examining the ADRs related to ACT, reasons for non-reporting and important factors in a decision to report; focus groups; Assess practice &amp; problems in PV system &amp; quality control of ACTs &amp; ways to solve them; structured interviews and documentary review: 1- Policy, law &amp; regulation; 2- Systems, structures and stakeholder coordination; 3- Signal generation and data management; 4- Risk assessment</td>
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<td>Author(s), publication year</td>
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<td>Alshammari, T. M. et al. (2020)(86)</td>
<td>To investigate and provide an overview of the current situation and on the activities of the national pharmacovigilance centres in Arab countries.</td>
<td>Cross-sectional study</td>
<td>Arab countries (members of the League of Arab States)</td>
<td>National PV Centres</td>
<td>15 countries: Algeria, Egypt, Jordan, Iraq, Kuwait, Libya, Lebanon, Morocco, Oman, Palestine, Kingdom of Saudi Arabia, Sudan, Tunisia, United Arab Emirates, and Yemen</td>
<td>Self-administered questionnaires by representative s of National PV Centres</td>
<td>A previously conducted survey carried out by WHO UMC</td>
<td>1- Country &amp; respondent background information; 2- Overview of PV programme; 3- Spontaneous reporting; 4- PV activities; 5- Level of support: funding, staff, &amp; software; 6- Usefulness of information from PV activities; &amp; 7- Registry availability; Pertinent information missing. Programme features &amp; development plans might have changed since the time of the study. Not all countries responded.</td>
<td>31</td>
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<tr>
<td>Author(s), publication year</td>
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<td>Study design</td>
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<tr>
<td>Barry, A. et al. (2020)(184)</td>
<td>To conduct a comparative assessment of the current national PV system at the respective NMRAs in Ethiopia, Kenya, Rwanda, and Tanzania for future targeted capacity-building interventions to be carried out by the PROFORMA project.</td>
<td>Cross-sectional descriptive study</td>
<td>Ethiopia, Kenya, Rwanda, and Tanzania</td>
<td>National PV Centres housed within the NMRAs</td>
<td>Between 2 &amp; 4 NMRA staff members working in PV from each country</td>
<td>Structured interviews with key informants (NMRA staff working in PV) and documentary review</td>
<td>East African Community (EAC) Harmonized PV Indicators tool (derived from the WHO PV indicators and the IPAT) supplemented with a few additional indicators from the WHO Global Benchmarking Tool (GBT) for evaluation of national regulatory systems</td>
<td>EAC Indicators tool: 1-Policy, law, and regulation; 2-Systems, structures, and stakeholder coordination; 3-Signal generation and data management; 4-Risk assessment and evaluation; and 5-Risk management and communication; WHO Global Benchmarking Tool: 1-</td>
<td>Findings for some indicators may have changed since assessment. Some personal knowledge, experience, &amp; opinions of regulators were not possible to verify from other sources.</td>
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<tr>
<td>Author(s), publication year</td>
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<tr>
<td>Barry, A. et al. (2021)(185)</td>
<td>To assess and compare the pharmacovigilance systems and practices</td>
<td>Cross-sectional descriptive study</td>
<td>Ethiopia, Kenya, Rwanda, and Tanzania</td>
<td>Public Health Programmes</td>
<td>2-3 national NTD program staff members in Kenya, Tanzania, and</td>
<td>Structured interviews with key informants (staff)</td>
<td>East African Community (EAC) Harmonized Pharmacovigil</td>
<td>Guidelines ensuring encouragement of different stakeholders to report ADRs and Adverse Events to MAH and/or NMRA; 2- Legal provisions and regulations allowing NMRA to require safety and effectiveness studies; 3- Legal provisions, regulations, &amp; guidelines requiring designation of person as in charge of PV system.</td>
<td>Not possible to verify all information gathered through structured</td>
<td>30</td>
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<tr>
<td>Author(s), publication year</td>
<td>Study aim</td>
<td>Study design</td>
<td>Study setting</td>
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<td>Chan, C. L. et al. (2017)(194)</td>
<td>To review the status of the development of pharmacovigilance in the Association of Southeast Asian Nations (ASEAN) and the relevance of quantitative signal detection algorithms (QSDA) in the ASEAN context. Also, to compare findings in these countries against more ASEAN member countries and a group of non-ASEAN countries having close working relations in the area of PV with Singapore: Australia, Canada, Japan, South Korea, Switzerland, UK, and the USA</td>
<td>Not reported</td>
<td>National Pharmacovigilance Centre</td>
<td>16 countries: 9 ASEAN countries with Myanmar excluded: Brunei Darussalam, Cambodia, Indonesia, Lao People’s Democratic Republic, Malaysia, Philippines, Singapore, Thailand, and Vietnam; and 7 non-ASEAN countries: Australia, Canada,</td>
<td>members from the national NTD programme and documentary review</td>
<td>Indicators tool for Public Health Programmes (PHPs) (derived from the WHO pharmacovigilance indicators and the IPAT)</td>
<td>generation and data management; 3- Risk assessment and evaluation; and 4- Risk management and communication.</td>
<td>interviews.</td>
<td>31</td>
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<tr>
<td>Author(s), publication year</td>
<td>Study aim</td>
<td>Study design</td>
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<td>Ejekam C. S. et al. (2020) (192)</td>
<td>Assess structures, processes, &amp; outcomes of P activities in three selected public health programmes (National Malaria, Tuberculosis (TB), HIV/AIDS) in Nigeria using the WHO PV Indicators and identify possible challenges to achieving the outcomes.</td>
<td>Cross-sectional mixed-method study</td>
<td>Nigeria</td>
<td>Public Health Programmes (PHPs)</td>
<td>National PV centre and 3 PHPs</td>
<td>Structured and semi-structured interviews with key informants from National PV Centre and PHPs and documentary review</td>
<td>WHO Pharmacovigilance Indicators</td>
<td>safety monitoring; 5- Management of ADR reports and signal detection; and 6- The relevance of a QSDA in their respective countries</td>
<td>did not capture types &amp; volume of medicines used in various countries.</td>
<td>30</td>
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<tr>
<td>Kabore, L. et al. (2013)(186)</td>
<td>To evaluate Burkina Faso's early-stage drug safety monitoring system through a comprehensive system-based approach.</td>
<td>Descriptive cross-sectional study</td>
<td>Burkina Faso</td>
<td>NMRA, public health programmes (PHPs) and hospitals</td>
<td>16 participants (1-3 participants per institution)</td>
<td>Structured interviews with key informants from the NMRA, six PHPs, and five hospitals, as well as documentary review</td>
<td>Indicator-Based Pharmacovigilance Assessment Tool (IPAT)</td>
<td>1- Policy, law and regulation; 2- Systems, structures and stakeholder coordination; 3- Signal generation and data management; 4- Risk assessment and evaluation; and 5- Risk management and communication; and opinions regarding the current PV system</td>
<td>IPAT limitations: 1. IPAT's sensitivity and specificity have not been established; 2. Possible imprecision in the quantification of responses in the scoring process; 3. Assessment was reliant on respondents' declarations; 4. Local adaptation may be necessary due to the tool's limited testing and validation. Limitations related to evaluation process: Generalisability and reproducibility of study may be affected due to limited sample in number and diversity.</td>
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<td>Kaewpanukrongsi, W. &amp; Anantachoti, P. (2015)(196)</td>
<td>To assess the performance of the Thai National Pharmacovigilance Centre (NPVC) to identify gaps and areas for improvement</td>
<td>Not reported</td>
<td>Thailand</td>
<td>National Pharmacovigilance Centre</td>
<td>10 participants (8 from the national pharmacovigilance centre and 2 executive staff from the Thai NPVC)</td>
<td>Interviews (using semi-structured questionnaires) with and observation of NPVC staff, in-depth interviews</td>
<td>Open-ended questions: Domains and indicators for NPVC performance assessment</td>
<td>1- Policy, plan and structural support, 2- Safety surveillance, 3- Risk management, and 4-</td>
<td>Not reported</td>
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<tr>
<td>Study</td>
<td>Research Question</td>
<td>Methodology</td>
<td>Health Regions</td>
<td>Number of Participants</td>
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<td>Maigetter, K. et al. (2015) (187)</td>
<td>To describe the PV systems in India, Uganda, and South Africa. Also, to analyse the extent to which the three countries conformed to the minimum pharmacovigilance requirements by the WHO.</td>
<td>Documentary review: pharmaceutical regulation, including regulatory frameworks and capacity; use of medicines; and PV, including descriptions of the adverse event (AE) reporting systems. Interviews: Regulatory systems and policies concerning PV.</td>
<td>India (IN), Uganda (UG), and South Africa (SA)</td>
<td>39 participants (20 from India, 8 from Uganda, and 11 from South Africa)</td>
<td>NVivo software was used to allow for deductive thematic analysis of the interview transcripts. Reliance on interviews with key informants. Some details regarding budget and staff, as well as composition and functioning of the national advisory committee, were not uniformly available.</td>
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<td>Mugauri, H. et al. (2018) (189)</td>
<td>To evaluate the antiretroviral-adverse drug reaction (ARV-ADR) surveillance system in Harare City, Zimbabwe</td>
<td>Descriptive cross-sectional study and surveillance system evaluation</td>
<td>National PV Centre</td>
<td>52 Health Personnel involved in the ARV-ADR surveillance from 2 hospitals and 100 Health Personnel from another hospital</td>
<td>Updated Centres for Disease Control and Prevention (CDC) guidelines for Evaluating</td>
<td>Questionnaire: determine health workers' knowledge of operations &amp; usefulness of surveillance</td>
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<td>Harare City to identify the reasons for underreporting and recommend solutions.</td>
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<td>clinics, as well as interviews with healthcare workers using an interviewer-administered questionnaire</td>
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<td>Public Health Surveillance Systems and checklist derived from the WHO assessment criteria for a PV system’s stability status (WHO PV Indicators) system; Checklist: evaluates availability of reporting forms, case definitions &amp; means for communicatio n. Patient records: number of ARV ADR cases documented, captured, &amp; missed by surveillance system. Hospital &amp; clinic notifications: evaluating system simplicity, data quality, completeness, acceptability, sensitivity, timeliness &amp; representativ e ness. PV indicator checklist: core &amp; complimentar y process</td>
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<tr>
<td>Study</td>
<td>Description</td>
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<td>Methods</td>
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<td>Muringazuva, C. et al. (2017) (188)</td>
<td>To evaluate the ADR Surveillance System (ADRSS) to assess the system performance and reasons for not notifying on time.</td>
<td>Kadoma City, Zimbabwe</td>
<td>Regional PV System</td>
<td>47 HCPs from six health facilities which offered Mass Drug Administration (MDA)</td>
<td>Interviewer administered questionnaire, checklists, and record review (outpatient registers, reports on ADRSS, meetings' minutes)</td>
<td>Descriptive cross-sectional study and surveillance system evaluation</td>
<td>System simplicity, stability, acceptability, and completeness; Interviewer administered questionnaire information on health worker knowledge on the ADRSS; checklist was used to assess the availability of the resources needed for running the ADRSS.</td>
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<tr>
<td>Mustafa, G. et al. (2013) (193)</td>
<td>To investigate the ADR reporting system and to suggest possible ways of improving the method of reporting.</td>
<td>Lahore, Pakistan</td>
<td>Regional health facilities (hospitals)</td>
<td>84 Doctors and 52 Pharmacists from 30 different hospitals in Lahore</td>
<td>Structured interviews using investigator administered questionnaires</td>
<td>Prospective observational study</td>
<td>Questionnaire based on different ADR systems of developed countries, literature evaluation, Questionnaire 1: General hospital information including ADR systems; Questionnaire 2: Doctors'</td>
<td>Availability of only one notification made it difficult to assess the quality of data</td>
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<tr>
<td>Authors</td>
<td>Study Title</td>
<td>Study Objectives</td>
<td>Study Design</td>
<td>Study Setting</td>
<td>Sample Size</td>
<td>Methodology</td>
<td>Results and Challenges</td>
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<tr>
<td>Nwaiwu, O. et al. (2016)(190)</td>
<td>To evaluate PV practices in pharmaceutical companies in Nigeria.</td>
<td>Descriptive study</td>
<td>Lagos, Nigeria</td>
<td>Pharmaceutical Companies</td>
<td>31 companies</td>
<td>Self-administered questionnaire distributed to designated company staff.</td>
<td>Questionnaire adapted from existing drug safety laws and guidance and online PV auditing checklists.</td>
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<tr>
<td>Opadeyi, A. O. et al. (2018)(191)</td>
<td>To assess the status of PV structure, processes, outcomes and impact in the South-South zone of Nigeria using the WHO PV indicators.</td>
<td>Cross-sectional descriptive study</td>
<td>South-South Zone of Nigeria</td>
<td>Regional health facilities (hospitals)</td>
<td>6 hospitals</td>
<td>Structured interviews with focal pharmacovigilance persons or committees in hospitals and review of hospital records</td>
<td>Modified WHO PV Indicators (Core Indicators). Background information, structural indicators, process indicators, outcome/impact indicators.</td>
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Sampling method used prone to selection bias & sampling error. Companies participating in study may have differed from those that did not.

Absence of trained PV personnel hindered the provision of results for the PV process indicators. Structural PV indicators fail to fully capture the PV system's functionality. Overall poor documentation limited indicators’ derivation. Outcome/impact indicator derivation required in-depth survey not possible to execute by young PV systems. Need for scoring system.
<table>
<thead>
<tr>
<th>Qato, D. M. (2018)(89)</th>
<th>To describe the current landscape of PV in the Arab and Eastern Mediterranean (EM) region.</th>
<th>Descriptive cross-sectional study</th>
<th>Arab and Eastern Mediterranean Region countries</th>
<th>National PV Centre</th>
<th>21 countries: Afghanistan, Algeria, Comoros Islands, Djibouti (excluded from final mean calculations), Egypt, Jordan, Iran, Iraq, Kuwait, Libya, Lebanon, Morocco, Oman, Pakistan, Palestine, Qatar, Kingdom of Saudi Arabia, Sudan, Tunisia, the UAE, Yemen</th>
<th>Self-administered questionnaires by pharmacovigilance leadership (official national contact for the WHO PIDM).</th>
<th>Combination of WHO PV Indicators and Indicator-Based PV Assessment Tool (IPAT).</th>
<th>Three domains of PV performance: Structure, process, and impact</th>
<th>Not all countries in geographical region of interest represented either due to non-/ incomplete response. Survey was only developed in English. Potential for reporting bias.</th>
</tr>
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<tr>
<td>Rorig, K. D. V. and de Oliveira, C. L. (2012)(199)</td>
<td>To evaluate the implementation and operation of the PV programme in the</td>
<td>Not reported</td>
<td>Brazil</td>
<td>Pharmaceutica l companies</td>
<td>50 companies</td>
<td>Self-administered questionnaire by pharmaceutica l companies’ PV sector, regulatory</td>
<td>Not reported</td>
<td>1- Company identification, its origin and the characterizatio n or absence of a PV programme;</td>
<td>31</td>
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<tr>
<td>Shin, J. Y. et al. (2019)</td>
<td>To survey the collection and management of adverse effect reports in 21 Asia-Pacific Economic Cooperation (APEC) countries, compare the PV status and systems by country, and finally, to harmonize PV regulation in the APEC region.</td>
<td>Not reported</td>
<td>Asia-Pacific Economic Cooperation (APEC) region countries</td>
<td>National PV Centre</td>
<td>15 countries: Australia, Brunei, Chile, Indonesia, Malaysia, Mexico, Papua New Guinea, Peru, Philippines, Singapore, Taiwan, Thailand, Japan, South Korea, and the USA</td>
<td>Self-administered questionnaires by heads of PV teams from PV agencies</td>
<td>Modified WHO PV Indicators</td>
<td>Three domains: Structure, process, and outcome of PV system.</td>
<td>Not all countries in the region responded to the survey. Did not include all questions and answers from WHO's PV indicators. The tendency for arbitrary interpretation regarding questions on regular PV education.</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Methodology</td>
<td>Countries</td>
<td>PV Centre</td>
<td>Study Design</td>
<td>PV Systems’ Function and Performance</td>
<td>Findings</td>
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<tr>
<td>Suwankesawong, W. et al.</td>
<td>2016</td>
<td>Cross-sectional study</td>
<td>ASEAN countries: Brunei Darussalam, Cambodia, Indonesia, Lao People’s Democratic Republic, Malaysia, Myanmar, Philippines, Singapore, Thailand, and Vietnam</td>
<td>National PV Centre</td>
<td>8 countries: Cambodia, Indonesia, Laos, Malaysia, the Philippines, Singapore, Thailand, and Vietnam</td>
<td>Self-administered questionnaire by ASEAN countries’ PV representatives and contact persons.</td>
<td>Application of WHO requirements to national PV systems only, therefore findings may not be generalisable to PV in the entire community</td>
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<tr>
<td>Wilbur, K.</td>
<td>2013</td>
<td>Not reported</td>
<td>Arabic-speaking Middle Eastern countries</td>
<td>National Pharmacovigilance Centre</td>
<td>11 countries: Bahrain, Egypt, Iraq, Jordan, Kingdom of Saudi Arabia, Kuwait, Oman, Palestine, Qatar, United Arab Emirates, and Yemen</td>
<td>Self-administered questionnaire by the head of centres responsible for medication safety</td>
<td>UMC Assessment of Country PV Situation questionnaire (February 2008)</td>
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</table>

Certain responses may be different since original deployment of questionnaire. Accuracy & completeness of information provided could be affected depending on individual completing questionnaire. Not all countries formally participated so regional situations.
| Zhang, X. et al. (2019)(197) | To assess the current status of ADR reporting and monitoring in pharmaceutical manufacturers, drugstores, and medical institutions in China. | Cross-sectional study | Chinese provinces (East: Jiangsu and Guangdong; West: Shaanxi and Sichuan; and Centre: Henan and Hebei) | Pharmaceutica l manufacturers', drugstores', and medical institutions' PV systems | 589 institutions (194 pharmaceutical manufacturers, 191 drugstores, and 204 medical institutions) | Self-administered questionnaire by ADR reporters in charge of drug safety (e.g. heads of vigilance units and drug safety coordinators) at Pharmaceutica l manufacturers, drugstores, and medical institutions | A questionnaire based on previous studies | 1- Current status of the ADR monitoring system; 2- Basic resources for ADR reporting; 3- ADR reporting; and 4- Other PV activities | Data might not fully reflect current ADR monitoring and reporting systems in China. It was assumed that the respondents had full access to all current, relevant information. The information supplied by respondents was not verified or validated. The study did not target all the adverse drug reaction reporting and monitoring institutions or all 34 provinces in China. Only 3 institution types were included, and data collection focused on the institutional level rather than the individual level. Low response rate. |
4.4.3. Studies' coverage of WHO pharmacovigilance indicators

When investigating the included studies' coverage of the 63 WHO PV indicators, the studies achieved an average score of 17.2 (see Figure 4.2). The highest score was 33.0(184) and the lowest was 4.0(190). Studies placed a higher emphasis on evaluating 'Core Indicators' compared to 'Complementary Indicators' as demonstrated by the median and average scores obtained for Core (12.0 and 11.6/27 respectively) versus 4.0 and 5.6/36 for complementary. Studies obtained higher median and average scores for structural indicators (8.0 and 7.0/10 for Core and 4.0 and 3.3/11 for Complementary respectively) compared to process (3.0 and 2.7/9 for Core along with 1.0 and 1.5/13 for Complementary respectively) and outcome indicators (2.0 and 1.9/8 for Core and 0 and 0.8/12 for Complementary).

4.4.4. Regions' and countries' pharmacovigilance performance

4.4.4.1. Total pharmacovigilance system performance

The average and median scores achieved by all countries were 14.86 and 15.0/63 respectively. Although 51% of countries had a higher-than-average total score and 49% had a score above the median, none of them achieved more than 40% of the WHO indicators. The Middle East and North Africa achieved the highest average total score (15.89), and Latin America and the Caribbean the lowest (10.5). In comparison, the highest median score was achieved by the Middle East and North Africa (18.0), and the lowest was achieved by South Asia (10.0). The highest achieving country was Tanzania (26.0). Bahrain, Syria, Djibouti, and Myanmar all scored zero. See Figures 4.3 and 4.4 for the regions' and countries' aggregate scores respectively.

4.4.4.2. Core indicators performance

Out of a possible score of 27 for Core indicators, the average was 9.27 while the median was 9.0. East Asia and the Pacific achieved the highest average score (10.17), whereas South Asia had the lowest (7.3). On the other hand, in terms of the median score, the highest was observed in Sub-Saharan Africa (11.5), and the lowest was in South Asia (7.0). The highest-scoring countries among the different regions were Nigeria, Indonesia, and Malaysia (15.0), whereas Bahrain, Syria, Djibouti, and Myanmar scored zero.
Figure 4.2. Included studies’ aggregate scores (out of a possible total of 63) for coverage of WHO pharmacovigilance indicators.
Figure 4.3. Aggregate scores (out of a possible total of 63) of studied countries' pharmacovigilance systems by region.
Figure 4.4. Aggregate scores (out of a possible total of 63) of studied countries' pharmacovigilance systems.
**Structural indicators**

For Core Structural indicators, the average score for the 51 countries was 6.5 and the median was 7.0. The highest average and median scores, regionally, were observed in Sub-Saharan Africa (7.07 and 8.5 respectively), whereas the lowest were observed in Latin America and the Caribbean (5.0 and 5.5 respectively). Egypt had the highest country-level score (10.0) while Bahrain and Syria, Djibouti, and Myanmar scored zero.

In most countries (92%) it was reported that a facility for carrying out PV activities existed. Similarly, it was indicated that PV regulations existed in 80% of the studied countries. There were inconsistencies in the reported information concerning this indicator in Oman, Yemen, and Cambodia. In Oman, two studies (86, 88) reported that such regulations were present, whereas Qato (89) reported that they were absent. In Yemen, Qato (89) reported the presence of regulations, whereas Alshammari et al. (86) indicated the opposite. Similarly, with respect to Cambodia, conflicting information was reported by Suwankesawong et al. (195) and Chan et al. (194). In all such cases, the latest published results were adopted.

Concerning resources, regular financial provision for conducting PV activities was reported as present in only 35% of countries, most of which were among the highest achieving countries overall. There was an inconsistency in the information provided for this indicator in Oman and the United Arab Emirates (UAE) with two studies (86, 88) stating that this was present, whereas one (89) stated that it was not. In terms of human resources, it was found that 75% of the studied countries possessed dedicated staff carrying out PV activities.

It was reported that most countries (86%) possessed a standardised ADR reporting form as part of the system. However, only in 16 countries was it highlighted whether the form provided for reporting medication errors; counterfeit/substandard medicines; therapeutic ineffectiveness; misuse, abuse, or dependence on medicines; or reporting by the general public.

Only in four countries (China, Egypt, Ethiopia, and Uganda) was it reported that PV was incorporated into the national curriculum of healthcare professionals (HCPs). In 43% (n=22) of countries, it was either unknown or it was indicated that a tool for the dissemination of PV information did not exist. In contrast, it was reported that in
63% of the countries a PV advisory committee was present as part of the PV system. Information regarding this indicator was inconsistent between Qato(89) and Alshammari et al.(86) with the former reporting that Jordan and Tunisia did possess an advisory committee, yet the latter reporting the opposite.

Process indicators
The overall average and median scores for Core Process indicators were 2.06 and 2.0/9 respectively. The highest average score was in East Asia and the Pacific (2.9), whereas South Asia (1.0) achieved the lowest. Similarly, in terms of the median score, East Asia and the Pacific (3.0) was the highest while South Asia (1.0) was the lowest. No country achieved a higher score than Malaysia (7.0), while seven countries scored zero.

The absolute number of ADR reports received per year by the PV system in the assessed countries ranged from zero (Afghanistan, Bahrain, Comoros, Qatar, and Rwanda) to 50,000 (Thailand). Most countries (n= 27) received less than 10,000 reports per year, with Iran reporting the highest yearly rate (7,532 reports) and Laos and Lebanon reporting the lowest rate (3 reports). Only four countries reported receiving 10,000 reports or more yearly, namely China (32,513 reports), Malaysia (10,000 reports), Singapore (21,000 reports), and Thailand (50,000 reports). The remaining 20 countries either did not receive any reports or no data was provided.

The number of ADR reports increased over time in 12 countries (Algeria, Cambodia, Egypt, Iraq, Jordan, Kuwait, Morocco, Oman, Palestine, Saudi Arabia, Tunisia, and Yemen), whereas they decreased in eight countries (Laos, Malaysia, Philippines, Singapore, Sudan, Thailand, the UAE, and Vietnam). The percentage of total annual reports satisfactorily completed and submitted to the PV centre was reported only in Nigeria (maximum of 84.6%).

Only in Singapore and Thailand, it was reported that the cumulative number of reports present in the national database was more than 100,000. On the other hand, 17 countries had less than 20,000 reports in their database. Some inconsistencies were present in the data for this indicator reported by Suwankesawong et al.(195) and Chan et al.(194) for Malaysia, the Philippines, Singapore, and Vietnam. In each of these countries, the number reported by the former was higher than the latter.
Overall, information regarding the provision of ADR reporting feedback was poor with it being reported that in all the countries studied it was either not performed or no information was provided. Documentation of causality assessment was also poor as it was indicated that it was performed only in Ethiopia (2%), Kenya (5.5%), Tanzania (97%), and Zimbabwe (100%). In terms of the percentage of reports submitted to the WHO, this was reported only in Vietnam (28%) and Zimbabwe (86%).

Among the countries which reported performing active surveillance; Algeria was the most active with 100 projects followed by Tunisia and Morocco with 50 and 10 activities respectively, and the remaining countries all with less than seven.

**Outcome indicators**

The average and median scores overall for the Core Outcome indicators were 0.69 and 1.0/8 respectively. Countries from East Asia and the Pacific (0.92) had the highest average score collectively, whereas South Asia (0.33) had the lowest. In terms of the median score, Sub-Saharan Africa (1.0) was the highest, whereas South Asia (zero) had the lowest. Nine countries achieved the highest score (2.0), while 25 countries only scored zero.

Signal detection was reported to have occurred in 10 countries with the highest number observed in Kenya (31 signals), whereas the lowest (zero) was observed in Brunei, Cambodia, Chile, Papua New Guinea, Peru, Rwanda, and Vietnam. The reported number of signals detected was above 10 in only three countries: Kenya, Tanzania (25 signals) and Singapore (20 signals). Among the 23 countries where information regarding the number of regulatory actions taken was reported, the highest number of actions taken was in Egypt (930 actions), whereas the lowest number (zero actions) was taken in 15 countries.

The number of medicine-related hospital admissions per 1,000 admissions was only reported in Nigeria and ranged from 0.01 to 1.7. The reporting of pertinent data regarding the remaining five outcome indicators (CP3 – CP8) was inadequate as no information was provided for any of the countries investigated.

### 4.4.4.3. Complementary indicators performance

For Complementary indicators, the overall average and median scores were 5.59 and 6.0/36 respectively. The Middle East and North Africa (6.89 and 8.5 respectively)
achieved the highest average and median scores among the regions, whereas Latin America and the Caribbean (3.5 and 4.0 respectively) achieved the lowest. The highest-scoring country was Tanzania (12.0), whereas Bahrain, Syria, Djibouti, and Myanmar scored zero.

**Structural indicators**
For Complementary Structural indicators, the average and mean scores were 4.24 and 4.0/11 respectively. The highest average and median scores were achieved by the Middle East and North Africa (5.44 and 6.0 respectively), whereas Latin America and the Caribbean (2.5 and 3.0 respectively) had the lowest. Five countries achieved a score of 8.0, namely Jordan, Saudi Arabia, the UAE, Ethiopia, and Tanzania. Seven countries scored zero.

Three-fourths of the studied countries were reported to possess dedicated computer facilities to carry out PV activities as well as a database for storing and managing PV information. There was inconsistency in the data reported for Libya regarding the presence of a computer as Qato(89) indicated its presence, whereas Alshammari et al.(86) reported it as absent. It was indicated that in 47% of the countries functioning communication facilities such as telephone, fax, or internet were available. A library containing reference materials on drug safety was found to be available in only 19 countries. In all the countries studied, it was either reported that they did not have a source of data on consumption and prescription of medicines, or no information was available.

In all 51 countries investigated, it was either reported that web-based PV training tools for both HCPs and the general public were not available, or no information was reported. It was found that in nearly 60% (n=30) of the countries studied training courses for HCPs were organised by the PV centre. There was insufficient information to determine whether training courses for the general public were organised in any of the countries investigated.

**Process indicators**
The 51 countries achieved average and median scores of 1.4 and 1.0/13 respectively for the Complementary Process indicators. Regionally, the highest average and median scores were achieved by the Middle East and North Africa (1.44 and 2.0 respectively), while the lowest scores were achieved by Latin America and the
Caribbean (both 1.0). The highest total scores were achieved by Kenya and Tanzania (both 4.0), while 12 countries scored zero.

Data regarding the percentage of healthcare facilities that had a functional PV unit (i.e., submitting ≥ 10 reports annually to the PV centre) was reported for seven countries. However, only three of the seven countries reported a number above zero (Kenya 0.14%, Tanzania 0.26%, and Zimbabwe 2.2%).

In terms of the total number of reports received per million population; it was found that Singapore had the highest number (3853 reports/year/million population), while Laos had the lowest (0.4 reports/year/million population). In most countries (n=17), it was indicated that HCPs represented the primary source of submitted ADR reports. It was reported that medical doctors were the primary HCPs to submit ADR reports in five countries, namely Lebanon (100%), Libya (50%), Morocco (50%), Tunisia (96%), and Yemen (90%). It was reported that manufacturers were the primary source of ADR reports in eight countries, namely Algeria (71%), Jordan (90%), Kuwait (93%), Mexico (59%), Pakistan (88%), Palestine (100%), Saudi Arabia (50%), and the UAE (72%).

The number of face-to-face training sessions conducted over the last year was only reported in Kenya (12 sessions) and Tanzania (9 sessions) and were for HCPs. The number of HCPs who received face to face training over the previous year was only reported in Ethiopia (90,814), Tanzania (76,405), Rwanda (43,725), and Kenya (8,706). No information was found in any of the papers concerning the complementary process indicators 4, 6, and 9 to 13.

**Outcome indicators**

Out of a possible score of 12, the total average score achieved for Complementary Outcome indicators by the studied countries was zero as no information was reported concerning these indicators.

### 4.5. Discussion and summary

Despite the recent growth of PV among developing countries, there has been a gap in efforts to evaluate PV systems' performance. The narrative literature review presented in this chapter, which is the first of its kind, synthesised current research evaluating developing countries' PV systems' performance thereby providing an in-
depth understanding of factors affecting PV system performance. Using the WHO PV indicators (both core and complementary) as a framework, this review focused on identifying the areas of strength and weakness within these countries' PV systems. The review also helped identify where different developing countries' systems lay on the performance level spectrum. Moreover, the features associated with better-performing systems were highlighted. The insights from this review can be used to inform recommendations for addressing areas requiring intervention or modification, particularly within countries with PV systems at a nascent stage of development.

A total of 21 out of 8,482 unique studies were included, covering 51 countries. Out of a total possible quality score of 36, most studies were rated as medium (7) or high (14). The review revealed that a distinct lack of standardisation exists regarding the approach for evaluating PV systems. Furthermore, the 63 WHO PV indicators were not all assessed as, overall, both studies' coverage of the WHO PV indicators and developing countries' PV system performance were both low. There was a mix of some indicators which were present in most or all studies/countries, while others were universally absent or only sporadically present. In terms of the number of WHO PV indicators covered; studies obtained an average score of 17.2 out of a possible 63. Overall, system performance in the 51 countries covered was low (14.86 out of 63) with scores ranging from 0 to 26. A higher overall average score was obtained in the 'Core' (9.27 out of 27) compared to the 'Complementary' (5.59 out of 36) indicators. Overall performance for the 'Process' and 'Outcome' indicators was lower than that of the 'Structural' indicators.

High performing PV systems in developing countries studied in this review were distinguished by the presence of a budget specifically earmarked for PV, a means of communicating drug safety information to stakeholders (e.g., a newsletter or website), and technical assistance via an advisory committee. On the other hand, lack of incorporation of PV into the national curriculum of HCPs and underreporting of ADRs plagued both high and low performing systems.

This review has a few limitations. First, the published studies included in the review were very heterogeneous and differed in their aim, structure, content, method of evaluation, and targeted level of PV system/activity, which may limit the extent of generalisability of this review's findings. This was partially overcome by applying the WHO indicators as a means of standardising the extracted information. Second, a
limitation of the WHO PV indicators is the lack of a scoring system to quantifiably measure PV system performance. This was overcome by the development of a scoring system thus enabling a comparison of a country's PV system performance status against the WHO PV indicators and that of other countries. The narrative literature review presented in this chapter demonstrated that despite the existence of literature providing an overview or description of the PV systems or activities being carried out in Arab and other developing countries, there was a scarcity of research providing an in-depth exploration of these countries’ PV systems' performance and the factors impacting it. These findings led to the second stage of this programme of work – the examination of the structures, processes, and outcomes of the PV systems with differing levels of performance within three Arab countries – which will be presented in the next chapter.
Chapter Five: Study Two – Strengths and weaknesses of the pharmacovigilance systems in three Arab countries: a mixed-methods study using the WHO pharmacovigilance indicators

5.1. Introduction

The narrative literature review of developing countries’ PV systems in the previous chapter (Chapter Four) demonstrated that overall system performance among developing countries was poor and varied widely from one country to another. (201) Similarly, Arab countries’ PV systems were found to be at different stages of maturity, with many still in the early stages of development based on their system performance scores.

As previously described in the Background (Chapter One), effective implementation of the Arab GVP guideline requires improvement in the existing PV systems in these countries. Literature on PV systems in the Arab World has mainly focused on surveying these countries’ systems and providing a descriptive overview of their characteristics. (86, 88, 89) However, no studies have been conducted that set out to provide an in-depth exploration of the PV situation within the individual countries.

An important step towards strengthening PV systems in the region involves maintaining oversight over implemented systems to ensure their efficiency and effectiveness. (7) There has been a long held interest in cross-country comparisons of health systems and policies as understanding systems, processes, and developments in one group of countries can help inform learning and implementation in another (132). To enhance drug safety and optimise efforts aimed at supporting the development and strengthening of PV systems in Arab countries, there is an imperative to assess the current state of PV systems and their performance in the individual countries and to recommend options to address identified gaps.
This chapter presents Study Two’s methods and findings. The study was a cross-sectional mixed method study involving document review, interviews with key informants from the NPVC and the pharmaceutical industry, and a survey directed at the PV leadership in three Arab countries, namely Jordan, Oman, and Kuwait. Members of the NPVC and the pharmaceutical industry are both involved in carrying out the activities essential to the proper functioning of the PV system and therefore are crucial to understanding the strengths and challenges facing PV systems in their respective countries.

A version of this chapter is a paper entitled “Strengths and weaknesses of the pharmacovigilance systems in three Arab countries: a mixed-methods study using the WHO pharmacovigilance indicators” which has been published (open access) in International Journal of Environmental Research and Public Health. 2022, Volume 19, Issue 5, Article number 2518. Digital object identifier (DOI): https://doi.org/10.3390/ijerph19052518.(177)

5.2. Aim
This study aimed to explore and evaluate PV systems' structures, processes, and outcomes in three Arab countries, with differing levels of performance, to identify their areas of strength and weakness to inform recommendations, which will lead to the strengthening of their PV systems as well as those of other Arab and developing countries with nascent PV systems.

5.3. Methods
The methods presented here complement the methodology described in Chapter Three which provided the methodological justification and decisions of the mixed-methods design undertaken. The American Psychological Association (APA) Journal Article Reporting Standards for Mixed Methods Research(202) were used as a guide to describe the procedure of the methods and key decisions employed in this study.

5.3.1. Study Design
A mixed-methods research design to address this study's aim was employed. This study's design is underpinned by the WHO PV indicators(7). This was carried out using, document review, face-to-face semi-structured interviews, and a self-completion questionnaire.
5.3.2. Study Setting
Given that this programme of research is concerned with strengthening PV systems and policy implementation to facilitate the implementation of the guideline on GVP for Arab countries, it follows that along with Kuwait, other Arab countries be studied. It was deemed suitable to select two cases of Arab countries with higher-performing PV systems than that of Kuwait which, based on the results of Study One (Chapter Four), were similar to Kuwait in terms of geographical proximity and size, namely Jordan and Oman. Although Oman's PV system was not found to be among the highest performing PV systems in the Arab World, it represents an interesting case as it is considered a middle ground between Kuwait and Jordan in terms of its PV systems' performance level. The Arab countries in which this study and Study Three (Chapter Six) were set in possessed surface areas of 89,320; 309,500; and 17,820 km²(203) with total populations of 10,203,140; 5,106,622; and 4,270,563 persons respectively.(204)

5.3.3. Study participants identification, selection, sampling, and recruitment

5.3.3.1. Qualitative phase
Initially, the participants targeted for the interviews consisted of current or immediate past employees of the national medicines regulatory authority (NMRA) in the selected countries (namely Jordan Food and Drug Administration (JFDA), Oman Directorate General of Pharmaceutical Affairs and Drug Control (DGPA&DC), and Kuwait Drug and Food Control Administration (KDFCA)) with direct involvement in implementing the countries' PV policy.

During the early stages of the study, and in line with the flexibility of research design afforded by the qualitative approach(205), a decision was made to widen the inclusion criteria. This allowed for the inclusion of individuals who were either current or immediate past employees working in/for other stakeholder organisation(s) (e.g., different types of pharmaceutical companies) who were involved in the practice or implementation of the national PV policies in these countries. This decision came about during the initial data collection with participants from the NMRA in Jordan as it became evident that such individuals were also involved in the implementation of the national PV policies and/or guidelines. As such, it was concluded that these individuals would be able to provide
significant insights. This change was undertaken after obtaining approval to amend the study design.

The main inclusion criteria for participants in the study was having experience in the field of PV such as current or immediate past employees working in/for a stakeholder organisation(s) whose work involves the implementation of the national PV policies and/or guidelines including:

1. Current or immediate past employees within the three Arab countries' NMRAs/NPVCs responsible for carrying out PV activities on a routine basis.
2. Current or immediate past Head of Department/Team Leader in which PV activities are being carried out within the three Arab countries' NMRAs/NPVCs.
3. Current or immediate past policymakers, specifically those with a connection to the country’s PV or drug safety policies, e.g., the Director of the NMRA.
4. Current or immediate past employees working in/for different types of pharmaceutical companies e.g., Qualified Person for Pharmacovigilance (QPPV) operating within any of the three Arab countries.

A mixture of purposive and snowball sampling methods was employed to conduct qualitative interviews. Purposive sampling served as a means of identifying and selecting individuals who were considered to be especially knowledgeable about or experienced with the study's subject of enquiry.(206) Snowball sampling was used because the researcher required the knowledge of insiders to locate people for the study.(207) The sample size for the study consisted of the number of individuals that would be purposively sampled from the NMRA and other stakeholder organisations (primarily the pharmaceutical industry) in the three countries under investigation. Therefore, it was deemed appropriate that interviews be conducted with a sample of 12 to 20 individuals to achieve maximum variation sampling.(208) These figures are also indicated as those required to reach the point of data saturation.(209)

The PV leadership (whose names and contact details were obtained beforehand through contacting the WHO UMC and requesting the information) in each of the three countries acted as a gatekeeper with whom initial contact was made via e-mail. Each country's gatekeeper was responsible for contacting potential participants from the NMRA and the pharmaceutical industry. Participants wishing to participate in the
study contacted the researcher directly via his contact details provided in the invitation letter and PIS. Additional participants were recruited via referral from interviewees provided they satisfied the inclusion criteria.

5.3.3.2. Quantitative phase

Participants for the survey were the PV leadership identified as the official national contact for the WHO PIDM in the three countries.

Purposive sampling was employed for carrying out the survey. The NPVCs in the three study countries represented the sample population. The PV leadership in all three countries were contacted by email and invited to participate in the study.

5.3.4. Data collection

5.3.4.1. Qualitative phase

Documents reviewed were either electronic or paper-based published by the NPVC in each country. The documents reviewed from each country were available online either on the NMRA’s or UMC websites or were sought from the key informants or the PV leadership at each study site and included the following:

1- Jordan: PV law titled "The Pharmacovigilance Directives", guideline titled "Guidelines for Detecting & Reporting Adverse Drug Reactions - Individual Case Safety Reports for Healthcare Professionals", as well as online ADR and product quality reporting forms


3- Kuwait: Circulars issued by the NMRA directed at pharmaceutical companies regarding the PV reports required to be submitted to the NPVC based on the requirements set out in the Arab GVP guideline as well as the ADR and product quality reporting forms.

Interviews were conducted sequentially from April through December 2019, starting in Jordan, followed by Oman, and finally Kuwait. This sequential approach enabled the use of the insights gained from earlier in later interviews, and particularly to sense check potential recommendations in Kuwait, the least developed country with
regards to their pharmacovigilance systems. The interviews conducted for this study and Study Three (Chapter Six) were conducted as a single set of interviews.

The semi-structured interviews were conducted in English by the researcher with the participants individually on a face-to-face basis at their place of work or an agreed location (coffee shop/café). With participants’ consent (written and verbal), the interviews were audio-recorded using an encrypted digital audio recording device and were transferred and stored on a secure and encrypted computer network drive at the University of Manchester. Recorded interviews were transcribed verbatim independently by a University of Manchester approved transcribing company. Extensive field notes were taken during the interviews and participants also completed a pre-interview questionnaire capturing background information such as demographics (see Appendix XI). For interviewees declining audio-recording the interview, extensive written notes were taken.

The interview topic guide (Appendix XIII) consisted of two parts to address the aim of this study and that of Study Three (Chapter Six). The section of the interview guide pertaining to this study was informed primarily by the WHO PV indicators(7) and literature on PV in developing countries(8, 171, 210, 211) (see Chapter Six for information on interview topic guide section pertaining to Study Three). The section in the topic guide dedicated to this study focused on examining the key PV structures, systems, and mechanisms in the three countries with an enquiry of perceived system strengths and weaknesses. Proposed recommendations for strengthening PV systems in countries with nascent systems in addition to soliciting the views of Kuwait's participants' regarding implementing some of these recommendations.

5.3.4.2. Quantitative phase

Upon completion of interview data analysis, it was deemed necessary to collect additional empirical data to support the inference made from the data that the differences identified between Jordan, Oman, and Kuwait's PV systems reflect differences in the actual performance of these systems. To achieve this, it was decided that a questionnaire would be employed. The questionnaire used in this study was informed by the WHO PV indicators(7). It was deemed more appropriate to consider using a validated tool that had been previously used rather than
attempting to construct a new survey for use in this study. The choice of tool was
guided by the narrative literature review (Chapter Four) which aided in filtering the
available tools that could be used to achieve the aim of the study.

The survey focused on the "process" and "outcome" indicators which were divided
into two sections each covering the "core" and "complementary" sets of the
indicators as outlined in the WHO PV indicators manual.(7) The process indicators
assessed the PV activities in the PV centres by focusing on the processes that
describe the collection, collation, analysis, and evaluation of ADR reports. The
outcome indicators measured the extent of realisation of the countries' PV systems' objectives.(7)

The questionnaire (Appendix XIV) was distributed electronically via email as a
Microsoft Word document to the PV leadership in the three study countries between
July and November 2021 with monthly reminders in between. The PV leadership
were asked to complete the survey and return it to the researcher via email.

5.3.5. Data analysis

5.3.5.1. Qualitative phase
The documents reviewed along with the interview transcripts and field notes were
analysed by the researcher using the Framework Method. Analysis of documentary
and interview data was assisted using the software package NVivo®, which is used to
organise and analyse qualitative data(212). Both deductive and inductive approaches
were used to identify themes as they were linked to the data itself as well as fit
within the theoretical framework of the study.

Analysis of the qualitative data followed the five key stages involved in the
Framework Method, namely familiarisation, coding, identifying a thematic
framework, charting data into a matrix and interpreting the data.(213) The
familiarisation stage involved the researcher immersing himself in the collected data
thus becoming familiar with it. In this case, it entailed listening to the recorded audio
of the interviews as well as reading and re-reading the transcripts and any additional
notes recorded at the time. The second stage, coding, involved using the NVivo®
software to code all relevant data. Coding involved highlighting segments of text that
directly match the themes in the interview guide. The development of additional codes was
performed based on both 'open coding' (i.e. coding anything that might be relevant
from as many different perspectives as possible) as well as based on the themes in theories and concepts, i.e. the WHO PV indicators(7). The coded data from the interviews were then summarised in a matrix for each theme comprising of one row per participant and one column per code and inserted into corresponding cells in the matrix using Microsoft Excel®. Connections within categories were made and key similarities and differences were identified.

5.3.5.2. Quantitative phase

The quantitative data obtained via the questionnaire were absolute numbers, percentages, and rates, which were entered into Microsoft Excel® and calculated as determined by the relevant indicator. Scores were assigned to each category of indicators, which were then used to compare the countries based on their total performance score. Each indicator was scored separately, then a final score was calculated for each country based on the 63 indicators. For the structural indicators, scores of 1, 0.5, or 0 were given depending on whether the indicator was satisfied, partially satisfied, or did not satisfy the WHO's recommendations respectively. For the process and outcome indicators, a score of 1 was given if the answer provided was >0, otherwise, it was scored as 0. Where an indicator (structure, process, or outcome) is made up of subset indicators, the score of 1 was divided equally among each of the subset indicators (e.g., where the indicator is divided into subsets "a" and "b" each will be worth 0.5). The response data were tabulated and displayed as a radar chart to allow for visualisation of each country's PV system's performance.

5.3.5.3. Mixed methods phase

Data collected from the qualitative and quantitative phases will be merged in a convergent design. Integration through narrative using the weaving approach whereby both the qualitative and quantitative findings were interpreted and then reported on a theme-by-theme or concept-by-concept basis.(214)

5.3.6. Ethical approvals and considerations

Approval to conduct the study was obtained from UREC (Appendix I). The decision to widen the inclusion criteria to allow for the inclusion of individuals working in PV in different types of pharmaceutical companies made during data collection in Jordan was granted UREC approval via an amendment (Appendix II). UREC approval via amendment was also granted for the survey carried out as part of this
The senior management of the NMRAs in the three countries granted permission to conduct the study based on their standard protocol after receiving an e-mail with a letter requesting permission to conduct the study at their respective organisations (Appendices IV – VI). Copies of the approval letters issued by the NMRAs' senior management in these countries were submitted to UREC as part of the ethics application (Appendix VII – IX).

All prospective participants (interviews and survey) received a participation invitation letter (Appendix XV) and a participant information sheet (PIS) (Appendices XVI and XVII) containing details about the study such as the aim of the research, reasons for being selected, and what is required of them if they choose to participate. Once this was completed, they were given at least 24 hours to read the PIS and decide on participating in the study. This period also served as a means of providing them with time to enquire about any aspects of the study that they found to be unclear and/or in need of additional information. Those wishing to participate in the interviews portion of the study were provided on the day of the interview with a consent form (Appendix XVIII), which included a clause requesting their permission to be audio recorded that they were asked to complete and sign. With respect to the questionnaire, the completion and return of the questionnaire was taken as implied consent.

Participants’ confidentiality and anonymity were attained through the anonymisation of the interview transcripts by assigning participants an ID number as a means of concealing their identity and no personal information related to them was recorded. This ID number served throughout the study as a means of referring to the results obtained from the interview. Furthermore, direct quotes from participants used in the study were anonymised using these ID numbers to ensure they were not linkable to anyone who agreed to participate in the study.

As part of the study maintaining confidentiality, participants were requested not to mention names of colleagues, companies, or individuals that they interact with as part of their work during the interview. In the case that the name of any such persons was uttered, it was promptly removed from the interview audio data during transcription.
5.4. Results

A total of 56 participants were interviewed (n=17 in Jordan, n=16 in Oman, and n=23 in Kuwait). Interviews were conducted at the participants' place of work and lasted between 30 and 90 minutes. Only two participants (one in each of Oman and Kuwait) were not audio-recorded upon their request. In addition to the interviews with employees of the national PV centres and the pharmaceutical companies, two more were conducted with individuals from the regional PV centres in Jordan. The background information questionnaire completed prior to the interview (see Appendices XIX through XXI for complete results) identified 41 of the participants as female with ages ranging between 25 and 70 years. Participants were mostly pharmacists (n=48) and mainly employed by the pharmaceutical industry (n=38). Work experience in the field of PV for the sample was between one- and 17-years.

The questionnaires sent to the PV leadership requesting data on the process and outcome indicators were only completed by the NPVCs in Oman and Kuwait (but not Jordan). The following sections present the results obtained from the recorded interviews and the completed questionnaires. The study findings from the interviews and the survey were triangulated and presented in what follows as themes as informed by the WHO PV indicators. The key themes identified are outlined in Table 5.1. To illustrate the extent of each country’s participants' agreement regarding particular PV system strengths and weaknesses, the terms few (n ≤ 4 participants), some (n = 5 – 8 participants), many (n = 8 – 11 participants), and most (n ≥ 12 participants) are used.
Table 5.1. Themes and subthemes extracted based on the WHO PV indicators

<table>
<thead>
<tr>
<th>Themes/Subthemes</th>
<th>Core Indicators</th>
<th>Core Structural Indicators</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Core Indicators</td>
<td>Core Structural Indicators</td>
</tr>
<tr>
<td></td>
<td>Existence of a pharmacovigilance centre, department, or unit with a standard accommodation</td>
<td>Existence of a statutory provision (national policy, legislation) for pharmacovigilance</td>
</tr>
<tr>
<td></td>
<td>Existence of a medicines regulatory authority or agency</td>
<td>Existence of any regular financial provision (e.g., statutory budget) for the pharmacovigilance centre</td>
</tr>
<tr>
<td></td>
<td>The pharmacovigilance centre has human resources to carry out its functions properly</td>
<td>Incorporation of pharmacovigilance into the national curriculum of the various healthcare professions,</td>
</tr>
<tr>
<td></td>
<td>Existence of a national ADR or pharmacovigilance advisory committee or an expert committee in the setting capable of providing advice on medicine safety</td>
<td>Existence of a computerized case-report management system</td>
</tr>
<tr>
<td></td>
<td>Total number of ADR reports received in the previous calendar year also expressed as number of ADRs per 100,000 persons in the population</td>
<td>Complementary Indicators</td>
</tr>
<tr>
<td></td>
<td>Current total number of reports in the national database</td>
<td>Complementary Structural Indicators</td>
</tr>
<tr>
<td></td>
<td>Percentage of total annual reports satisfactorily completed and submitted to the national pharmacovigilance centre in the previous calendar year</td>
<td>Complementary Process Indicators</td>
</tr>
<tr>
<td></td>
<td>Number of signals detected in the past 5 years by the pharmacovigilance centre</td>
<td>Percentage of healthcare providers aware of and knowledgeable about ADRs per facility</td>
</tr>
<tr>
<td></td>
<td>Number of regulatory actions taken in the preceding year as a consequence of national pharmacovigilance activities</td>
<td>Percentage of patients leaving a health facility aware of ADRs in general</td>
</tr>
<tr>
<td></td>
<td>Core Outcome/Impact Indicators</td>
<td>Number of face-to-face training sessions in pharmacovigilance organized in the previous year for:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>a. health professionals</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b. the general public</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Number of individuals who received face-to-face training in pharmacovigilance in the previous year:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>a. healthcare professionals</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b. the general public</td>
</tr>
<tr>
<td></td>
<td>Complementary Outcome/Impact Indicators</td>
<td>Complementary Outcome/Impact Indicators</td>
</tr>
<tr>
<td></td>
<td>Number of preventable ADRs reported in the previous year out of the total number of ADRs reported</td>
<td>Percentage of preventable ADRs reported in the previous year out of the total number of ADRs reported</td>
</tr>
<tr>
<td></td>
<td>Number of medicines-related congenital malformations per 100,000 births</td>
<td>Number of medicines-related congenital malformations per 100,000 births</td>
</tr>
<tr>
<td></td>
<td>Number of medicines found to be possibly associated with congenital malformations in the past 5 years</td>
<td>Number of medicines found to be possibly associated with congenital malformations in the past 5 years</td>
</tr>
</tbody>
</table>
5.4.1. Overall performance

The three countries' PV systems were evaluated for the 63 WHO PV indicators which contain 27 "Core" and 36 "Complementary" indicators. The PV systems of Jordan, Oman, and Kuwait achieved aggregate scores of 8, 11, and 11 respectively for the "Core" indicators and 9, 18, and 7 respectively for the "Complementary" indicators. The "Process" and "Outcome" indicators for Jordan which were not supplied were scored as 0. A complete breakdown of the total scores according to each group of indicators is provided as a visual representation in Figure 5.1.

![Figure 5.1. Six-axis radar diagram showing Jordan, Oman, and Kuwait’s pharmacovigilance systems' scores for the six main categories of WHO PV indicators.](image)

5.4.2. Core indicators

5.4.2.1. Core structural indicators

Existence of a pharmacovigilance centre

The WHO indicates that a prerequisite of a functional PV system is the presence of a dedicated space (i.e., a centre, department, or unit) for PV activity, which is officially recognised and/or accredited by the country's ministry of health (MOH). Despite all three countries possessing a department or unit with a standard accommodation for conducting PV activities, only in Kuwait was the PV centre not officially recognised by the country's MOH and hence operated as an unofficial unit (sub-section) of the NMRA's Drug Registration Department. A few NPVC and industry participants in Jordan and Oman pointed to their countries' PV centres'
official recognition as a strength because it gave the NPVC increased visibility and significance. See Table 5.2 for a summary of the results for this group of indicators.

"This [the establishment of an official PV department as a strength] is because it was a section of a department before, therefore was not that much importance placed on the section in terms of the reports received and increasing their numbers." (Participant 1, NPVC, Oman)

Some NPVC and industry participants from Kuwait believed that their system's lack of a dedicated and officially recognised NPVC represented a weakness because it resulted in a lack of authority and autonomy and prevented the system from being fully functional. It also meant that the country lacked an official reference point for PV which stakeholders could interact with.

"The lack of a dedicated PV department is a weakness... the dedicated department is very important to act on a legal basis with proper staff, with proper infrastructure, with proper independent decisions, to have the full structure, full capacity to work with a proper PV system." (Participant 17, NPVC, Kuwait)

A few members of Jordan's NPVC and the regional PV centres believed that the NPVC's affiliation with the NMRA was both a point of strength in some respects and a point of weakness in others. The affiliation was considered a strength due to the NPVC's ability to take advantage of the NMRA's extended reach and authority. However, the NPVC's dependence on the JFDA meant that it lacked autonomy in its decision making which prevented it from fully and adequately carrying out its functions.

"Being part of the regulatory body is good for PV in that you have the tools, you have the law, you can go see patient files, do further investigations within the hospitals. That's why I think it's our strength to be part of the regulatory body." (Participant 7, NPVC, Jordan)

There was a consensus among Kuwait's participants that having an independent NPVC would be the ideal scenario. However, this was envisioned as a long-term goal rather than a short-term solution. In the short to medium term, it was perceived as more beneficial if PV remained under the umbrella of the authority as a stand-alone department separate from drug registration. A few participants from Kuwait's
NPVC believed that establishing an NPVC as an independent entity was difficult due to the costs involved which made it unlikely to receive approval by decision-makers.

“In a country like ours, to get a centre approved, get the budget, financially that means there’s a lot of employees to have a centre. And the whole idea, to sell it to a minister at the Ministry of Health, to propose that idea, that would cost a lot of money and a lot of time. People don’t want that, you know? Especially as we have such a small population.” (Participant 1, NPVC, Kuwait)

Only interviewees from Jordan and Oman noted the existence of regional PV centres/departments as part of their PV systems. A few NPVC participants from Jordan and Oman and a few from Jordan's regional PV centres cited their presence as part of their countries' PV systems as a strength as they reduced the workload placed on the NPVC by acting as hubs for collecting ADR reports, carrying out training for HCPs, and drug safety information dissemination in their regions.

"So, they [the regional PV centres] are in governmental hospitals, and they are important because they act as facilitators to information regarding issues such as quality or safety reports made by patients or healthcare providers.” (Participant 1, NPVC, Jordan)

A few of the regional PV centre participants from Jordan cited the regional PV centres' lack of interconnectivity and therefore a lack of information sharing amongst them, a lack of authority to take action concerning ADR reports received and performing PV inspections as challenges facing the system.

"...the peripheral centres at moment are run by individuals, and because we don’t do a full-time job this means we rely on the JFDA. Having independence means that I can do my own training, have my own infrastructure, develop my own system, and tailor a system that is more appropriate for my institute rather than following the guidelines, or the forms or the regulations, or even the system of the JFDA, which is highly bureaucratic.” (Participant 4, regional PV centre, Jordan)

It was noted from participants from both sectors in the three countries that the PV systems in Jordan and Oman were established earlier than Kuwait's (1992 in Oman, 2001 in Jordan, and 2008 in Kuwait). In addition, the centres in both Oman and Jordan obtained full membership in the WHO Program for International Drug Monitoring (PIDM) since 1995 and 2002 respectively. In contrast, Kuwait only
obtained full membership in 2021. A few NPVC and industry participants in Jordan cited the NPVC’s early establishment as a strength of the PV system in the country as it contributed to its employees gaining a wealth of knowledge and experience in PV over time compared to those in other countries in the region.

"[The] first [strength of the pharmacovigilance system] is the early establishment of the pharmacovigilance department within the JFDA, which was in 2001. Therefore, we have a good deal of knowledge and experience in pharmacovigilance." (Participant 6, NPVC, Jordan)

A few participants from Jordan’s NPVC and regional PV centres noted the significance of being a member of the WHO Program for International Drug Monitoring (PIDM) due to what it entails in terms of the support obtained from the WHO. This included assistance in the initial establishment of the PV system through staff training and providing low-cost IT solutions e.g., a national ADR database. Another benefit of membership in WHO’s PIDM was access to VigiBase which has a wealth of international ADR data that could be used for comparison purposes.

"[A] Major contribution of being a member in the WHO, [is] having the IT system because we cannot develop our own IT system. So, this is something very helpful to have the VigiFlow, VigiBase assist you doing data mining, doing signal generation, organising your database, it’s costly if you want to generate your own database, which is a very important thing in pharmacovigilance to have and maintain the database, the ICSR database." (Participant 7, NPVC, Jordan)

Setting up a PV system with a proper structural framework was among the recommendations put forward by a few NPVC participants in Jordan and Oman as well as a few from the industry in Oman. The system was envisioned to include relevant departments (sections) within the NPVC as well as regional branches across the country.

"...from our experience here in Jordan, as I said you need a national centre, and after that, if you have peripheral centres, or you can have like a pharmacovigilance committee in each hospital so that they can liaise and communicate with the staff [at the national centre]." (Participant 3, regional PV centre, Jordan)
Table 5.2. Comparison of Core Structural WHO pharmacovigilance indicators' performance in Jordan, Oman, and Kuwait

<table>
<thead>
<tr>
<th>Indicator item</th>
<th>Assessment</th>
<th>Jordan</th>
<th>Oman</th>
<th>Kuwait</th>
</tr>
</thead>
<tbody>
<tr>
<td>CST1</td>
<td>Existence of a pharmacovigilance centre, department, or unit with a standard accommodation</td>
<td>Rational Drug Use and Pharmacovigilance Department</td>
<td>Department of Pharmacovigilance and Drug Information</td>
<td>Quality Assurance Unit – not officially recognised</td>
</tr>
<tr>
<td>CST2</td>
<td>Existence of a statutory provision (national policy, legislation) for pharmacovigilance</td>
<td>Law titled &quot;The Pharmacovigilance Directives&quot;</td>
<td>Only &quot;Guideline on GVP in Oman&quot;</td>
<td>Only memos issued to companies</td>
</tr>
<tr>
<td>CST3</td>
<td>Existence of a medicines regulatory authority or agency</td>
<td>Jordan Food and Drug Administration (JFDA)</td>
<td>Directorate General of Pharmaceutical Affairs and Drug Control (DGPA&amp;DC)</td>
<td>Kuwait Drug and Food Control Administration (KDFCA)</td>
</tr>
<tr>
<td>CST4</td>
<td>Existence of any regular financial provision (e.g. statutory budget) for the pharmacovigilance centre</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>CST5</td>
<td>The pharmacovigilance centre has human resources to carry out its functions properly</td>
<td>5 full-time employees</td>
<td>5 full-time employees</td>
<td>5 full-time and 1 part-time employee</td>
</tr>
<tr>
<td>CST6</td>
<td>Existence of a standard ADR reporting form in the setting</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>CST6a</td>
<td>Availability of relevant fields in standard ADR reporting form to report medication errors</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>CST6b</td>
<td>Availability of relevant fields in standard ADR reporting form to report suspected counterfeit/substandard medicines</td>
<td>Separate form</td>
<td>Yes</td>
<td>Separate form</td>
</tr>
<tr>
<td>CST6c</td>
<td>Availability of relevant fields in standard ADR reporting form to report therapeutic ineffectiveness</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>CST6d – Availability of relevant fields in standard ADR reporting form to report suspected misuse, abuse and/or dependence on medicines</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>CST6e – Availability of a standard ADR reporting form for the general public</td>
<td>Same form as for HCPs</td>
<td>Same form as for HCPs</td>
<td>Same form as for HCPs</td>
<td></td>
</tr>
<tr>
<td>CST7 – Existence of a process in place for collection, recording, and analysis of ADR reports</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>CST8 – Incorporation of pharmacovigilance into the national curriculum of the various healthcare professions</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>CST8a – Medical doctors</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>CST8b – Dentists</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>CST8c – Pharmacists</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>CST8d – Nurses or midwives</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>CST8e – Others – to be specified</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>CST9 – Existence of a newsletter, information bulletin and/or website as a tool for dissemination of information on pharmacovigilance</td>
<td>Newsletter and website</td>
<td>No</td>
<td>Newsletter</td>
<td></td>
</tr>
<tr>
<td>CST10 – Existence of a national ADR or pharmacovigilance advisory committee or an expert committee in the setting capable of providing advice on medicine safety</td>
<td>Health Hazard Evaluation Committee</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>
Participants from both sectors in Kuwait expressed their support for the idea of establishing regional PV centres within the different healthcare institutions (i.e. hospitals and clinics) across the country. This stemmed from the view that such a system would offer more control over the reporting process.

"At the government level, government hospitals, it's very easy for them to assign a person or some department ... internally and he communicates and passes on this information all safety-related [sic] to the authorities. And there can be some kind of instructions or circular for the private hospitals that they can bind them that they should have an assigned person to collect from the hospital the data and transfer to the KDFC." (Participant 7, pharmaceutical industry, Kuwait)

Existence of a statutory provision (national policy, legislation) for pharmacovigilance
An important element of a PV system is the existence of an authoritative instrument, e.g., a national policy document or a legislative provision enacted by the appropriate arm of government to support PV activities. Only Jordan's system possessed legislation for PV. A few participants from the Jordanian NPVC referred to the presence of a legal statute for PV as a strength of the system, which provided them with the necessary tools to monitor and enforce the implementation process across all stakeholders.

"If you have the law, you have the power to enforce your vision. So, the law is with you, and you can then monitor the implementation of pharmacovigilance tasks whether in the local manufacturer agents or healthcare providers." (Participant 7, NPVC, Jordan)

A few participants from Kuwait's NPVC and pharmaceutical industry believed that the lack of a PV legal framework was a shortcoming as it meant that PV activities were undertaken without legal backing thus preventing members of the NPVC from forcing companies to comply with decisions on PV e.g. performing a leaflet change. Interestingly, none of Oman's participants mentioned the absence of a statutory provision as a weakness as part of the discussion on system strengths and weaknesses.

"...we feel tied up with the fact that we haven't got a legal framework, so that's a big weakness... the activities are being carried out, but the activities are being carried out with no
A few participants from Kuwait's NPVC and Jordan's pharmaceutical industry recommended the establishment of a statutory provision for PV. This was seen as essential for ensuring that all PV activities performed in the country by the various stakeholders were based on a legal framework. Kuwait's NPVC participants and many from the industry were supportive of the idea of passing a law for PV indicating that having a law would provide support decisions taken by the authority.

“...you need to be supported, you need a legal framework, a legal backup for your decisions because, at the end of the day, you are dealing with a market, you're dealing with patients, and you're dealing with the healthcare system, so definitely you need a legal framework, a law to support you.” (Participant 17, NPVC, Kuwait)

In contrast, a few industry participants questioned the benefit of such a law given that most companies were already mindful of ensuring that they were compliant with pharmacovigilance issues (e.g. ADR reporting) as they were concerned for their reputations.

“The companies are already mindful of reporting any issue. They are already afraid for their reputations in the market and so don’t want any problem to occur, so they are careful to report any safety issue relating to their products to the ministry. I don’t know what a law would do.” (Participant 12, pharmaceutical industry, Kuwait)

Existence of a medicines regulatory authority or agency

A country's medicines regulatory authority or agency acts as an important stakeholder and focal point for promoting PV. Jordan's NMRA was the only one that was independent of the country's MOH. A few participants from the industry in Jordan cited the NMRA's autonomy in decision-making and authority in dealing with pharmaceutical companies as a strength of the PV system.

"The fact that the drug authority and the PV centre are separate from the MOH is, in my opinion, a strength. ... A drug authority, which is an entity that gives and takes back the marketing authorisation, are controlling the industry through this, so if you don't report, and you don't have a system, and you are not compliant with regulations, we have the authority to withdraw your marketing licence. The MOH does not have this authority.” (Participant 14, pharmaceutical industry, Jordan)
**Existence of any regular financial provision (e.g., statutory budget) for the pharmacovigilance centre**

Availability of a regular and sustained funding source is necessary for running a PV system. All three countries lacked a dedicated PV budget, thus financial resources were obtained through the NMRA's (Jordan) or the MOH's (Oman and Kuwait) budget. However, only a few participants from the NPVC, regional PV centres, and PI in Jordan commented on this issue as hindering activities such as training workshops for healthcare providers (HCPs) or awareness-raising campaigns. Hence, there was a reliance on obtaining funding from outside sources.

"...we don't have a budget for things like printing materials, conducting training outside. When you perform training outside you need coverage to sponsor the event, to provide meals for those attending. We don't have a budget here at the Jordan Food and Drug Administration (JFDA) for our department for these activities. So, you need sponsors from outside to implement these things." (Participant 2, NPVC, Jordan)

**Existence of human resources to carry out pharmacovigilance functions**

A PV system needs trained staff based on the expected total full-time equivalents required to enable the PV centre to fulfil all its essential duties and responsibilities. All three countries' PV systems were similar in terms of the number of staff working at the NPVC. The three countries' NPVC members and a few industry participants, as well as a few participants from Jordan's regional PV centres, agreed that staff shortages were a weakness. This caused delays in work that must be done regularly or on a scheduled basis, e.g. entering ADR reports in the national database, review of PV reports i.e. periodic safety update report (PSUR) and risk management plan (RMP), or publication of a bulletin/newsletter for PV information dissemination.

"It's [the lack of staff] affecting our work in that we have many PV activities to do, for example, we have to enter reports onto the VigiFlow, which should be done regularly, but is not. So, once we have time then we are entering our reports into VigiFlow. So, this is affecting our implementation, for example, we should by now have completed the inspection on all companies and all drug stores, but we have not. There is also training and awareness campaigns, which is not being done according to the scheduled program." (Participant 2, NPVC, Jordan)
"This [staff shortage] is the major factor, because for example when you want to study a PSUR you need teamwork to be able to do this quickly. The files for the PSUR are large. One person cannot review every file for every medicine. Also, we are receiving PSURs every six months for every medicine." (Participant 1, NPVC, Oman)

A few of Jordan's and Oman's NPVC and industry participants pointed to the scarcity of individuals with PV expertise and staff turnover due to the large workload that came with working in PV which exacerbated this problem. This, in turn, meant a loss of continuity in terms of the team members working in the department in addition to the loss of time and effort spent in training them.

"...the turnover of staff between the departments also, it is a weakness that we spend time and money to do training for [a] certain individual and then he will go to another department.” (Participant 7, NPVC, Jordan)

A few participants from both the NPVC and industry in all three countries recommended that more personnel possessing prior training in PV be recruited both within the NPVC itself and within the regional centres as focal points to augment the existing NPVC staff to help cope with the workload.

"... [A recommendation would be to hire] more pharmacists [who] are properly and adequately trained from the start and have a plan in place in order to have a number of them in place as a focal point. Having in place nominated individuals who are prepared specifically for the purpose of working within the PV centres." (Participant 10, pharmaceutical industry, Oman)

**Incorporation of pharmacovigilance into the national curriculum of the various healthcare professions**

Oman was the only country where PV was incorporated into the national curriculum of HCPs (pharmacists and nurses), though none of the participants from the country commented on this issue as part of the discussion on system strengths and weaknesses. Contrastingly, a few industry participants from Jordan and Kuwait believed that PV's lack of incorporation into HCPs curriculums was contributing to a lack of knowledge and awareness regarding ADR reporting among health workers and as such was a shortcoming of their respective countries' PV systems.
"...in other countries, HCPs' awareness is very high. It is part of their education in the universities. Here, it's not implemented yet, so the HCPs, they are shaky, shall we inform or not? How to report? When to report? What to report? Still, their awareness and the level of education... [has] not reached the level of other people [in other countries], so it's still not high. The awareness level is not high." (Participant 13, pharmaceutical industry, Kuwait)

A few industry participants from Jordan and Kuwait opined that PV be taught at the undergraduate level to future HCPs as a means of building their capabilities and capacities starting from the foundational level.

"...we will need young blood, a new generation that is trained. And this will give them job opportunities because today there is no going back in pharmacovigilance we only want to move forward. There isn’t a company that is established that doesn’t have pharmacovigilance. They will hire people. Where will they hire these people from? You have to build these capabilities and competencies and we have to start from the universities." (Participant 15, pharmaceutical industry, Jordan)

Existence of a national ADR or pharmacovigilance advisory committee or an expert committee in the setting capable of providing advice on medicine safety

The WHO PV indicators include the existence of a qualified committee that can provide advice and technical assistance as an important component of the PV system. Only Jordan had a PV advisory committee consisting of HCPs representing different sectors known as the Health Hazard Evaluation Committee. A few members of Jordan's NPVC and regional PV centres viewed the presence of this committee, which provided advice to the NPVC based on its members' varied expertise as a strength.

"Another positive is the presence of the Health Hazard Committee, which has benefitted us a lot since it is composed of individuals representing different sectors and from different healthcare professions." (Participant 6, NPVC, Jordan)

In comparison, a few members of Oman's NPVC viewed the absence of such an advisory committee from their system as a weakness.

"...I always think that we [the NPVC] are sitting in a remote position and we are not in the practising side... we are not able to find out whether it is the prejudice among the healthcare professionals or the patients that they say it is ineffectiveness, or
whether it is actual ineffectiveness which is happening.”
(Participant 5, NPVC, Oman)

The issue of creating a national PV advisory committee was viewed positively by interviewees from both the NPVC and the pharmaceutical industry in Kuwait. However, there were differences in opinion concerning the representation of the pharmaceutical industry on the committee. Participants from the NPVC along with a few from the pharmaceutical industry were opposed to the idea primarily based on the potential conflict of interest that may arise either when a product in question belongs to a company that is represented in the committee or when the product is from a competitor. Adding to this was the difficulty of selecting a single individual that would be able to represent the interests of the multitude of existing companies.

"I think that the companies shouldn't be involved in this [being part of a national PV advisory committee] because it should be someone neutral.” (Participant 5, pharmaceutical industry, Kuwait)

On the other hand, industry participants favouring pharmaceutical companies' membership in the advisory committee pointed to companies' knowledge and experience that can serve as a valuable contribution in any discussion.

"These big companies have experience in other regions, so they can contribute new ideas and perspectives. I think it would be helpful [if they were part of a national PV advisory committee].” (Participant 20, pharmaceutical industry, Kuwait)

5.4.2.2. Core process indicators

Number of ADR reports received in the previous year and current total number of reports in the national database

The WHO identifies the number of ADR reports received annually as one of the measures of the PV system's activity. The volume of reports generated within the population in Oman was higher than in Kuwait (31.88 versus 16.58 reports/100,000 population respectively). Similarly, the WHO's guidance refers to the number of cumulative reports in the national ADR database since its inception as another measure of system activity. Oman's NPVC had collected more ADR reports since the PV systems' inception than Kuwait's (19,731 versus 890 reports respectively). A few NPVC and regional centre participants in Jordan and the NPVC in Kuwait in addition to some industry participants from Jordan all cited low ADR-reporting rates
as a weakness in their PV systems. Interestingly, a few industry participants from Oman mentioned that this was a problem mainly within the private healthcare sector. Low ADR reporting rates prevented the NPVCs from obtaining a clear view of ADR prevalence in the country and hindered making locally relevant drug safety decisions. Participants cited multiple reasons for the low ADR reporting including poor knowledge, awareness, and/or attitude of reporters towards PV, and lack of mandatory HCP reporting legislation. See Table 5.3 for a summary of the results for this group of indicators.

"Although HCPs may encounter patients with ADRs, some of them don't know that [they have encountered an ADR], or some of them don't know that they have to report it, or that it's important to report it. So, I think that one weakness is that not all HCPs report ADRs." (Participant 3, regional PV centre, Jordan)

A few NPVC and industry participants from Jordan as well as a few from Kuwait's NPVC and some from the industry believed that HCPs' under-reporting stemmed from the absence of mandatory reporting requirements and a lack of action by the country's health authorities concerning this issue. Therefore, among their suggested recommendations was the need to establish governmental rules and regulations directed for HCPs mandating ADR reporting as was the case for pharmaceutical companies.

"I think they [the authority] have to make it [HCP’s ADR reporting] something similar to the companies in how they obligate us to report. They must obligate physicians to report. Maybe it’s [the obligation to report] something from the association [of physicians] or the Ministry of Health that any physician that wants to renew his/her license to have a certain number of reports, so pharmacovigilance becomes part of the physician's professional practice." (Participant 10, pharmaceutical industry, Jordan)

Kuwait's participants' opinions regarding obligatory HCP ADR reporting as was the case for pharmaceutical companies as a solution to the problem of ADR under-reporting was mostly divided along the private-public lines. Those in favour were mostly from the pharmaceutical industry, while those against it were mostly from the NPVC. Those in support of the idea believed that HCPs were unwilling to report unless it was mandatory with non-compliance entailing punishment.
“If it’s [the solution for under-reporting] only increasing awareness no one will respond, but when it is made obligatory, all physicians will respond and even the patients themselves will be happy with such a decision as it would represent a type of protection for them.” (Participant 6, pharmaceutical industry, Kuwait)

In comparison, a few interviewees from the NPVC and the industry in Kuwait believed that HCPs’ willingness to perform this task should stem from the desire to ensure patient safety and that such a rule could only be put in place if HCPs were better prepared in terms of awareness and training.

“...if they [healthcare professionals] feel that we are helping them and they are helping us, there is mutual benefit, I believe this is much better than making it obligatory.” (Participant 17, NPVC, Kuwait)

**Percentage of total annual reports satisfactorily completed and submitted in the previous year (2020)**

Oman had a higher percentage of satisfactorily completed ADR reports submitted to their NPVC compared to Kuwait (84.3% versus 58.9% respectively), and unlike in Kuwait, these reports were submitted to WHO's VigiBase. When asked about their views on the strengths and weaknesses of the PV system, a few members of Jordan's regional PV centres and Kuwait's NPVCs cited poor quality of ADR reports as a weakness and thus a significant proportion of the ADR reports received were of little value.

"Even though we have 1000 reports, I believe that 70-80% of them are of poor quality. And I know that in one year I provided the PV centre with more than 160 reports, and I later found out that only 40 of them were very useful. ...But unfortunately, we never worked on the reports in terms of their quality, we never did statistics on the reports, we don't know what the gap is, what is the problem with our reports, why are our reports not of good quality.” (Participant 4, regional PV centre, Jordan)
Table 5.3. Comparison of Core Process WHO pharmacovigilance indicators' performance in Oman and Kuwait

<table>
<thead>
<tr>
<th>Indicator item</th>
<th>Assessment</th>
<th>Oman</th>
<th>Kuwait</th>
</tr>
</thead>
<tbody>
<tr>
<td>CP1</td>
<td>Total number of ADR reports in the previous year (2020)</td>
<td>1,628</td>
<td>708</td>
</tr>
<tr>
<td></td>
<td>CP1a – Total number of ADR reports received in the previous year per (2020) 100,000 people in the population</td>
<td>31.88*</td>
<td>16.58*</td>
</tr>
<tr>
<td>CP2</td>
<td>Current total number of reports in the national database</td>
<td>19,731</td>
<td>890†</td>
</tr>
<tr>
<td></td>
<td>CP3 Percentage of total annual reports acknowledged and/or issued feedback</td>
<td>N/A</td>
<td>100%</td>
</tr>
<tr>
<td>CP4</td>
<td>Percentage of total reports subjected to causality assessment in the previous year (2020)</td>
<td>N/A</td>
<td>58.9%</td>
</tr>
<tr>
<td>CP5</td>
<td>Percentage of total annual reports satisfactorily completed and submitted to the NPVC in the previous year (2020)</td>
<td>84.3%</td>
<td>58.9%</td>
</tr>
<tr>
<td></td>
<td>CP5a – Of the reports satisfactorily completed and submitted to the NPVC, percentage of reports committed to the WHO database</td>
<td>84.3%</td>
<td>N/A</td>
</tr>
<tr>
<td>CP6</td>
<td>Percentage of reports of therapeutic ineffectiveness received in the previous year (2020)</td>
<td>0.80%</td>
<td>N/A</td>
</tr>
<tr>
<td>CP7</td>
<td>Percentage of reports on medication errors reported in the previous year (2020)</td>
<td>4.4%</td>
<td>N/A</td>
</tr>
<tr>
<td>CP8</td>
<td>Percentage of registered pharmaceutical companies that have a functional pharmacovigilance system</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>CP9</td>
<td>Number of active surveillance activities that are or were initiated, ongoing, or completed in the past 5 years</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

N/A Indicates data not available
*Calculated using World Bank country total population data for the year 2020
†Figures based on data entry from 3rd quarter of 2019, prior data lost.

5.4.2.3. Core outcome indicators

Number of signals detected in the past 5 years

According to the WHO, the PV system's ability to detect signals indicates its capability of ensuring drug safety. Neither Oman's nor Kuwait's NPVC had detected any signals during the past five years (Table 5.4). Interestingly, none of the participants in these two countries cited this issue as being a weakness of their respective countries' PV systems. However, a few participants from Jordan's NPVC, regional PV centres, and PI pointed out that the inability to detect signals arising from the data obtained through local ADR reporting was a weakness of the system.
The lack of signal detection hampered drug safety decision-making and was attributed to the low quantity and quality of submitted ADR reports.

“One of the reasons [for the deficiency in signal detection] is that we don’t have enough data, quality data, and the people at the PV centre focus on collecting the reports without taking it for a further step of analysis and investigation. I think this as well is an issue that our industry has because it is not only the duty of the healthcare system or the health authorities but also one of the responsibilities of the MAH.” (Participant 4, regional PV centre, Jordan)

**Number of regulatory actions taken in the preceding year (2020) consequent to NPVC activities**

The WHO points out that the number of regulatory actions taken by the NPVC provides a measure of regulatory decisions made, based on PV activities, to ensure drug safety. Although regulatory actions exclusively based on local PV data were not taken by the NPVCs in both Oman and Kuwait. The PV leadership in Oman noted that regulatory actions had been taken based on a combination of local and other countries' data. A few participants from Kuwait's NPVC cited this issue as weakness of the system when discussing the problem of low ADR reporting rates.

"...we need more reporting to have our own decision-making process based on our own data in Kuwait. We don't want to depend on international data. We need to depend on our own data to take into consideration our lifestyle, our raised diet, concurrent medications, morbidity and so on...." (Participant 17, NPVC, Kuwait)
Table 5.4. Comparison of Core Outcome WHO pharmacovigilance indicators’ performance in Oman and Kuwait

<table>
<thead>
<tr>
<th>Indicator item</th>
<th>Assessment</th>
<th>Oman</th>
<th>Kuwait</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO1</td>
<td>Number of signals detected in the past 5 years by the NPVC</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CO2</td>
<td>Number of regulatory actions taken in the preceding year (2020) consequent to NPVC activities</td>
<td>2*</td>
<td>N/A†</td>
</tr>
<tr>
<td>CO2a</td>
<td>Product label changes (variation)</td>
<td>–</td>
<td>N/A</td>
</tr>
<tr>
<td>CO2b</td>
<td>Safety warnings on medicines</td>
<td>–</td>
<td>N/A</td>
</tr>
<tr>
<td>CO2b(i)</td>
<td>– to health professionals</td>
<td>–</td>
<td>N/A</td>
</tr>
<tr>
<td>CO2b(ii)</td>
<td>– to the general public</td>
<td>–</td>
<td>N/A</td>
</tr>
<tr>
<td>CO2c</td>
<td>Drug withdrawals</td>
<td>–</td>
<td>N/A</td>
</tr>
<tr>
<td>CO2d</td>
<td>Other restrictions on the use of medicines</td>
<td>–</td>
<td>N/A</td>
</tr>
<tr>
<td>CO3</td>
<td>Number of medicine-related hospital admissions per 1,000 admissions</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>CO4</td>
<td>Number of medicine-related deaths per 1,000 persons served by the hospital per year</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>CO5</td>
<td>Number of medicine-related deaths per 100,000 persons in the population</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>CO6</td>
<td>Average cost (US$) of treatment of medicine-related illness</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>CO7</td>
<td>Average duration (days) of medicine-related extension of hospital stay</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>CO8</td>
<td>Average cost (US$) of medicine-related hospitalisation</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

– Indicates data not provided
N/A Indicates data not available
*Based on a combination of local and external data
†Indicated in interviews that actions taken based on a combination of local and external data

5.4.3. Complementary indicators

5.4.3.1. Complementary structural indicators

Existence of a computerised case-report management system

A few NPVC interviewees from Jordan and Oman cited their centres’ use of the WHO-provided case-report management system VigiFlow as a strength because it provided them with a database for report management and storage as well as performing statistical analysis. Table 5.5 provides a summary of the results for this group of indicators.

"We have VigiFlow, not all countries have VigiFlow. This means that we have a system. We know where to enter our data, we carry out statistical analysis." (Participant 10, NPVC, Oman)
In comparison, interviewees in Kuwait indicated that the NPVC did not have access to a computerised case-report management system, which hindered their ability to adequately analyse local data.

"...the IT system [is a weakness], it's very important for our work to get a proper database and to have a system such as the VigiFlow or the VigiLyze and VigiBase to help get a broader vision of the different cases worldwide. For signal detection, it's very important to have a system as well, to help get the proper signal as quickly as possible and as efficiently as possible."

(Participant 17, NPVC, Kuwait)

A related challenge cited by a few industry participants in Kuwait was the NPVC's reliance, for the most part, on a manual system for managing PV reports and correspondence. This was viewed as time-consuming and inefficient given the amount and frequency with which documents had to be submitted thus resulting in delays.

"...things here [in Kuwait] are manual. In other countries they send, they receive electronically and receive confirmation that it has been submitted. Based on the large number of reports we receive from our principals this is very difficult for us."

(Participant 7, pharmaceutical industry, Kuwait)

In contrast, some industry participants from the three countries, a few NPVC participants from Jordan and Kuwait, and a few participants from Jordan's regional PV centres mentioned a lack of awareness regarding PV among both HCPs and the public as a weakness. Participants further believed this to be one of the main reasons for the low ADR reporting rate.

"...the awareness campaigns are still not strong enough. We don't hear in Kuwait, I didn't hear that there is a committee for PV or an awareness campaign, to increase awareness of the patients."

(Participant 13, pharmaceutical industry, Kuwait)
Table 5.5. Comparison of Complementary Structural WHO pharmacovigilance indicators’ performance in Jordan, Oman, and Kuwait

<table>
<thead>
<tr>
<th>Indicator item</th>
<th>Assessment</th>
<th>Jordan</th>
<th>Oman</th>
<th>Kuwait</th>
</tr>
</thead>
<tbody>
<tr>
<td>ST1</td>
<td>Existence of a dedicated computer for pharmacovigilance activities</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>ST2</td>
<td>Existence of a source of data on consumption and prescription of medicines</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>ST3</td>
<td>Existence of functioning and accessible communication facilities in the NPVC</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>ST4</td>
<td>Existence of a library or other reference source for drug safety information</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>ST5</td>
<td>Existence of a computerised case-report management system</td>
<td>VigiFlow</td>
<td>VigiFlow</td>
<td>No</td>
</tr>
<tr>
<td>ST6</td>
<td>Existence of a programme (including a laboratory) for monitoring the quality of pharmaceutical products</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>ST6a</td>
<td>The programme (including a laboratory) for monitoring the quality of pharmaceutical products collaborates with the pharmacovigilance programme</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>ST7</td>
<td>Existence of an essential medicines list which is in use</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>ST8</td>
<td>Systematic consideration of pharmacovigilance data when developing the main standard treatment guidelines</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>ST9</td>
<td>The pharmacovigilance centre organises training courses for:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ST9a</td>
<td>HCPs</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>ST9b</td>
<td>the general public</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>ST10</td>
<td>Availability of web-based pharmacovigilance training tools for:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ST10a</td>
<td>HCPs</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>ST10b</td>
<td>the general public</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>ST11</td>
<td>Existence of requirements mandating MAHs to submit PSURs</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>
5.4.3.2. Complementary process indicators

*Percentage healthcare providers and patients aware of and knowledgeable about ADRs and number of training sessions organised in the previous year (2020)*

Neither Oman nor Kuwait possessed data on HCPs' and patients' awareness levels. Oman's NPVC had organised more PV training sessions for HCPs and therefore trained more individuals compared to Kuwait's. However, neither country's NPVC had organised training sessions for the public. A few participants from Oman's NPVC and industry believed that HCPs' increased levels of PV awareness was a point of strength which contributed to improved ADR reporting. This observation was attributed, in part, to the NPVC's continuous efforts to increase awareness levels. Table 5.6 provides a summary of the results for this group of indicators.

"A point of strength is that there is now awareness. I feel the first step that we took was to increase awareness of HCPs and the general public. This resulted in us receiving many reports."

(Participant 10, NPVC, Oman)

In contrast, some industry participants from the three countries, a few NPVC participants from Jordan and Kuwait, and a few participants from Jordan's regional PV centres mentioned a lack of PV awareness among HCPs and the public as a weakness. Participants believed this to be a key reason for low ADR under-reporting.

"...the awareness campaigns are still not strong enough. We don't hear in Kuwait, I didn't hear that there is a committee for PV or an awareness campaign, to increase awareness of the patients."

(Participant 13, pharmaceutical industry, Kuwait)

Participants from the NPVC and industry in all three countries recommended that more efforts be made towards increasing PV and ADR reporting awareness regarding among HCPs and patients by educating them about its benefits.

"So we have to teach physicians, pharmacists, nurses, and all people that this topic is important and very expensive to health authorities, and reporting is essential, whether reporting is done to the health authority or the pharmaceutical company it doesn’t matter. What’s important is that the information is delivered, because this is the only way we can reduce the incidence and the occurrence of these adverse events."

(Participant 14, pharmaceutical industry, Jordan)
<table>
<thead>
<tr>
<th>Indicator item</th>
<th>Assessment</th>
<th>Oman</th>
<th>Kuwait</th>
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<tbody>
<tr>
<td>P1</td>
<td>Percentage of healthcare facilities with a functional pharmacovigilance unit (i.e. submitting ≥ 10 reports to the NPVC in the previous year (2020))</td>
<td>70%</td>
<td>N/A</td>
</tr>
<tr>
<td>P2</td>
<td>Percentage of total reports sent in 2020 by the different stakeholders includes:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>P2a – medical doctors</td>
<td>8.9%</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>P2b – dentists</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>P2c – pharmacists</td>
<td>81.9%</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>P2d – nurses or midwives</td>
<td>0.12%</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>P2e – the general public</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>P2f – manufacturers</td>
<td>8.8%</td>
<td>&gt;95%</td>
</tr>
<tr>
<td>P3</td>
<td>Total number of reports received per million population per year (2020)</td>
<td>318.80*</td>
<td>165.79*</td>
</tr>
<tr>
<td>P4</td>
<td>Average number of reports per number of HCPs per year (2020) includes:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>P4a – medical doctors</td>
<td>198</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>P4b – dentists</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>P4c – pharmacists</td>
<td>1,474</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>P4d – nurses or midwives</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>P5</td>
<td>Percentage of HCPs aware of and knowledgeable about ADRs per facility</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>P6</td>
<td>Percentage of patients leaving a health facility aware of ADRs in general</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>P7</td>
<td>Number of face-to-face training sessions in pharmacovigilance organised in the previous year (2020) for:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>P7a – HCPs</td>
<td>2</td>
<td>0†</td>
</tr>
<tr>
<td></td>
<td>P7b – the general public</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>P8</td>
<td>Number of individuals who received face-to-face training in pharmacovigilance in the previous year (2020):</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>P8a – health professionals</td>
<td>55</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>P8b – the general public</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>P9</td>
<td>Total number of national reports for a specific product per volume of sales of that product in the country (product specific) from the industry</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Table 5.6. Comparison of Complementary Process WHO pharmacovigilance indicators' performance in Oman and Kuwait.
<table>
<thead>
<tr>
<th>Indicator item</th>
<th>Assessment</th>
<th>Oman</th>
<th>Kuwait</th>
</tr>
</thead>
<tbody>
<tr>
<td>P10</td>
<td>Number of registered products with a pharmacovigilance plan and/or a risk management strategy among the MAHs in the country</td>
<td>105</td>
<td>N/A</td>
</tr>
<tr>
<td>P10a – Percentage of registered products with a pharmacovigilance plan and/or a risk management strategy from MAHs in the country</td>
<td>-</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>P11</td>
<td>Percentage of MAHs who submit periodic safety update reports to the regulatory authority as stipulated in the country</td>
<td>29%</td>
<td>14%</td>
</tr>
<tr>
<td>P12</td>
<td>Number of products voluntarily withdrawn by market authorisation holders because of safety concerns in 2020</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>P12a – Number of summaries of product characteristics (SPCs) updated by market authorisation holders because of safety concerns</td>
<td>-</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>P13</td>
<td>Number of reports from each registered pharmaceutical company received by the NPVC in the previous year (2020)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

- Indicates data not provided
N/A Indicates data not available
*Calculated using World Bank country total population data for the year 2020
†Covid-19 pandemic restricted carrying out face-to-face training sessions
5.4.3.3. Complementary outcome indicators

*Percentage of preventable ADRs reported and number of medicines-related congenital malformations*

Only in Oman were figures available on the percentage of preventable ADRs and medicine-related birth malformations and both were low. No information was reported on the remaining eight indicators in this group for either Oman or Kuwait (Table 5.7). Figure 5.2 provides a visual illustration of the areas of strength and weakness of the three studied countries' PV systems.

**Table 5.7.** Comparison of Complementary Outcome WHO pharmacovigilance indicators' performance in Oman and Kuwait.

<table>
<thead>
<tr>
<th>Indicator item</th>
<th>Assessment</th>
<th>Oman</th>
<th>Kuwait</th>
</tr>
</thead>
<tbody>
<tr>
<td>O1</td>
<td>Percentage of preventable ADRs reported out of the total number of ADRs reported in the preceding year (2020)</td>
<td>3.54%</td>
<td>N/A</td>
</tr>
<tr>
<td>O2</td>
<td>Number of medicines-related congenital malformations per 100,000 births</td>
<td>1</td>
<td>N/A</td>
</tr>
<tr>
<td>O3</td>
<td>Number of medicines found to be possibly associated with congenital malformations in the past 5 years</td>
<td>2</td>
<td>N/A</td>
</tr>
<tr>
<td>O4</td>
<td>Percentage of medicines in the pharmaceutical market that are counterfeit/substandard</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>O5</td>
<td>Number of patients affected by a medication error in hospital per 1,000 admissions in the previous year (2020)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>O6</td>
<td>Average work or school days lost due to drug-related problems</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>O7</td>
<td>Cost savings (US$) attributed to pharmacovigilance activities</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>O8</td>
<td>Health budget impact (annual and over time) attributed to pharmacovigilance activity</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>O9</td>
<td>Average number of medicines per prescription</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>O10</td>
<td>Percentage of prescriptions with medicines exceeding manufacturer's recommended dose</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>O11</td>
<td>Percentage of prescription forms prescribing medicines with potential for interaction</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>O12</td>
<td>Percentage of patients receiving information on the use of their medicines and on potential ADRs associated with those medicines</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

- Indicates data not provided
N/A Indicates data not available
In the case where the PV system component is present the country's name(s) is/are mentioned and vice versa in the case where the PV system component is absent.

*Indicates PV system component present but represents an area of weakness based on study results.

**Figure 5.2.** Areas of pharmacovigilance system strength and weakness in Jordan, Oman, and Kuwait.

### 5.5. Discussion and summary

This study employed the core and complementary WHO PV indicators(7) to evaluate the structures, processes, outcomes, and identify the areas of strength and weakness of PV systems at different levels of development in three Arab countries (Jordan, Oman, and Kuwait). While previous studies have set out to provide an overview of the status and performance of Arab countries' PV systems, this study goes beyond these studies to provide a deeper exploration of the study countries' PV facilities, set-
up dynamics, and outcomes. The use of a mixed-methods approach involving participants with intimate knowledge of PV policy and practice from both the NPVC and the pharmaceutical industry in their respective countries permitted the identification of the implemented PV systems' areas of best practice and challenges both qualitatively and quantitatively. The insights gained can be used for the development of a strategy towards improving patient safety through the development of a high performing PV system, particularly within countries with systems at a nascent stage of development (such as Kuwait).

This study's findings suggest that despite the presence of an operational PV system in all three countries, their performance and achievements require suitable and sustained improvement as they fall short in several indicators. The study found that, structurally, the main shortcomings of the PV systems in the three countries were the lack of an officially recognised and independent PV department within the NMRA (Kuwait), PV legislation (Oman and Kuwait), dedicated budget (all three countries), manpower shortage (all three countries), incorporation of PV into the national curriculum of HCPs (Jordan and Kuwait), a national advisory committee (Oman and Kuwait), and a computerised case-report management system (Kuwait). Process-wise, it was demonstrated that there was a perceived lack of awareness of PV and that ADR reporting rates were considered low in all three countries. In terms of outcomes, the results showed that all three countries had deficiencies in terms of signal detection and performing regulatory actions based on local PV data.

5.5.1. Study strengths and limitations
This study has some limitations. Despite the WHO PV indicators' usefulness as a tool for evaluating PV system performance, obtaining information on the indicators is dependent on facilities' recordkeeping quality. Members of the NPVCs in the studied countries lacked awareness regarding measuring indices to monitor and evaluate PV system performance and therefore neither collected nor kept records of such data. This limited the collection of information on some of the indicators. Assessment of some of the process and outcome indicators included as part of the tool require the assistance of individuals with expertise in areas such as diagnostics or health economics, which are not readily available in developing countries. The absence of the Jordanian PV system's process and outcome indicators' data prevented
the study from presenting a more complete picture of the areas of its strength and weakness in comparison to the other two countries studied.

The strength of this study lies in the fact that it is the first publication using a fully validated tool (i.e., the WHO PV indicator) to assess PV in Jordan, Oman, and Kuwait. Second, this study employed interviews with key stakeholders which facilitated gaining a deeper understanding of the areas of strength and weakness of these countries' PV systems beyond that obtained by relying on the assessment tool alone. Third, the study used document review to verify captured findings thus counteracting potential recall bias from the study participants. Having dealt with the aspects of the programme of research pertaining to PV system performance, the following chapter will explore the mechanism of and factors acting as impediments or facilitators to the implementation of PV policy in Jordan, Oman, and Kuwait.
Chapter Six: Study Three – A qualitative exploration of pharmacovigilance policy implementation in Jordan, Oman, and Kuwait using Matland's ambiguity-conflict model

6.1. Introduction

In Chapter One (Background) it was noted that in the interest of preserving public health and maintaining confidence in the healthcare system, national governments implement policies in the form of a PV system to ensure the quality, safety, and effectiveness of approved drugs according to the WHO's guidelines.(4-7) Study One(201) in Chapter Four highlighted that like other developing countries, Arab countries differ significantly in their systems' performance level. The findings from Study Two(177) in the previous chapter (Chapter Five) showed that there were differences in the level of performance of the implemented PV systems in these three countries and showed that although Jordan, Oman, and Kuwait all use the GVP for Arab countries as a basis for their PV systems, they still differ in several aspects.

As Arab countries seek to implement the Arab GVP guideline; and given PV's importance as part of a country's public health policies' portfolio, understanding the mechanism(s) of policy implementation and the factors influencing it can inform best practice in nascent systems in the region. Experience gleaned from the study of the implementation of policies has demonstrated that adopted policies are not always implemented as expected and do not necessarily achieve their intended results.(109, 130) Moreover, policymakers frequently focus on outputs or outcomes while ignoring the implementation process which could reveal the barriers to effective implementation.(131) Therefore, learning about the implementation process can assist in gaining a better understanding of the factors impacting policies' success or failure.(133)
This chapter presents the workstream carried out for Study Three, which involved conducting qualitative interviews with key informants from the NPVC and the pharmaceutical industry in Jordan, Oman, and Kuwait. Therefore, there was a need to further explore the role of PV policy implementation in these countries. This study was designed and executed to address the limited literature concerning the mechanisms of, and factors influencing, PV policy implementation in Arab countries with PV systems at different levels of performance.


6.2. Aim

This study aimed to compare the mechanisms and factors influencing PV policy implementation in Arab countries with established systems to inform PV policy implementation in a country with a nascent system.

6.3. Method

The methods presented here complement the methodology described in Chapter Three where the methodological justification and decisions of the qualitative design undertaken are provided. The consolidated criteria for reporting qualitative research (COREQ) (see Appendix XII for checklist) were used as a guide to describe the procedure of the methods and key decisions employed in this study.(216)

This study employed a qualitative study design (comparative case study approach) involving semi-structured interviews conducted by the researcher (Hamza Garashi) to address the aim of this study. As indicated in the previous chapter (Five), a single interview using a two-part interview topic guide was used to carry out this study in conjunction with Study Two (Chapter Five). The part of the interview topic guide (Appendix XIV) used for this study was informed by Matland's(115) ambiguity-conflict model (previously described in Chapter Three, section 3.3.2) and existing literature on policy implementation research(102, 114, 217). Therefore, the processes of participant selection, sampling, and recruitment; data collection; data analysis; and
ethical approvals and considerations were followed as those described for Study Two (see Chapter Five, sections 5.3.2.1, 5.3.3.1, 5.3.4.1, and 5.3.5 respectively). Matland's ambiguity-conflict model of policy implementation was applied here as a theoretical framework in the context of the facilitators and barriers to policy implementation, as well as participants' perceptions regarding ambiguity and conflict towards the PV policy.

To establish the type of policy implementation process followed in the study countries, the interviews focused on exploring the levels of and factors impacting policy ambiguity and conflict during the policy implementation process. This was achieved by identifying the facilitators and barriers to policy implementation, as well as participants' perceptions regarding ambiguity and conflict through enquiring about their understanding and acceptance of its goals and means. Proposed recommendations for strengthening PV policy implementation in countries with nascent systems were also solicited.

The analysis employed both an inductive and deductive approach to develop themes that provided rich and detailed descriptions of the dataset whilst mapping onto Matland's ambiguity-conflict model. Connections within the themes were made and key similarities and differences between countries as well as between participants from the two sectors were identified.

6.4. Results

The results presented here draw on interviews with 56 participants (17 participants in Jordan, 16 in Oman, and 23 in Kuwait). All members of the NPVC in the three countries (n = 5 per country) participated in the study along with an additional two members of the regional PV centres in Jordan. Most participants were pharmacists (n = 48) and mainly came from the pharmaceutical industry (n = 38). Further detail can be found in Appendices XIX to XXI.

The findings of the study are presented in the form of a comparison between the three countries divided into two parts. The first part covers the two dimensions of Matland's model, namely the levels of ambiguity and conflict associated with the pharmacovigilance policy present in Jordan, Oman, and Kuwait. The second part covers the factors that impacted both policy ambiguity and conflict along with participants' recommendations regarding PV policy implementation in countries with
nascent PV systems. To illustrate the extent of each country’s participants' agreement surrounding these issues, the terms few (n ≤ 4 participants), some (n = 5 – 8 participants), many (n = 8 – 11 participants), and most (n ≥ 12 participants) are used.

6.4.1. Participants' perceptions of policy ambiguity and conflict

To assess ambiguity and conflict levels of the policy’s goals and means in the three countries, participants’ opinions on the extent of clarity of the country's PV policy and its means of implementation were sought. Regarding conflict, participants’ views on whether they agreed with the policy's goals and its method of implementation were solicited. Figure 6.1 reflects the position of each country on the ambiguity-conflict matrix based on participants’ perceptions of their country’s policy ambiguity and conflict.

<table>
<thead>
<tr>
<th>Conflict</th>
<th>Low</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>Administrative (Jordan and Oman)</td>
<td>Political</td>
</tr>
<tr>
<td>High</td>
<td>Experimental (Kuwait)</td>
<td>Symbolic</td>
</tr>
</tbody>
</table>

Figure 6.1. Study countries’ position on the ambiguity-conflict matrix based on perceptions of policy ambiguity and conflict. Adapted from Matland (115)

6.4.1.1. Perceptions concerning policy ambiguity

Overall, participants' responses pointed to low levels of perceived policy ambiguity in Jordan and Oman. National pharmacovigilance centre members in the two countries unanimously described their policies’ goals and means as clear. Many industry participants in Jordan agreed with this view, however, Oman’s industry participants had mixed views with some believing that the policy was ambiguous.
"It's [the policy] clear, it’s easy to understand, and if you have any questions, you can find it." (Participant 2, NPVC, Jordan)

"They [the national centre] still have to clearly define what they actually want from others and what they are actually going to implement... little more clear statements and definitions should be given from the Ministry, the authority who's implementing." (Participant 4, pharmaceutical industry, Oman)

Participants' responses in Kuwait indicated that perceived policy ambiguity levels were high overall. While members of the national centre all agreed that the policy's goals and means were clear, many industry participants had the opposite view.

"...when it comes to implementing the [pharmacovigilance] system, still there is no clear guidance or clear regulation regarding this..." (Participant 18, pharmaceutical industry, Kuwait)

6.4.1.2. Perceptions concerning policy conflict

Participants' responses pointed to policy conflict levels being low overall in the three study countries. National pharmacovigilance centre participants in each country were all in agreement with their policies' goals and means. Furthermore, many industry participants in Jordan and Oman, as well as most in Kuwait indicated the absence of policy conflict.

"I agree [with the pharmacovigilance policy] because I'm able to perform the tasks that are requested." (Participant 8, pharmaceutical industry, Jordan)

6.4.2. Factors impacting policy ambiguity and conflict

In what follows, the themes extracted from the interviews are presented whilst identifying which group and which country they came from to allow for the comparison of the similarities and differences between them. Emerging themes were mapped onto Matland's model(115) to identify the process and factors associated with successful PV policy implementation in the study countries as well as recommendations for strengthening this process.

The main themes extracted from the interviews were: political support, stakeholder involvement, training, policy characteristics, implementation planning, and pharmaceutical company-related factors. In what follows, the impact of the underlying factors pertaining to each theme will be first discussed as related to
policy ambiguity followed by its impact on policy conflict. Table 6.1. summarises the results for the three study countries.

Table 6.1. Factors impacting policy ambiguity and conflict in Jordan, Oman, and Kuwait

<table>
<thead>
<tr>
<th></th>
<th>Ambiguity</th>
<th>Conflicts</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Jordan</td>
<td>Oman</td>
</tr>
<tr>
<td>Political support</td>
<td>Decrease</td>
<td>Decrease</td>
</tr>
<tr>
<td>Stakeholder involvement</td>
<td>Decrease</td>
<td>Decrease</td>
</tr>
<tr>
<td>Training</td>
<td>Decrease</td>
<td>Decrease</td>
</tr>
<tr>
<td>Policy characteristics</td>
<td>Decrease</td>
<td>Decrease</td>
</tr>
<tr>
<td>Implementation planning</td>
<td>Decrease</td>
<td>Decrease</td>
</tr>
<tr>
<td>Company-related factors</td>
<td>Decrease</td>
<td>Decrease</td>
</tr>
</tbody>
</table>

6.4.2.1. Political support

Participants from the NPVC and regional PV centres in Jordan all agreed that decision-maker (political) support was a contributing factor to reducing policy ambiguity. This view was also held by a few industry members of the in Jordan and Oman. Participants outlined how decision-makers engaged and communicated with policy implementors throughout the entire implementation process to minimise policy ambiguity by ensuring that there was an understanding of how it was to be carried out. Participants also identified decision-makers' role in providing implementors with continuous support and encouragement which made them feel valued and increased confidence levels which helped in increasing the efficiency of the implementation process.

“I feel that the administration was constantly supporting us. ...I never got the impression that what we [members of the National Pharmacovigilance Centre] were doing was underestimated, and they [the administration] would discuss things with us such as why certain things were done. There was an understanding.”
( Participant 1, NPVC, Jordan)

In contrast, in Kuwait, a few national centre participants and some from the industry pointed to decision-makers' (both within the Ministry of Health (MOH) and KDFCA) lack of encouragement or support as a barrier contributing to increased ambiguity. Moreover, PV policy implementation was reported by a few NPVC and
industry participants as the result of the personal endeavours of some of the staff at KDFCA. This lack of support resulted from what a few participants representing both sectors believed to be a lack of awareness of the subject of PV and thus the minimisation of its importance.

“People think it’s not a serious thing. I’m not supposed to mention names or something, [but] there are people in charge who think what we do is very simple.” (Participant 1, NPVC, Kuwait)

Political (managerial) support was cited by a few participants from Jordan's national and regional centres, as well as a few pharmaceutical industry participants from Jordan and Oman as a facilitator as it reduced the conflict in policy implementation means. This was evident in providing the NPVC with official recognition, independence within the NMRA’s organisational structure, and binding the policy to the law (in Jordan). This provided the NPVC with the necessary legitimacy, importance, and authority to be able to carry out the implementation process. This further expedited obtaining approvals for conducting activities including training workshops, awareness campaigns, and conferences.

"In terms of [facilitators] within the Directorate, there is the support of the administration... The support of the administration is exemplified in the way they provide us with resources, or how they refine our skills, the planning, how they send us to courses or workshops related to pharmacovigilance. Another example is the director, who tries to teach us new things, keeping us updated with the latest information... So, there is communication." (Participant 10, NPVC, Oman)

In Kuwait, MOH decision-makers' lack of political will towards issues related to pharmacovigilance acted as a barrier to policy implementation according to a few participants from the national centre and some from the pharmaceutical industry. Participants believed that this stemmed from decision-makers’ resistance to (or fear of) change. Examples of this included the lack of official recognition of the NPVC or the lack of a statutory provision for pharmacovigilance. This pointed to the presence of some conflict between implementors and decision-makers surrounding the policy means. The belief among these participants was that this was in part due to these decision-makers’ lack of understanding of pharmacovigilance's importance.
"The barriers of the implementation...the key personnel, the key personnel don’t know anything about pharmacovigilance. So that’s why I’m assuming that they will not implement such or they will not recognise such a guideline or such a mandate because of the knowledge, their knowledge. They don’t know what pharmacovigilance is." (Participant 18, pharmaceutical industry, Kuwait)

A few participants from the NPVC and PI in Oman recommended gaining the support of decision-makers within the country's health authority as being a crucial first step in ensuring successful policy implementation. They believed that achieving successful implementation would not be possible without it since it gave the policy legitimacy.

"...you need to have the support of the health authorities, the higher up health authorities to implement the PV because without that you can’t do anything. Because to implement pharmacovigilance you need legal, the legal background for it."  (Participant 7, NPVC, Oman)

6.4.2.2. Stakeholder involvement

Many participants from Jordan's PI and a few from Oman's described the collaboration between the NPVC and other stakeholders during the policy development process as a facilitator. Participants described the examples of the pharmaceutical industry in Jordan and Oman being allowed to review and provide feedback on the policy during the drafting process, or other key stakeholders, such as the University of Jordan, or other departments in Oman being involved in the policy's development. This participation had an important role in facilitating implementation through defining clear policy goals and thus reducing policy ambiguity and increasing consistency in implementation among the various stakeholders.

"In the beginning, the JFDA prepared a draft guideline, and several companies received a copy of the draft guideline and they asked us to give our opinion and if we had any comments, which we did, and they took some comments into consideration until the final guideline was published." (Participant 14, pharmaceutical industry, Jordan)

Most participants in Kuwait (representing both sectors) were either unaware of or revealed that the pharmaceutical industry did not play a role in the policy
development process. Participants described how the policy was issued as a memo from KDFCA without any prior involvement from the industry, with a few NPVC participants revealing that the industry's feedback was only obtained after the policy had been issued. This acted as a barrier because it led to some implementors from the pharmaceutical industry viewing the policy as ambiguous due to their lack of understanding of how the policy was to be implemented (i.e., policy means).

"[A barrier to policy implementation was] The companies not understanding the guidelines clearly." (Participant 21, pharmaceutical industry, Kuwait)

A few participants from each of Jordan's NPVC and the pharmaceutical industry also outlined the importance of the collaboration between both sides in the competency building of their countries' HCPs in developing a robust PV system. This helped increase awareness levels and led to a reduction in policy ambiguity as illustrated by participants' observations of increasing yearly ADR reporting rates.

"So, it was not only the Health Authority wanting to implement the guideline. It was done hand in hand with the marketing authorisation holders, applicants, experts, and expert working groups. There were effective communication channels, effective competency building, and all groups working hand in hand. This was the major contributor to successful implementation." (Participant 5, pharmaceutical industry, Jordan)

Some participants from Jordan, many from Kuwait (almost equally represented by both sectors in the two countries), and a few from Oman (the majority from the pharmaceutical industry) shared the belief that, despite their efforts, HCPs', the public's, and pharmaceutical company managers' lack of knowledge, awareness, or understanding of the pharmacovigilance policy remained a major obstacle to implementation. They believed that these issues stemmed from these stakeholders’ perceived ambiguity regarding the goals and/or the means of implementing the policy. As such, both the national centre and the industry still struggled with ADR under-reporting.

"... they [HCPs] don't know how to report or they don't know the importance of reporting. They're saying they don't know where to report, how to report, what they have to do if this is the case..." (Participant 7, pharmaceutical industry, Kuwait)
Like policy ambiguity, many industry participants from Jordan and a few from Oman indicated the importance of stakeholder involvement in the policy development process as a facilitator for its implementation by reducing policy conflict. Stakeholder involvement meant that agreement could be reached between all parties concerning its goals and means, which contributed to a reduction in resistance and subsequent delays in implementation.

"...we [members of the NPVC] discussed the subject [the PV policy] with the marketing authorisation [holders] and the pharmaceutical companies it was well accepted. And because whatever we mentioned in our guideline, it was discussed with them and agreed with them." (Participant 7, NPVC, Oman)

In terms of policy conflict, a lack of stakeholder involvement was an obstacle to implementation. A few participants from the NPVC in each of the three countries and from the Jordanian regional centres as well as some industry participants in both Jordan and Kuwait shared how this lack of involvement was connected to healthcare professionals’ negative attitudes (or resistance) towards implementing the policy. Similarly, a few NPVC participants in Oman and Kuwait and a few pharmaceutical industry participants in all three countries considered this negative attitude also existed among pharmaceutical company managers. In these cases, the policy was not viewed as a priority, but instead as an added burden that these stakeholder groups were forced to take upon themselves (i.e., conflict on policy goals and means). This lack of involvement was viewed as a contributing factor to the under-reporting of ADRs in the three countries.

"Maybe [one of] the barriers, [is] the company. Maybe in the beginning they were not very aware of the importance of pharmacovigilance in the companies. Because it's not stopping registration or marketing of any product. So, for the companies, it was not a priority to have a pharmacovigilance team in their companies." (Participant 8, pharmaceutical industry, Jordan)

Participants from both sectors in the three countries recommended the development of a partnership between the NPVC and the pharmaceutical industry. One area where this cooperation was deemed important was in conducting training of HCPs as well as in the efforts to increase awareness among the public. Furthermore, it was recommended that members of the national centre collaborate with those pharmaceutical companies which possessed experience in PV to train both the staff
within the NPVC as well as those of local companies to ensure proper implementation. Cooperation also should be extended to the development of policies, as it was deemed important to have input from all stakeholders. This would entail allowing companies to comment on and present their views on the proposed policy before it was finalised and formally issued. Furthermore, as part of the desired cooperation between the national centre and the pharmaceutical industry, it was proposed meetings be held with industry personnel to discuss the implementation plan and what would be required of them.

"...if you talk about how Oman started, they developed the draft guidelines and circulated it with all the agents and they communicated to the Ministry of Health, their manufacturers. So basically, [involving stakeholders in the policy development and implementation processes] that will be a great help for everyone." (Participant 8, pharmaceutical industry, Oman)

6.4.2.3. Training

Some industry participants in Jordan and a few in Oman cited the training provided by members of the NPVC in these countries to the industry as a facilitating factor, which made expectations clear and thus reduced policy ambiguity. This training was also recognised as helping to increase PV awareness, which in turn helped policy implementors develop a better understanding of the policy's goals and its means of implementation.

"...the authority had several workshops teaching the companies how to prepare a PSMF [pharmacovigilance system master file], a PSUR [periodic safety update report]. I think that also they had several workshops for healthcare professionals about pharmacovigilance, its importance, how to implement it, they tried to help people to some extent." (Participant 14, pharmaceutical industry, Jordan)

Unlike in Jordan and Oman, a few industry participants in Kuwait indicated that implementors from the pharmaceutical industry did not receive training regarding the policy. This lack of knowledge acted as a barrier and resulted in an implementation delay.

"We need to know from where to start, for example, where does the reporting cycle start? We see all this on paper, but we haven't yet actually implemented this into practice, nor do we know how to implement it. When they [the authority] issue guidelines they
should be cooperative with us so that we can understand and implement." (Participant 5, pharmaceutical industry, Kuwait)

A perceived implementation barrier cited by a few NPVC participants in Jordan and Oman was the lack of experience in PV of many of the centres' employees. This resulted in perceived policy ambiguity among some implementors who considered it to be the duty of members of the NPVC to explain and provide training on policy implementation. Interestingly, none of the participants cited training as a factor impacting policy conflict.

"... as a department it’s only been working since 2014 so we’re not talking about a long time. So, most of us [national pharmacovigilance centre staff] do not have that much experience. So, the low experience may be a reason [for difficulties in implementation]" (Participant 2, NPVC, Jordan)

Participants in all three countries stressed the necessity of having properly trained personnel within all organisations involved in the implementation of PV including healthcare institutions such as hospitals as well as pharmaceutical companies. A few industry participants from Jordan felt that the training of HCPs and industry personnel should be conducted in parallel. The training should include how, where, when, and what to report. Other industry participants from Jordan felt that training should start with teaching HCPs within healthcare facilities to introduce the subject in these institutions before focusing on the regulatory aspect. Participants emphasised the importance of providing hands-on in addition to theoretical training. Furthermore, training should not focus solely on practising HCPs but should extend to those still at the university level by adding the subject of PV to the undergraduate curricula of HCPs' degree programmes. This would widen the pool of individuals trained in PV available to hire in companies or within the NPVC. It would also ensure that the next generation of HCPs possesses the awareness and knowledge regarding PV when they enter the workforce.

“The PV should be taught during the pharmacy, during the bachelor, I think it’s missed everywhere and should be a very major subject to be studied because we came to know about it when we start working with the authority and distributor as a regulatory person, authority person, but we never heard about it.” (Participant 4, pharmaceutical industry, Kuwait)
A few participants from the pharmaceutical industry in Kuwait put forward the recommendation that NPVC staff members should be trained in the first instance to ensure that they fully understand the policy and what it entails. In addition, they should be evaluated once the training is completed to assess their levels of comprehension since they will be responsible for providing training to those working for the companies.

“The first thing I think immediately after they are issued the persons who will take afterwards, they should have the training for those. There should be training, and after that, there should be [an] evaluation for that training...” (Participant 7, pharmaceutical industry, Kuwait)

6.4.2.4. Policy characteristics

Participants in all three countries pointed to the nature of the policy itself as a facilitating factor for policy implementation. A few members each from the national centre and the pharmaceutical industry in Jordan and Oman pointed out that the policy was written in a manner that made it easier for implementors to understand its purpose and its means of implementation. It was also emphasised that the level of detail present within the policy helped reduce ambiguity. The Jordanian JFDA’s creation of checklists to accompany the policy simplified implementation, and in Oman, this was achieved through the creation of a national abridged version of the original Arab GVP guideline.

"...when we [members of the national pharmacovigilance centre] developed our own summarised guidelines this process [implementation] became easier; we were able to communicate properly with the companies. We were able to understand the companies and they were able to understand us." (Participant 1, NPVC, Oman)

"It [the policy] is a simplified version of the Arab GVP guidelines. The companies have informed [us] that it is quite to the point and simple." (Participant 14, pharmaceutical industry, Oman)

Some industry participants from Kuwait noted a lack of clarity and detail (i.e., policy ambiguity) on how to implement the policy (e.g., if medication errors were to be reported) and that there was inconsistency in the information being provided to them (e.g., submission of Periodic Safety Update Reports (PSUR)/Periodic Benefit-Risk Evaluation Reports (PBRER) for generic products). This led to companies
implementing the policy individually based on their own beliefs on what was required, leading to variations between them.

"... the guidelines are not very clear for Kuwait, it’s like all over.” (Participant 10, pharmaceutical industry, Kuwait)

“Sometimes I get a question about the PSURs for generics. In the EU [European Union], we don’t have to submit PSURs for generics, but in the Arab guideline it is mandatory. So, who should we follow?” (Participant 21, pharmaceutical industry, Kuwait)

As was the case with policy ambiguity, participants noted that the nature of the policy also impacted policy conflict. A few participants each from the NPVC and the industry in Jordan and Oman as well as many industry participants in Kuwait stressed the importance of the policy's compliance with both the Arab GVP guideline (and the European GVP guidelines from which it derived), as an important facilitator. This meant that the goals of the policy were aligned with those of regional and international guidance, which were centred on drug safety and hence decreased the likelihood of conflict occurring due to stakeholders' differing views.

"I agree with them [the policy goals], yes, because actually, these are international guidelines. We are not drafting something new. It is all adopted from international guidelines. There are of course certain things that might be customised according to the country, and I agree with them." (Participant 10, pharmaceutical industry, Jordan)

A few of the NPVC participants in Jordan and a few participants each from the NPVC and the industry in Oman described how the tailoring of the national policy according to the country's capabilities also acted as a facilitator for policy implementation by reducing policy conflict around its means of implementation. Participants elaborated that this was done through incorporating only those aspects of the Arab GVP guideline whose implementation was deemed achievable (when considering the local conditions) into the national policy. A few participants from the national centre and some from the industry in Kuwait also cited this factor as acting as a facilitator in reducing conflict associated with policy implementation.

"I have seen countries who have implemented very vast guidelines, but they don't know what is in it. So, some countries are... I mean their structure is not capable of implementing those guidelines which already stated to be in place. Whereas in Oman it is not the
case, their team have studied [the Arab GVP guidelines] and they have taken only the things that they can implement in this stage.”  
(Participant 9, pharmaceutical industry, Oman)

In terms of recommendations, participants from both sectors in Jordan pointed out that when developing a PV policy, it must be practical and direct. It was also proposed that when transposing the guideline on GVP for Arab countries into the national PV policy it be customised according to the country's market, capabilities, and facilities.

"Something that you have to have is to customise your Arab GVP guidelines according to your market, your capabilities, to your facilities..." (Participant 7, NPVC, Jordan)

6.4.2.5. Implementation planning

Only participants from Jordan (a few each from the NPVC and the industry) indicated that decision-makers in the country set up a formal working committee that was tasked with developing the operational aspects of the PV system. Therefore, an implementation plan was laid out whereby it was made clear to implementors how, when, and what aspects of the policy were to be implemented at a particular point in time, and this facilitated implementation by reducing ambiguity. Although participants in Oman did not indicate the establishment of a formal working committee, a few participants from the national centre and the industry pointed out that there was a constant line of dialogue between the industry and the NPVC during the different stages of the implementation process.

“They [the NPVC] first of all they started by insisting that you had to have as a company a pharmacovigilance department, not a department as such, but activities, and then you had to have a master file, and then, later on, they said that you should have a resident Omani pharmacist as a local safety person in Oman..."  
(Participant 3, pharmaceutical industry, Oman)

Another facilitator described by a few participants from the NPVC and many from the industry in Jordan was the national centre carrying out PV inspections, both during the initial stages of the policy implementation and once the policy was fully implemented. This reduced policy ambiguity among industry implementors since it allowed the national centre to not only monitor but also assist with policy implementation.
"In Jordan, they were able to accompany most of the companies and to provide them with guidance. For a while, maybe a year or two, even when they would say they were coming for an inspection; it was not so much an inspection as it was an assessment of the situation while providing guidance or recommendations..." (Participant 14, pharmaceutical industry, Jordan)

In contrast, participants from Kuwait agreed that an implementation plan was lacking for the KDFCA, which acted as an implementation barrier by causing ambiguity to companies in terms of how the policy was to be implemented.

"No [there were no steps taken from the authority with regards to the implementation of the policy], they just issue the policy, and they say, effective so and so date and we have to adhere to that." (Participant 10, pharmaceutical industry, Kuwait)

According to a few participants from both sectors in Jordan, a gradual implementation of the policy which involved not mandating policy implementation on all companies (particularly those with little experience in PV) from the outset facilitated implementation. It was explained that a stepwise approach, whereby aspects of the policy which were more achievable (e.g., developing a PSMF and ADR reporting forms) were focused on in the beginning, gradually moving onto more complex aspects (e.g., preparing PSUR/PBRER). This resulted in a smoother implementation process due to reduced conflict between stakeholders around the policy means.

"...they [the NPVC] were not tough from the beginning in that they published the guideline today and then required that they be implemented within the next month; they gave the companies sufficient time to have a PSMF, to know how to fill out the form, to adapt the timelines, all of these things." (Participant 14, pharmaceutical industry, Jordan)

A few participants from Kuwait's pharmaceutical industry viewed the NMRA's failure to provide them with an adaptation period before implementation, and the lack of an adequate timeframe for proper implementation, as barriers and a source of policy conflict. This contrasted with the situation in Jordan and Oman where participants from both sectors indicated that companies were afforded an adjustment period and a timeframe for policy implementation, thus avoiding policy conflict.
"In general, in Kuwait, the barriers would be that they impose things without giving a grace period. In other countries, when a new guideline is issued, they inform you that implementation will start from a certain date. They give you a grace period to prepare yourself." (Participant 5, pharmaceutical industry, Kuwait)

Despite indicating the presence of an implementation plan, a few participants from Jordan's NPVC, as well as a few from the industry, identified the absence of adequate funding as a barrier. Stakeholder views surrounding policy means were thus incompatible and resulted in policy conflict, which in turn hampered efforts in building awareness and conducting training workshops for stakeholders. In contrast, most participants from Oman and Kuwait did not highlight funding as a factor, indicating the absence of policy conflict.

"At the end of the day you are in the governmental sector, and in this country, we don’t have resources allocated for pharmacovigilance to promote awareness or other things that we need. We found solutions by forming collaborations with stakeholders, drug manufacturers and drug agents to do such events in Jordan." (Participant 7, NPVC, Jordan)

There was agreement among participants in all three countries on the difficulty of implementing the guideline on GVP for Arab countries as part of a national PV policy all at once. As such, it was recommended to adopt a gradual approach involving implementation of the easier aspects (e.g., creating a PSMF) then moving to the more complex (e.g., writing PSURs/PBRERs) as time passed. It was also mentioned that during the implementation process companies be given sufficient time in advance of the implementation deadline. Industry participants from Oman and Kuwait added that companies should be afforded an adjustment period e.g., one year to ensure that all their affairs were in order. During this period compliance with the regulations would be voluntary and once it ended, compliance would become mandatory, and non-compliance would result in penalties.

“…during the first one or two years, maybe, it has to be voluntary, give companies and the agents a grace period in order to digest and to do their action by employing new PV officers, to establish offices for the PV for each affiliate. … For the second year, you will have to mandate [compliance with] that guideline. And you have to give penalties for that.” (Participant 18, pharmaceutical industry, Kuwait)
Another recommendation put forward was, as part of the policy planning process, to encourage learning from the experiences of other countries in the region that have more mature PV systems. This could be done by studying their regulations and having employees of the NPVC travel to these countries to gain experience which could be useful in their own country.

"Obviously the easiest one [recommendation] is to send people to countries that have used and practised Arab GVP and learned from their mistakes so they don’t repeat the same mistakes, they can do others but at least what’s been tried, and people tell them with complete transparency the dos and don’ts, and what was done, what didn’t work, how it was changed, and how did we benefit." (Participant 14, pharmaceutical industry, Jordan)

6.4.2.6. Pharmaceutical industry-related factors

A few participants from the pharmaceutical industry in all three countries and a few from the NPVC in Oman believed that being a multinational company with experience operating in developed countries, where pharmacovigilance policies and regulations were more stringent acted, as a facilitator. Similarly, a few Jordanian and Kuwaiti industry participants thought that local companies which had licensing agreements with multinational companies facilitated policy implementation due to clauses in their agreements that required standards to be in place on par with those of the multinationals. This meant that there was less ambiguity due to the presence of a degree of familiarity with the guidance and hence policy implementation proceeded more smoothly.

"...most of the points that are in the [Arab GVP] guidelines it is already implemented by the multinational companies because it is part of the European guideline, so it was easy to implement by these pharmaceutical companies." (Participant 7, NPVC, Oman)

A few of Jordan's and Oman’s pharmaceutical industry participants pointed to the lack of harmonisation among Arab countries in implementing the Arab GVP guideline as part of their national policies. Each country in the region appeared to have its own set of rules and guidelines extracted from the same source, which confused companies operating in multiple countries in the region. This represented a source of conflict between the companies and the national pharmacovigilance centres.
“Sometimes external regulatory authorities having different requests acts as a barrier. There is a unified guideline, but no unified actions. So, we have the same guideline, but different requests, regulations in each country.” (Participant 15, pharmaceutical industry, Jordan)

Some industry participants and a few from the regional centres in Jordan as well as a few industry participants from Kuwait recommended that pharmaceutical companies' employees should be trained on how to develop their companies' PV systems. This is to ensure that they are carrying out their function adequately. Training should also focus on providing instruction on what is required and how it is put into practice. Training at each juncture should also involve ensuring an understanding of the logic and purpose behind every activity and/or component of the system.

“So, all of us as stakeholders are partners in this issue [PV]. So, it’s not about the authority obligating the industry to have a system, there has to be some kind of facilitation from the authority to the industry to make sure we are really having a system and we’re really implementing the system. It’s not about having [the] system documented.” (Participant 10, pharmaceutical industry, Jordan)

6.5. Discussion and summary

This study employed Matland's(115) ambiguity-conflict model of policy implementation to analyse and identify the type of PV policy implementation process in three Arab countries with differing levels of system performance (Jordan, Oman, and Kuwait). This in turn was used to inform recommendations for the implementation of a PV policy (incorporating the Arab GVP guideline) in countries with PV systems at a nascent stage of development (such as Kuwait). The qualitative approach based on interviews allowed for gaining a deep understanding of the mechanisms as well as the facilitators and barriers to pharmacovigilance policy implementation in Arab countries. Application of the two dimensions of Matland's(115) model (i.e., the levels of policy ambiguity and policy conflict in its development and implementation) provided a novel yet manageable approach to identifying the process and factors associated with successful PV policy implementation.

Factors reducing policy ambiguity in Jordan and Oman included: decision-makers’ guidance to implementors, stakeholder involvement in the policy's development and
implementation, training of policy implementors throughout the implementation process, clearly outlined policy goals and means, and presence of a strategic implementation plan with appropriate timelines as well as a monitoring mechanism. In contrast, policy ambiguity in Kuwait stemmed from the absence or lack of attention to these factors. Factors reducing policy conflict included: the policy's compliance with internationally recognised standards and the policy's fit with local capabilities (all three countries), decision-makers' cooperation with and support of the national centre as well as stakeholders' agreement on policy goals and means (Jordan and Oman) and adopting a stepwise approach to implementation (Jordan).

Applying Matland's model (115) to the factors impacting the PV policy implementation process in conjunction with participants’ views on its ambiguity and conflict enabled the discernment of policy ambiguity and conflict levels within the three countries, and the type of implementation strategy being followed. The presence of both low policy ambiguity and conflict in Jordan and Oman points to the presence of a structured approach to policy development and implementation (i.e. administrative implementation). In Kuwait however, while participants’ views and the cited factors impacting policy point to high ambiguity, there were differences in terms of policy conflict. On the one hand, participants’ views surrounding policy conflict pointed to low conflict. On the other hand, the factors impacting policy implementation pointed to an increase in conflict. Taking these findings together suggests that policy implementation in Kuwait fell in between the "experimental implementation" and “symbolic implementation” processes. These could be the underlying reasons for Kuwait's PV system falling behind those in Jordan and Oman as was detailed in Study Two (Chapter Five).

6.5.1. Study strengths and limitations

This study has a few limitations. First, there was potential for response bias to occur due to interviewees’ hesitation of criticising decision-makers, which was mitigated by assuring participants of their anonymity and the confidentiality of their views. Second, participants' responses could have been exaggerated or contained inaccuracies because they were reliant on memory. This was minimised by confirming information from more than one participant, comparison with information from the literature, and correspondence with the participants for clarification purposes. Finally, the views of HCPs or patients were not explored.
A major strength of the study lies in its use of a theoretical framework adapted from policy implementation research to guide the study. The study's use of a qualitative approach is also a strength as it provided detailed insights into the policy implementation process in the three study countries which allowed for comparison between them. Finally, the inclusion of members of the pharmaceutical industry, who are required to comply with the requirements set out by countries’ NMRAs, provided an alternative perspective on the issues concerning PV policy implementation than those employed within the NPVC thus enriching the data. The next chapter will present a discussion of the overall findings of the programme of research.
Chapter Seven: Discussion, proposed recommendations, and conclusion

7.1. Introduction

This chapter discusses the findings obtained from carrying out the programme of research, illustrating how this research addressed the overall study aim, and presenting the original contributions it makes to extending existing knowledge on PV system performance, strengths and weaknesses, and policy implementation. First, a summary of the overall programme of research is provided. Second, an integrated discussion of the key findings from each study in the context of existing literature is presented. The programme of research’s strengths and limitations are considered next. This leads to suggestions for future research and the researcher’s reflections on the research carried out. Finally, recommendations in the form of a strategy for strengthening PV system performance and policy implementation will be provided, followed by the conclusion.

7.2. Summary of the overall programme of research

The overall aim of this programme of research was to characterise the key factors impacting PV performance and policy implementation in select Arab World countries at different stages of performance and implementation to inform recommendations for strengthening PV system performance and policy implementation in Kuwait (and other countries with nascent PV systems).

To achieve the overall aim there were four overarching objectives:

1- To identify and synthesise recently published research pertaining to the evaluation of the characteristics, performance, and/or effectiveness of PV systems in developing countries.

2- To explore implemented PV system structures, processes, and outcomes in addition to strengths and limitations in Kuwait and two other Arab countries with more mature PV systems
3- To explore the mechanisms and factors acting as impediments or facilitators to the implementation of PV policy in Kuwait and two other Arab countries with more mature PV systems.

4- To formulate recommendations for strengthening PV policy implementation and subsequent system performance, specifically in Kuwait, but also in other Arab countries with nascent PV systems.

These objectives were achieved by employing a convergent mixed methods approach involving three studies. Each of these three studies carried out had specific aims which contributed to addressing the overall aim and objectives of the programme of research. The first study, which addressed objective one, was a narrative literature review of peer-reviewed published literature using the WHO PV indicators(7) as a framework to provide a synthesis of up-to-date evidence surrounding PV systems’ performance in developing countries. The second study also used the WHO PV indicators(7) and addressed the second objective by examining the structures, processes and outcomes alongside the strengths and limitations of the implemented PV systems in three Arab countries (Jordan, Oman, and Kuwait) which were selected due to being at different points on the performance spectrum. This study employed a mixed-methods approach involving document review, semi-structured interviews with key informants from the NMRA and the pharmaceutical industry, and a survey directed at the PV leadership in the three countries. The third study addressed objective three by using Matland’s ambiguity-conflict model of policy implementation(115) to explore the processes of and the perceived factors impacting PV policy implementation in the same three Arab countries (Jordan, Oman, and Kuwait). Use of a predominantly qualitative approach to perform studies Two and Three (Chapters Five and Six respectively) was viewed as the most appropriate given Study One’s (Chapter Four) findings that there was a need for an in-depth exploration of the characteristics of Arab countries’ PV systems and approaches to PV policy implementation. Integration of the findings and interpretation from the three studies addressed the final objective of proposing recommendations for strengthening PV policy implementation and subsequent system performance in Kuwait and other Arab countries where PV is at a nascent stage of development.
7.3. Integrated discussion and critical interpretation of findings

Below is an integrated summary of the key findings from this programme of research's three studies in the context of their respective frameworks and existing literature concerning PV and policy implementation respectively. The first section presents a synthesis of findings related to PV systems' performance, while the second presents those related to PV policy implementation.

7.3.1. Lack of standardisation

By synthesising recently published peer-reviewed evidence concerning the evaluation of the characteristics, performance, and/or effectiveness of PV systems in developing countries using the WHO PV indicators(7) as a framework, a lack of standardisation of the tools employed to evaluate PV systems became evident. While some studies focused only on the WHO indicators, others used assessment tools developed by other organizations including the United States Agency for International Development (USAID), East African Community (EAC), the US Centre for Disease Control (CDC), or some combination of these.

The narrative literature review (Chapter Four) also found that not all 63 WHO indicators were assessed in the included studies. Overall, studies' coverage of the WHO PV indicators was mixed of some indicators which were present in most or all studies, while others were universally absent or only sporadically present. Generally, indicators that were either universally absent or only sporadically present in the studies/countries in this review belonged to the Process and Outcome indicator classes. In terms of the reviewed studies, both the Complementary Process and Outcome indicators' presence was mixed with some being universally absent (e.g., number of reports from each registered pharmaceutical company received by the NPVC in the previous year and cost savings attributed to PV activities respectively) and others being sporadically present (e.g. number of face-to-face training sessions in PV organised in the previous year and average number of medicines per prescription respectively). Most of the Core Process and Outcome and Complementary Structural indicators were sporadically present (e.g. percentage of reports on medication errors reported in the previous year, average cost of treatment of medicine-related illness, and existence of an essential medicines list which is in
use respectively), whereas most of the Core Structural indicators were frequently present (e.g. the NPVC has human resources to carry out its functions properly) and only a few were sporadically present (incorporation of PV into the national curriculum of the various HCPs). This necessitated the inclusion of data from not only the results sections but also from other sections of the reviewed studies such as the 'Background' or 'Discussion'. In other instances, inferences were made for certain indicators based on the information provided for others. A notable example was inferring the presence of a computer for PV activities when it was indicated that a computerized case-report management system existed as part of the system.

Evaluation is defined as the systematic and objective assessment of the relevance, adequacy, progress, efficiency, effectiveness, and impact of a course of action in relation to objectives while considering the resources and facilities that have been deployed. (218) An evaluation based on only a few indicators is not likely to provide a complete, unbiased evaluation of the system since multiple indicators are needed for tracking the implementation and effects of the system. (200) While the optimal number of indicators required to perform a proper assessment is likely to vary depending on the objectives of the evaluation, it could be argued that, based on definition, addressing the full set of "Core" indicators should be required to provide a complete evaluation. (154) This highlighted an important gap in the literature which was the scarcity of research providing an in-depth exploration of countries’ PV systems' performance and policy implementation as well as the factors impacting them.

7.3.2. PV systems' performance

7.3.2.1. Overall PV system performance

Studies One and Two (Chapters Four and Five respectively) found that despite the presence of an operational PV system in most countries, their performance and achievements require suitable and sustained improvement as they fall short in several indicators as overall PV system performance was low reflecting their immaturity. The two studies demonstrated that, generally, indicators that were found to be either universally lacking or only sporadically available as part of the studied countries' PV systems belonged to the Process and Outcome indicator classes. More specifically, all the Complementary Outcome indicators were found to be universally lacking.
among the studied countries. The Core Outcome and Complementary Process indicators' presence was found to be mixed with some being universally lacking (e.g., number of medicine-related deaths and respectively and total number of product-specific national reports per volume of sales of that product in the country from the industry respectively) while others were sporadically present (e.g., number of signals detected in the past five years and percentage of healthcare facilities with a functional PV unit). Most of the Core Process (e.g., percentage of submitted ADR reports acknowledgement or issued feedback) indicators were found to be sporadically present. Therefore, PV system performance was found to be low in terms of the 'Process' and 'Outcome' indicators. This reflects immaturity and the inability to collect and utilise local data to identify signals of drug-related problems and to support regulatory decisions. (128, 171, 210, 211) On the other hand, most of the Core Structural (e.g. an organised centre to oversee PV activities) and some of the Complementary Structural (e.g. existence of a dedicated computer for PV activities) indicators were found to be frequently present among the studied countries. Hence, performance with respect to the Structural indicators was relatively high. This points to government policymakers taking active steps towards establishing a PV system as a means of improving drug safety. (6, 13)

7.3.2.2. Factors impacting PV system performance

Study One (Chapter Four) demonstrated that higher-performing PV systems in developing countries were distinguished by the presence of a budget specifically earmarked for PV, a means of communicating drug safety information to stakeholders (e.g., a newsletter or website), and technical assistance via an advisory committee. On the other hand, lack of incorporation of PV into the national curriculum of HCPs and underreporting of ADRs plagued both high and low performing systems.

Study Two (Chapter Five) found that the three studied countries' PV systems' strengths were related to the presence of "Core" structural indicators including a dedicated and officially recognised NPVC (Jordan and Oman), PV legislation (Jordan), and a national PV advisory committee (Jordan); as well as "Complementary" structural indicators e.g., a computerised case-report management system (Jordan and Oman). Contrastingly, weaknesses were attributed to the absence of "Core" structural indicators including a dedicated and officially recognised NPVC
(Kuwait), PV legislation (Kuwait), regular financial provision (Jordan), adequate staff numbers (Jordan, Oman, and Kuwait), and a national PV advisory committee (Oman). Other weaknesses were commonly shared by all three countries and related to low performance in "Core" process indicators (ADR reporting rates) and "outcome" indicators (signal detection).

A triangulation of the finding from the two studies suggests that the difference in PV system performance in Kuwait compared to that in Jordan and Oman can be attributed to the following factors: organisation and structures, legislation, resources; PV as part of HCPs curriculum, ADR reporting rates and signal detection; as well as stakeholder knowledge, awareness, and attitudes towards PV. These will be explored in further detail in the following sections.

**Organisation and structures**

An interesting finding from Study Two (Chapter Five) was the unique situation of Kuwait's NPVC and its impact on PV system performance. The study demonstrated how the NPVC's lack of official recognition from both Ministry of Health (MOH) and NMRA officials weakened PV system performance as Kuwait did not have a formal PV system thus preventing the PV system from being fully operationalised. Findings from Study Two regarding the NPVC's status in Jordan and Oman demonstrated how official recognition provided the NPVC with increased visibility and significance to stakeholders thus strengthening the system. Study Two's findings regarding Kuwait differed from those in Study One (Chapter Four) where no instances were found of a country having a NPVC as part of the PV system but the centre not being officially recognised. These findings indicate the need for educational efforts focusing on highlighting PV's value as part of public health policy targeted at decision-makers to bring the importance of the issue to their attention as a means of gaining political support.

The existence of a NPVC points to the country's commitment to accomplishing PV objectives. National governments' legitimisation of the NPVC acts as a facilitator to the mobilisation of the adequate and sustainable resources required for the stable operation of the system. Moreover, the absence of official endorsement acts as a barrier to effective implementation due to it causing resistance among implementors thus slowing the process.
Study One found that developing countries possessing a tool for disseminating PV information as part of their system achieved higher performance scores than those that did not. Interestingly, Study Two found that despite this tool being present in Jordan and Kuwait (but not Oman), neither its presence nor absence was found to be considered a significant strength or weakness. The differences in the findings between Studies One and Two could be due to these countries' (i.e., Jordan, Oman, and Kuwait) systems' immaturity.

The WHO indicates that an expected function of a country's PV system is the effective dissemination of information related to medicines' safety to both healthcare professionals and the public. The lack of such a tool from the structure of many developing countries' systems points to the absence of clear routine and crises communication strategies. The use of a drug bulletin has been cited as an effective tool for improving safety communication between stakeholders as well as increasing ADR reporting.

Study One showed that a feature of better performing PV systems was the presence of a PV/ADR advisory committee as part of the system's structure. Study Two highlighted how the presence of a national PV advisory committee composed of individuals with different areas of expertise in Jordan strengthened the PV system. Its absence in Oman and Kuwait, however, was found to be a limitation of these countries' PV systems as it meant that their NPVCs missed out on the benefit of receiving expert feedback to support decision-making regarding drug safety issues.

The WHO views the existence of a national advisory committee as an essential part of the PV system given its influential role in providing a clear communication strategy, as well as technical assistance via its input to the drug regulatory process. Evidence from industrialised countries has demonstrated the value of having such a committee's scientific and clinical advice to support and promote drug safety. The presence of such a committee also inspires confidence of HCPs and provides a significant contribution to public health as, without clear communication, poor awareness of healthcare issues would prevail. Oman and Kuwait could benefit from obtaining technical support from other Arab countries with more established PV systems and/or the UMC via information sharing or site visits as a means of overcoming their lack of a PV advisory committee.
**Legislation**

Study One demonstrated that a common characteristic among higher-performing systems in developing countries was the presence of a statutory provision for PV. Study Two's findings helped detail the effect of this indicator on the PV system by demonstrating how the government-enacted PV legislation in Jordan represented an important strength of the country's PV system because it granted it the authority to enforce and monitor implementation. Contrastingly, in Oman and Kuwait, the absence of PV legislation was perceived to be a system limitation that deprived the NPVCs of the authority to enforce drug safety surveillance.

The development of a national PV policy and other legislative instruments is an important measure to ensure the sustainability and effectiveness of PV structures\(^\text{(171)}\). Laws and the regulations which are derived from them to guide implementation are necessary to provide PV with legal backing. Moreover, the presence of a clear legal framework accompanied by matching regulations ensures greater compliance and enforcement compared to relying on guidelines and normative practices which are not specifically binding\(^{(7, 226)}\) These findings point to the need for countries with nascent systems to develop policy and legal frameworks to adequately undertake drug safety surveillance.

**Resources**

In Study One it was shown that most developing countries with higher-performing PV systems had a dedicated budget for PV. However, in Study Two, it was found that despite all three study countries not having a dedicated budget for PV, only in Jordan was this brought up as a system limitation that deprived the NPVC of the ability to carry out activities such as PV promotion, education, and training, or the hiring of additional staff. A possible explanation for this could be that both Kuwait and Oman are considered high-income countries, whereas Jordan is an upper-middle-income country according to the World Bank.\(^{\text{(227)}}\)

The presence of appropriate funding is important in ensuring that the basic needs and running costs of the PV system are provided.\(^{(7)}\) The absence of dedicated and sustained funding for PV negatively impacts effective system operation since it prevents the development of the extensive infrastructure required for an effective PV system.\(^{(10)}\) According to the WHO, funding allows the carrying out of PV activities in the setting.\(^{(7)}\) Furthermore, it "signifies a gesture, the commitment and political
will of the sponsors and the general importance given to pharmacovigilance.” (7, p. 20) It is only when the other structural components of a PV system are paired with a regular and sustainable budget that real action and long-term planning can be achieved. (228-230) Any investment in PV should consider the substantial diversity in country characteristics such as size and population as well as the anticipated rate at which the system is going to generate reports. (6, 231) These findings suggest that countries struggling with financial resources should explore methods of funding PV activities outside of government funding such as the development of public-private partnerships in areas that are mutually beneficial but do not compromise the national PV system’s ability to ensure drug safety.

In Study One, developing countries with a PV system possessing human resources to carry out its functions properly were found to have achieved higher performance scores than those that did not. However, there was little information regarding the quantity or quality of the human resources carrying out activities as part of the system. In Study Two it was shown that despite all three countries’ PV systems having human resources to carry out their functions, a common limitation was that their numbers were deemed to be insufficient. Therefore, the NPVC faced difficulty in carrying out essential PV activities such as entering ADR reports into the national database, review of PV reports (i.e., PSURs and RMPs), and conducting training workshops and awareness campaigns.

A positive correlation exists between the presence of a comparatively large number of qualified personnel employed as part of the PV system and the level of progress achieved. (91) The optimum staff number for a functional PV centre should be balanced against need and funds, and take into account the total population, scope of products, and the mode of PV activities (195). Guidance from the WHO recommends that at least one of each of the following should be employed to support the full-time staff in carrying out the day-to-day PV activities: secretarial and data entry staff as well as an IT expert (232). None of the studied countries was equipped with such personnel thus placing an increased burden on existing staff. Countries with nascent systems can draw upon international and regional partners to overcome manpower limitations.

In Study One developing countries with the highest performing PV systems were all found to possess dedicated computing facilities to carry out PV activities and used a
computerised case-report management system. In Study Two it was shown that although all three countries' NPVCs possessed dedicated computers for carrying out day-to-day activities, only Jordan and Oman (but not Kuwait) had a computerised case-report management system (VigiFlow), which offered them the advantage of ensuring report accuracy and the use of statistics for analysis. Access to VigiFlow allows a cost-effective means of possessing a comprehensive (otherwise expensive) database with the added benefit of access to the WHO's global ADR reporting data.(171)

Study Two also found that a high percentage of reports received were of low quality, combined with possibly limited NPVC staff's expertise meant that the data analysis option offered by the presence of VigiFlow was not used, further emphasising the importance of targeted training for reporters and NPVC staff. The WHO's designation of the existence of a dedicated computer for PV activities and a computerised case-report management system as "complementary" indicators(7) highlighted that the guidance may not adequately reflect the importance of technology in facilitating reporting and subsequent data management. Considering the advancement of, and access to, information technology globally, it may be time for the WHO to reclassify these indicators as "Core".

Stakeholder participation and engagement

Studies One and Two both found that ADR reporting rates were low overall. Study Two provided further insights regarding the reason for the low ADR reporting rates as it was found that a major contributing factor was lack of participation in the reporting process, which is, in part, due to NPVCs' lack of emphasis on carrying out public engagement via training and sensitisation campaigns. Another finding was that the PV systems in the majority of countries investigated did not include methods of active PV such as cohort or prescription event monitoring pointing to almost total reliance on a spontaneous reporting system for the collection of ADR reports which acts as a contributing factor for the low number of ADR reports.

Low ADR reporting rates point to the PV system's inability to collate data on the safety, quality, and effectiveness of marketed drugs that have not been tested outside the confines of clinical trials. Consequently, system processes and outcomes, including data analysis, signal identification, regulatory actions, and communication and feedback mechanisms, remain stagnant.(233) Therefore, efforts must be made to
increase public engagement to raise awareness concerning the importance of PV and ADR reporting as a means of counteracting ADR reporters' lack of participation. Engaging ADR reporters (i.e. HCPs and patients) and the provision of feedback can support PV systems across various settings, e.g. regulatory bodies, pharmaceutical companies, and healthcare facilities.(234, 235)

Study Two demonstrated that a consequence of the low ADR reporting rates was that there was a reliance on decisions made by other countries'/regions' NMRAs (particularly the USFDA and the EMA) for performing local regulatory actions concerning drug safety. This suggests the information collected by these systems is insufficient and/or inadequate to identify signals of drug-related problems and to support local regulatory decisions.(210) The PV system's ability to detect signals "underscores its relevance in identifying safety problems and promoting the safe use of medicines."(7, p. 33) Moreover, the absence of regulatory actions points to a non-functional or dysfunctional system and a failure to monitor drug safety.(7)

The WHO's guidance points to the number of ADR reports received by the system as being an indicator of PV activity in the setting, the awareness of ADRs and the willingness of HCPs to report.(7) Despite underreporting being a significant barrier to the effective functioning of PV systems in both developing and developed countries(58, 228), reporting rates have been demonstrated to be lower in developing countries than in developed ones.(236) Based on international evidence, it is reasonable to expect a developed system to target an annual reporting rate of 300 reports per million inhabitants.(237) Countries struggling with under-reporting should utilize the WHO's global database (VigiBase) as a reference for monitoring drug-related problems.(210) Furthermore, data from countries with similar population characteristics and co-morbidities receiving smaller numbers of ADR can be gathered into a single database which would allow an analysis of the pooled data to provide relevant solutions.(10, 210) As such, it might be beneficial to set up inter-country collaborative efforts with the ultimate goal of consolidated reporting to VigiBase.(210) It would also be beneficial for countries to consider diversifying their ADR reporting sources by employing more active methods of drug safety surveillance for example by using population-based surveillance systems (cohort studies) as an adjunct for detecting ADRs, particularly those that are already known.(238)
**PV as part of healthcare professionals' curriculum**

In Studies One and Two PV was found to be absent from the national curricula of HCPs in most of the developing countries studied. Study Two highlighted how PV's absence from HCPs' curriculum negatively impacted the PV system as it contributed to HCPs' underreporting of ADRs. These findings suggest low levels of competency regarding PV and ADR-reporting as many HCPs in these countries lack adequate training in PV.

A successful PV system requires the presence of qualified personnel supplemented with access to the proper training as well as continuous professional development programmes which ensure the availability of individuals possessing the necessary level of expertise in PV. The absence of PV from HCPs' curriculum suggests their lack of preparedness to deal with drug safety issues they will encounter during their practice. (7) Given HCPs' responsibility to report ADRs during their practice, it is important that strategies that contribute to the promotion of PV by multidisciplinary teams in healthcare institutions be implemented. (239) Lack of undergraduate PV education and training contributes to low levels of knowledge, skills, and actions among HCPs. (239-241) These factors combined with negative attitudes have been linked to low and/or under-reporting of ADRs previously discussed here and confirmed by others. (233, 240, 242) According to the WHO, the importance of incorporating PV into the national curricula of HCPs stems from the positive effect early exposure to this subject has on sensitising them to issues regarding drug safety. (7) Studies have demonstrated that the implementation of PV-related training as a module or course for HCP students has a positive effect on their PV knowledge. (243-245) Therefore, this can help ingrain PV as part of HCPs' practice from the early stages of their careers. Despite the WHO's designation of PV as part of the curriculum as a "core" indicator, it may be advisable to designate this as a "complementary" indicator, and instead further emphasise a broader and longer-term strategy to ensure education in PV reporting, which would include HCPs' curricula.

**7.3.3. PV policy implementation**

Study Three (Chapter Six) employed Matland's (115) ambiguity-conflict model of policy implementation to analyse and identify the type of PV policy implementation process in three Arab countries with differing levels of system performance (i.e. Jordan, Oman, and Kuwait). This in turn was used to inform recommendations for
the implementation of a PV policy (incorporating the Arab GVP guideline) in countries with nascent PV systems (such as Kuwait). The qualitative approach based on interviews employed by the study allowed for gaining a deep understanding of the mechanisms as well as the facilitators and barriers to PV policy implementation in Arab countries. Application of the two dimensions of Matland's(115) model (i.e., the levels of policy ambiguity and policy conflict in its development and implementation) provided a novel yet manageable approach to identifying the process and factors associated with successful PV policy implementation. The study's findings suggest that the factors underlying successful PV policy implementation in Jordan and Oman were rooted in their respective approaches and include political will and/or support, policy characteristics, stakeholder involvement, training, and policy planning. In what follows, each of these factors will be discussed in the context of Matland's(115) model and other existing literature on policy implementation.

**Political will and/or support**

A key difference between Kuwait, Jordan and Oman with respect to PV policy implementation was related to the presence or absence of political support for PV. In Jordan and Oman policymakers were responsible for driving the policy implementation process and offered their support to implementors through continuous engagement and motivation. These actions reduced policy ambiguity and conflict by ensuring clarity and agreement regarding policy goals and means of achievement respectively. In contrast, political support was missing from Kuwait's PV policy process thus acting as an impediment that caused policy ambiguity to implementors regarding their roles. This would need to change to ensure implementors are motivated to follow through with implementation.

National governments play a key role in the planning and sustaining of PV systems.(246) Therefore, government support is fundamental to the establishment of a strong PV system and in ensuring that the system achieves its desired goals and continues its advancement.(81, 86, 87, 219, 247) Effective decisionmaker support has been demonstrated to motivate implementors to carry out their functions, whereas a lack of engagement by senior officials causes implementors to feel isolated and insecure.(248) This support also aids in the elimination of structural
obstacles conflicting with successful policy implementation such as resource shortages.\((249)\)

**Policy characteristics**

A distinct feature of Jordan and Oman's policies was their simplicity and attention to detail leading to low ambiguity thus making it easy for implementors to understand what was required of them. Kuwait's policy was not sufficiently clear in delineating the roles and responsibilities of each side, which is consistent with high ambiguity in Matland’s model\((115)\). This resulted in confusion among companies due to the information in the policy being incomplete. Studies have shown that policy clarity is a significant factor affecting policy implementation.\((114, 217, 250, 251)\) This is consistent with Matland’s model\((115)\) which relates policy ambiguity to the clarity of policy goals and the impact of local conditions on implementation. Policymakers in other Arab countries with nascent systems could learn from these experiences by developing a policy that clearly outlines the roles and responsibilities of all parties involved in the implementation process.

Governments of developing countries often devise policies with ambitious goals without considering the practicality of implementing them given the local contextual factors. This results in an implementation gap with many policy goals left unfulfilled.\((252)\) This issue relates to policy conflict within Matland's\((115)\) model which arises due to differences in stakeholders' views regarding how the policy goals are to be met. The Arab GVP guideline was designed as a model of best practice to be followed by countries in the region. However, it is flexible in allowing the individual countries to implement the parts that suit them at the time and based on the available resources and capacities.\((11)\) The three study countries' policies benefitted from this flexibility by focusing on aspects that could be practically implemented given their respective capacities allowing for a smoother (i.e. reduced conflict) implementation process. Therefore, this should be given greater consideration by policymakers when implementing future iterations of the policy.

**Stakeholder involvement**

In Jordan and Oman, the active involvement of members of the NPVC and the pharmaceutical industry in developing and implementing the PV policy contributed to a better understanding of its practical implementation (i.e., low ambiguity). Moreover, agreement of both sides meant less opposition (i.e., low conflict) during
policy implementation. However, in Kuwait pharmaceutical companies were not involved at any stage of the policy process. Consequently, pharmaceutical companies did not fully understand their responsibilities regarding the PV policy's implementation and thus viewed it as highly ambiguous. PV is an overarching issue requiring participation from all stakeholders for successful implementation. Stakeholder engagement and involvement in the policy development and implementation process has been identified as an important means of ensuring a sense of ownership of the policy.(253, 254) Stakeholders, depending on which group they belong to, may possess important information regarding an issue, be impacted by a policy decision, or be in a position to affect a policy decision.(253) In carrying out the dual role of purchaser and regulator of medicines, governments might lack important information which makes them reliant on the sector they are over-seeing (i.e. the pharmaceutical industry) to provide them with it.(255) Because of the knowledge and technology it possesses, the pharmaceutical industry is uniquely placed to contribute to policy development and implementation.

**Training**

In Jordan and Oman policy implementors from both sectors (i.e., the NPVC and PI) underwent training thus facilitating implementation by ensuring that all involved parties understood their roles and responsibilities (i.e., low ambiguity). In Kuwait however, the absence of training related to the policy meant that implementors (particularly from the industry) lacked knowledge regarding the policy (i.e., high ambiguity). Given the important role human resources play in the policy implementation process, ensuring proper training and orientation regarding the policy becomes a priority.(254) Properly trained policy implementors possess greater competency and self-belief to overcome obstacles that they may face.(251, 256, 257)

**Planning**

The presence of a strategic plan for the implementation process, which includes priorities, goals, and timelines, is an important prerequisite for successful policy implementation.(258) Furthermore, for a policy to be fully implemented, sufficient time is required, which is often underestimated by policymakers.(259) The highest level of policy implementation planning was observed in Jordan, while at the other end of the spectrum was Kuwait, where setting an implementation plan seemed to be neglected. Moreover, it was observed that Jordan and Oman's pharmaceutical
companies were provided appropriate implementation timeframes, which decreased policy conflict thus facilitating proper policy implementation. The lack of a comparable implementation timetable in Kuwait meant that implementation in some companies was delayed.

Part of Jordan's PV policy planning also meant having mechanisms in place for monitoring, evaluating, and enforcing policy implementation by conducting inspections of companies' PV systems and processes. This served as a tool for the NPVC to positively educate pharmaceutical companies on the proper implementation of the policy. Whilst Oman’s policy did contain provisions that would allow PV inspections to be undertaken in the future, this tool was not available in Kuwait. Therefore, these countries’ NPVCs were not able to evaluate companies' implementation of the policy and take corrective actions as required. The presence of such a mechanism permits continuous progress assessment, provides transparency as well as accountability and serves as a means of comparison across locations and time. Moreover, it serves as a means of obtaining feedback on policy implementation progress, which permits policymakers to make the necessary adjustments as needed. This points to policy implementation planning having a role in the reduction of policy ambiguity and conflict.

**Policy ambiguity and conflict and its relation to the implementation process**

Applying Matland's(115) model to the factors impacting the PV policy implementation process in conjunction with participants’ views on its ambiguity and conflict enabled the discernment of policy ambiguity and conflict levels within the three countries, and the type of implementation strategy being followed. The presence of both low policy ambiguity and conflict in Jordan and Oman points to the presence of a structured approach to policy development and implementation. This suggests that the implementation process' characteristics in these countries were consistent with what Matland(115) describes as "administrative implementation". Given that the implementors were clear about and supportive of the goals of the policy in this type of implementation, the primary strategy becomes ensuring that adequate resources are provided by those at the top. In Kuwait however, while participants’ views and the cited factors impacting policy point to high ambiguity, there were differences in terms of policy conflict. On the one hand, participants’
views surrounding policy conflict pointed to low conflict, while on the other hand, the cited factors’ impact pointed to an increase in conflict. This suggests policy implementation falling in between the "experimental implementation" and “symbolic implementation” processes. In both cases, success is variable across locations and is dependent on contextual factors such as the actors involved and resource availability. However, in the former, the process' focus is on learning about policy impacts.(115) While in the latter, successful outcomes are often “determined by the coalition of actors at the local level who control the available resources.”(115, p. 168) Both mechanisms are consistent with the differences in policy implementation by companies in Kuwait due to it occurring based on each company’s understanding. Therefore, it is recommended that policymakers follow a more structured process in developing and implementing pharmacovigilance policy to reduce ambiguity and conflict, thus moving in the direction of "administrative implementation".

7.4. **Strengths and limitations**

A strength of this programme of research was its combination of a narrative literature review of existing evidence of PV system performance along with a mixed-methods study of PV system strengths and weaknesses and a qualitative study of PV policy implementation in three Arab countries with different PV system performance levels. By adopting this novel approach of studying PV systems from the dual perspective of system performance and policy implementation, this programme of research's contribution brought more than just geographical diversity to the literature. The programme of research also shifted the focus of the evidence base away from the description of the structures of and practices carried out by Arab (and by extension developing) countries’ PV systems to provide a more critical understanding (or explanation) as to how factors affecting performance and implementation contribute to the differences existing between countries' PV systems' levels of development. Applying the WHO PV indicators(7) and Matland's(115) ambiguity-conflict model, which are considered to be well recognised in their respective fields, as theoretical frameworks provided a holistic understanding of the interplay of the multiple factors affecting PV system performance and policy implementation. The WHO PV indicators are a validated tool that facilitated conducting a comprehensive evaluation of PV system performance at the national
level, thus allowing benchmarking, and comparing countries' system performance to one another. Matland's ambiguity-conflict model provided a framework to understand mechanisms of policy implementation and the expected difficulties in implementation under different conditions.

One of the main limitations of the WHO PV indicators as a tool is that for each indicator, a specified limitation is mentioned in the WHO PV manual. For example, the structural indicators are limited in their ability to fully capture the functionality of the PV system where the response is dichotomous. Therefore, this necessitated asking follow-up questions to obtain more comprehensive information. Another limitation was the absence of a weighting and quantification scoring scheme. Therefore, a scoring scheme was designed for studies One (narrative literature review, Chapter Four) and Two (mixed-methods study, Chapter Five). However, neither study included any testing of the scoring scheme's reliability. Finally, there was a difficulty associated with obtaining the values for the outcome indicators since they usually require the assistance of individuals with expertise in areas such as diagnostics or health economics, which are not readily available in developing countries, to carry out in-depth studies involving standard protocols. This limitation was overcome through relying on the study participants, specifically the countries' PV leadership, to provide the information where available.

In terms of Matland's ambiguity-conflict model, one of its main limitations is that it avoids seeing the level of policy discretion as something explicitly chosen by policymakers, recognising how it may be a function of policy conflict. This gives rise to questions regarding the ease of labelling policies in the way that he does. Another criticism of this model relates to Matland's arguments relating to bottom-up implementation, specifically that policy implementors (i.e. members of the NPVC and pharmaceutical industry) are not particularly responsive to the patients that they ultimately serve. This goes against the fact that although street-level bureaucrats (i.e. local actors/policy implementors) are protected from patients via civil service, unions, and tenure rules, these do not protect them from the threat of patient distrust and hostility.

This programme of research's use of a mixed-methods approach enabled it to provide an evaluation of the strengths and weaknesses affecting PV systems' performance in the three study countries from both a qualitative and quantitative perspective. The
quantitative data permitted the characterisation and visualisation of countries' national PV systems' performance to understand PV system capacities. The qualitative data provided an in-depth understanding of the views and perceptions of PV stakeholders operating as part of the PV system in their respective countries. In addition, it provided detailed information on the policy implementation process and the factors impacting it. The use of theory in combination with a documentary review, analysis of key informants' views on PV system performance and policy implementation along with survey data on system performance indicators helped strengthen the development of feasible PV policy recommendations and an implementation plan for Kuwait. In terms of the contribution made by this programme of research, the accomplishments of each of the three studies are outlined in what follows.

Study One (Chapter Four) was the first study to review and synthesise evidence from published peer-reviewed studies focusing on the evaluation of PV system performance and activities in developing countries. The study provided an in-depth understanding of the various factors affecting PV system performance and activities. It also provided an up-to-date and comprehensive analysis of the areas of the PV systems in these countries which require improvement. In addition, the review allowed for a detailed comparison of countries belonging to different regions across the globe. The main limitation of this study was that only the author was involved in study selection and data extraction. However, this was mitigated via the supervisors' review of the extracted data and having discussions regarding any queries that arose.

Study Two (Chapter Five) was the first study to employ an internationally recognised and valid tool in the form of both the WHO's "Core" and "Complementary" indicators to explore the structures, processes, and outcomes as well as identify the strengths and weaknesses of three Arab countries' PV systems which were at different levels of performance. The use of a mixed-methods approach involving document review, key informant interviews, and a survey permitted the identification and triangulation of information regarding the implemented PV systems' areas of best practice and challenges both qualitatively and quantitatively. In this way, the study was able to minimise some of the shortcomings associated with the WHO PV indicators. The main limitation of this study relates to that of obtaining data for many of the "Process" and "Outcome" indicators which requires
adherence to good documentation and record-keeping practices within the setting being studied, which is not a common feature of nascent systems. Moreover, there was a general lack of awareness among NPVC staff regarding the use of measuring indices for PV system performance monitoring and evaluation, therefore much of this type of data was neither collected nor kept a record of.

Study Three (Chapter Six) was novel in its use of a theoretical model from the field of policy implementation research (i.e. Matland's(115) ambiguity-conflict model) to perform an exploration of the PV policy implementation process in three Arab countries with differing levels of system performance. This led to the identification of the processes and factors associated with successful PV policy implementation in Arab countries which in turn helped inform the development of recommendations for implementation of PV policy in countries with nascent systems. The qualitative approach employed by the study and the inclusion of members of the pharmaceutical industry as participants in the study represented a strength since it facilitated the collection of in-depth perspectives from both sides of the public-private divide. The main limitations were the potential for participant response or recall bias to occur given the use of interviews as a method of data collection.

7.5. Research implications

This programme of research has resulted in the development of recommendations for strengthening the PV system and a PV policy implementation plan to guide policymakers in Kuwait and other Arab and developing countries with nascent PV systems in their efforts in developing and implementing PV systems and policies (Section 7.8). It is hoped that the findings of this programme of research will assist in successful PV policy implementation and strengthening of the structures, processes, and outcomes of these countries' PV systems. Moreover, the findings and recommendations of this research can contribute to greater standardisation and consistency in terms of PV policy implementation and system performance.

The increase in access to and use of medicines globally accompanied by the ongoing development of new and more complex drugs has increased the number of ADRs occurring.(1, 3, 263) Moreover, quick approvals, prioritisation, and expedited reviews of applications for novel medications which have experienced an increase in
popularity in recent years (264) necessitate the development and implementation of more comprehensive and better-performing PV systems. This is especially the case in Arab and developing countries where, as demonstrated in Studies One and Two (Chapters Four and Five respectively), overall PV system performance is low, particularly in the areas of process and outcome compared to the structural aspects in place in the setting. This suggests that governments are realising the importance of having a PV system in place, however, these systems cannot adequately monitor and ensure medicines' safety following market release. (128, 171, 210, 211) Studies One and Two's findings showed that there is a need for greater prioritisation of PV by national governments as part of their public health policies' portfolio through providing the necessary legislative enforcements, resources, and expertise as part of a well-structured system in each country. Strengthening PV systems in Arab and other developing countries requires a multistakeholder approach thereby leading to greater synergy and better coordination in creating and sustaining advocacy and actions that support PV. More efforts are needed in coordinating regional efforts so that experience and expertise from advanced systems can be utilised in bolstering nascent systems. Study Two showed that the establishment of regional collaborations can help countries overcome shared barriers to drug safety monitoring such as the low number of ADR reports for signal detection and scarcity of individuals with technical expertise in PV through resource and data consolidation. Such collaborative efforts can also help in building capacity and assisting in the development of PV in countries with nascent systems. Furthermore, there is a need for applying a holistic approach that takes into account the resources and infrastructure available when addressing the gaps in each country.

In developing the guideline on GVP for Arab countries, the Arab League has provided its member countries with a significant amount of guidance regarding the activities to be carried out as part of their PV systems. (174) However, it can be argued that in the GVP guideline "there is not enough practical, crystal clear guidance for a G'X'P, and far too much breadth in the overall subject..." (265, p. 430) Moreover, there is little mention of how to handle some of the challenges faced by PV systems in the region such as ADR underreporting and poor quality of ADR reports. In developing countries, overly complex and burdensome national PV policies and systems are unlikely to be sustainable, especially in settings where
infrastructure and resources are limited. Therefore, this programme of research presents an approach for the strengthening national PV policy implementation and system performance moving from a core framework to the more advanced capabilities. This is further explained in what follows.

A significant finding from studies One and Two was that ADR reporting rates were low in Arab and developing countries. This hampered developing countries’ systems’ ability to detect signals and utilise local data to make regulatory decisions regarding drug safety that may be more appropriate to their local context than those taken in developed countries. Moreover, the two studies found that, in many countries, PV was absent from the curriculum of HCPs and that most countries' NPVCs did not provide PV training for patients which could be contributing to the low ADR reporting rate problem. Therefore, there is a need for more efforts by members of the NPVC to stimulate ADR reporting by the different groups of stakeholders as this represents the backbone of any functioning PV system. Given the limited resources available to many countries in the region, this could be achieved through performing joint campaigns with members of the pharmaceutical industry who are in a better position in terms of financial and human resources than the NPVC. These campaigns would include the distribution of educational materials, conducting workshops or seminars to promote PV and its importance. There is also a need for further emphasis to be placed on developing a broad and long-term strategy to ensure education in PV reporting, which would include HCPs' curricula through collaborations with educational institutions.

Findings from Study Three (Chapter Six) can help guide both the development and implementation of PV policy in countries with nascent PV systems. In this study, it was demonstrated that successful PV policy implementation was rooted in the mechanism of implementation followed, and in the presence or absence of different factors which impacted the degree of ambiguity and conflict associated with the policy's means and goals (e.g., political will/support, stakeholder involvement, policy clarity). These factors need to be acknowledged and taken into consideration by decision-makers in countries with nascent PV systems when formulating and implementing PV policy. For example, decision-makers’ relationships with implementors need to be strengthened through continuous engagement and communication to provide guidance and motivation. Similarly, it must be ensured
that all relevant stakeholders (including the NMRA, PI, and HCPs) are involved in the policy development and implementation processes whereby their feedback is taken into consideration. There is a greater need for stakeholder engagement through training and awareness building to increase capacity and participation in implementing the policy. It should be ensured that the developed policy be consistent with available capacities and capabilities. Similarly, it should be ensured that the policy clearly outlines the roles and responsibilities of all stakeholders involved in the implementation process and be bound into law. Planning should be carried out prior to policy implementation whereby the process’ needs in terms of resources are assessed, objectives and milestones with suitable timeframes are outlined, and suitable adjustment periods are provided. Policy implementation should follow a stepwise approach that is gradual whereby as time passes the aspects of the policy that are implemented increase in their level of complexity. There is a need to have in place a process for monitoring and evaluating policy implementation consistency, accuracy, and compliance which is non-punitive. The aforementioned factors suggest that policymakers follow a more structured process in developing and implementing PV policy to reduce ambiguity and conflict, thus moving in the direction of what Matland(115) describes as "administrative implementation".

From studies Two and Three (Chapters Five and Six respectively) it was revealed that there were differences in the three Arab countries' implementation of PV system structure, process, and outcome as well as PV policy thus pointing to a lack of harmonisation despite them being derived from a common source (i.e., the guideline on GVP for Arab countries). Effective PV must be global(266, 267), however, the question remains whether harmonisation of PV and regulatory actions among countries in the Arab World can be achieved given the disparity in the degree of PV system development, resource availability, and extent of implementation of the Arab GVP guideline among the different countries in the region.

Harmonisation of PV aims to increase worldwide consistency in the collection of safety information, increase the quality of safety reports, and expedite their regulatory review(267). Advocates of harmonisation argue that it reduces the administrative burden on companies’ PV systems by eliminating (or reducing) the amount of duplication of actions performed to satisfy the requirements of multiple jurisdictions thereby streamlining the overall process.(268) Furthermore, it is argued
that it results in increased international cooperation in PI regulation through the pooling of intellectual resources, thus improving regulatory efficiency and expertise. (269) However, the argument against harmonisation comes from countries' unwillingness to forego particular national interests and sovereignty as part of the process. (269) Moreover, there are scientific concerns that limit the extent to which harmonisation can occur. Differences in demographics between countries, drug volume usage, and drug toxicity susceptibility mean that there is no justification for combining safety data from different countries into a single pool and regarding it as homogenous. (269, 270) Furthermore, the heterogenous nature of different countries' data make the extrapolation of one country's data to another unjustified. (270) Added to this is the differences in the way different jurisdictions interpret, implement, and follow international safety reporting standards. (267)

Studies One and Two (Chapters Four and Five respectively) showed how there was a need for countries to form regional coalitions/partnerships for them to overcome limitations such as the under-reporting of ADRs which hamper signal detection and subsequently the ability to take regulatory actions. Furthermore, in Study Three (Chapter Six) it was demonstrated how lack of regulatory harmonisation among countries in the region represented a barrier to companies' successful implementation of PV policy in the individual countries. Based on this programme of research's findings and the arguments for and against harmonisation discussed above, it becomes evident that the ideal situation should represent a middle ground whereby involving a combination of mutual recognition, agreement on minimal substantive and procedural requirements that each country's system must satisfy and regulatory forbearance. (271) In this scenario although some freedom to regulate is forfeited, countries maintain their sovereignty and flexibility to make decisions based on national interests. (270, 271) NPVCs have developed electronic and paper-based methods to facilitate ADR reporting, however, variations exist regarding the data elements for ADR reporting. As a step towards harmonising PV activities, countries could begin by focusing on this activity. Differences exist in PSUR requirements in the different countries where products are marketed thus requiring a different format, content, period covered, and filing date. Hence, countries could focus on PSURs, specifically with respect to format and content, submission cycle, and requiring submission by MAHs of generic products. This would reduce confusion and
unnecessary duplication of work for MAHs and NPVCs and could have a positive effect on the quality of reports. Based on the findings from studies One and Two (Chapters Four and Five respectively), individual countries' NPVCs struggling with ADR under-reporting should make an effort to share their ADR reporting data. However, it must be ensured that any international analysis of ADR reports made to their NPVCs should preserve the integrity of the national ADR register and, where possible correlate the reports with the extent of national drug usage. (270) This could serve as a means of harmonising signal detection among countries in the region.

In developing the Arab GVP guideline, which aims to harmonise PV practices and regulations among Arab countries, the Arab League has taken into consideration the need for establishing regulatory harmonisation while maintaining member states' national regulatory sovereignty. Hence, the guideline is seen as a model of best practice and does not undermine the right of Arab countries' NMRA s to have additional or different requirements. (11) This also serves to enable countries' continuous planning of improvement and development of their PV systems. As previously stated, the research findings here suggest a lack of uniformity in the implementation of the Arab GVP guideline among Arab countries with each of them adopting the guideline differently thus making companies' efforts at maintaining compliance across different jurisdictions difficult. For harmonisation efforts to succeed requires the Arab League to take a more proactive role as a central organising force that prevents diverging national interests from hampering harmonisation efforts. (269)

7.6. Unanswered questions and future research

This programme of research provided an evidence base for policymakers and researchers concerning strengthening PV policy implementation and subsequently system performance. This could inform the development and implementation of a better harmonisation of PV policies and systems among Arab countries which can help ensure patient safety. Additionally, the innovative approach of adopting the combination of the WHO PV indicators and Matland's (115) ambiguity-conflict model of policy implementation in this programme of research provides a platform for future research which looks to explore how PV policy implementation and subsequent system performance can be improved, particularly in countries where PV
is in the nascent stage. Below is a description of what matters are left outstanding regarding the programme of research and the future work that could be carried out to resolve them.

7.6.1. Evaluation of PV systems of healthcare facilities and pharmaceutical industry

The findings from this programme of research provided an evaluation of Jordan, Oman, and Kuwait's national PV systems in terms of structure, process, and outcome and identified their areas of strengths and weakness. The question that remains unanswered here relates to the level of PV system performance within the healthcare facilities and the pharmaceutical companies operating in these countries. Therefore, there is a need to apply these indicators to the PV systems present in these settings to complement the evaluation conducted at the national level to ensure appropriate comparative analysis of the systems in the three countries.

7.6.2. Pharmacovigilance systems' outcomes evaluation

This thesis highlighted that outcome data for Arab countries' PV systems were lacking, therefore the effects (results and changes) of and due to PV activities being carried out as part of their systems could not be properly assessed. Data regarding the extent of realisation of the PV systems' objectives are of utmost importance as a tool for advocacy to persuade policymakers regarding the provision of resources. Consequently, there is a need to evaluate the impact of Jordan, Oman, and Kuwait's as well as other Arab and developing countries' PV systems from a financial and particularly patient safety perspective.

7.6.3. Identification of the factors impacting PV policy implementation for other stakeholders

The findings from this programme of research identified the factors impacting PV policy implementation in the three study countries from the perspective of the members of the NPVC and the pharmaceutical industry. This, however, meant that the perspectives of other stakeholders who play an important role in PV policy implementation were not considered. Future research could focus on the views of other stakeholder groups including HCPs, academics, and patients regarding the PV policy and its implementation in the study countries.
7.7. Reflections on the research

An important challenge to any programme of research relates to the issue of bias or potential distortion of the research outcomes due to unintended influence from the researcher and/or the research participants.(272) Therefore, ensuring research credibility through the process of personal reflection allows researchers to recognise that their involvement as an active participant in the research process shapes the nature of the process and the knowledge produced through it.(273) This may include reflecting on political and professional beliefs, social position, immigration status, sexual orientation, linguistic tradition, personal preferences, theoretical orientations, and emotional responses to participants.(274, 275) In what follows, the author's reflections on the research process based on his personal experience of the process are presented.

Research suggests that individuals conducting cross-cultural research should be 'insiders', which means that only those who share social, cultural, and linguistic characteristics with the research participants would be suitable to do the research.(276) Therefore, the fact that the researcher was an insider given his nationality and position as a member of Kuwait's NMRA as well as possessing a similar cultural and linguistic background as the participants involved in the study facilitated conducting the study. The insider status also allowed the researcher to gain the participants’ trust based on shared experiences which assisted in gaining an in-depth understanding of the situation being investigated. However, there were issues that the researcher had to consider as part of conducting studies Two and Three.

The nature of the subject of research meant that obtaining honest views from participants as part of the semi-structured interviews was a concern. This was because participation in the study entailed participants possibly being critical of decision-makers or being perceived as expressing negative views about the country or its PV system (particularly in the case where the participant was a foreign national residing in the country). Hence the researcher anticipated difficulty in obtaining information that may be deemed as sensitive thus negatively impacting the programme of research's credibility. For this reason, it was believed that a method that put the researcher in a one-on-one setting with each participant would be better suited as a means of data collection as opposed to one involving a group setting. As
such, it was decided that semi-structured interviews were better suited for data collection compared to focus groups. In hindsight, it is believed that this approach proved to be successful as it afforded the individual participants the necessary privacy to comfortably express their views without judgement.

As part of the data collection process, the researcher had prepared to take notes in the case where a participant did not consent to audio record the interview. As part of the process of establishing rapport, at the start of the interview, the researcher introduced himself to participants from the NPVCs in Jordan and Oman as well as members of the pharmaceutical industry in all three countries as a member of the Kuwaiti NMRA. It was also made clear that the study was being undertaken by the researcher in his role as a PhD student with the University of Manchester. It was important that participants' fears regarding the intentions of the interviews be allayed by explaining that the research's purpose was to develop a better understanding of the local contextual factors impacting PV to help improve PV in Kuwait and other Arab countries with nascent systems. As such, the study was not meant to serve as a criticism of the current situation or practices in their respective settings. Furthermore, it was made clear to participants at the outset that there were no right or wrong answers, particularly when it came to expressing their opinions on issues such as strengths and weaknesses or facilitators and barriers. Maintaining NPVC participants' confidentiality represented a challenge considering that there was only a small number of interviewees from each NMRA who fit the study's inclusion criteria which meant that complete anonymity could not be guaranteed. This issue was dealt with by assuring participants' that details of their participation and anything discussed during the interview would not be divulged to anyone. In addition, participants were assigned codes to conceal their identity.

The subject of the programme of research was of great interest to the researcher who possessed prior knowledge of aspects related to the drug regulation process in Kuwait. Hence, it was important to ensure that the researchers' personal opinions regarding the subject under investigation did not impact the need for impartiality when conducting the interviews and analysing the data by remaining open-minded. Efforts to reduce this included ensuring that questions asked were clear and neutral, showing unconditional positive consideration to participants' beliefs, and being mindful of his own assumptions.
In studies Two and Three (Chapters Five and Six), the interviews followed an iterative approach which allowed for extending the study sample to include members of the pharmaceutical industry. This was important because it not only provided the researcher with perspectives on the PV systems and policy implementation in the three countries by stakeholders who served as an important component and played an important role in PV but also because their participation provided an alternative perspective to that of members of the NPVC. This also helped provide a more balanced and comprehensive understanding of the situation in each country, particularly in the absence of the views of HCPs and patients.

7.8. Recommendations

Having identified the factors impacting PV system performance as well as the mechanism for and elements affecting successful PV policy implementation, it becomes possible to form a set of recommendations that are consistent with the literature surrounding PV and policy implementation and takes the findings from this programme of research into consideration. The recommendations are presented in two distinct sections: the first provides a list of recommendations for strengthening PV system performance and the second sets out the recommendations for PV policy implementation.

7.8.1. Recommendations for strengthening pharmacovigilance systems' performance

1- Lobby national governments and political parties on the importance of having a functional national PV system to obtain their commitment to supporting the system with legislation as well as suitable and sustained resources.

2- Develop a statutory provision outlining the respective obligations of MAHs and the NMRA to set up systems for PV to collect, collate, and evaluate ADRs and take the appropriate regulatory corrective actions to mitigate the risks certain medicines pose.

3- An assessment of the required resources must be carried out to ensure that the necessary resources are provided, including:
   a. Financial resources that consider country size and population as well as the anticipated rate at which the system is going to generate reports.
b. Human resources sufficient in number and possessing the necessary qualifications and expertise in PV considering the total population, scope of products, and the mode of PV activities.

4- Ensure the establishment of key organisational and infrastructure elements including:

a. A dedicated and officially recognised national PV centre (either an independent institution or as part of a governmental institution e.g. the NMRA) possessing its own organisational structure.

b. A standardised electronic and paper-based ADR reporting form that is easily accessible to all HCPs and patients in the country.

c. An information technology (IT) infrastructure inclusive of an electronic ADR database using the WHO's VigFlow software.

d. An independent national PV advisory committee made up of HCPs from different healthcare backgrounds to provide the NPVC with expert feedback regarding the quality of procedures including data collection, assessment, and interpretation as well as the communication of drug safety information.

5- Increase HCP awareness regarding PV and ADR reporting via lectures, workshops, scientific meetings, sessions at conferences, as well as printed educational materials and publications in professional journals.

6- Stimulate public participation in the ADR reporting process by disseminating information about reporting processes and attracting attention to the need to report ADRs through newsletter articles, programmes in general media, and sensitization campaigns.

7- Incorporate PV as part of HCPs' university curriculum as a long-term strategy.

8- Increase collaborative efforts with other countries in the region to reduce financial and logistical burdens and overcome shortages in expertise and information.
7.8.2. Recommendations for strengthening pharmacovigilance policy implementation

1- Strengthen decision-makers’ relationships with implementors through continuous engagement and communication to provide guidance and motivation.

2- Develop a local PV policy (or guideline) that is based on the "guideline on GVP for Arab countries" which clearly describes the goals and means of implementing the policy.

3- To ensure buy-in, understanding, and adoption of the policy, all relevant stakeholders (including health authority, industry, HCPs, and patients) should be involved in the policy development and implementation processes through meaningful and regular communication.

4- Organise training sessions and programmes regarding the policy, its goals, and its means of implementation involving both members of the pharmaceutical industry (MAHs and local agent companies) and HCPs to reduce ambiguity surrounding the policy.

5- Planning should be carried out prior to policy implementation whereby the process’ needs in terms of resources are assessed, priorities are set, objectives and milestones with suitable timeframes are outlined, and suitable adjustment periods are provided.

6- Have in place a process for monitoring and evaluating policy implementation consistency, accuracy, and compliance that is non-punitive that covers all stakeholders involved in the process.

7- Ensure that policy implementation follows a stepwise approach that is gradual whereby as time passes the aspects of the policy that are implemented increase in their level of priority and complexity.

7.9. Conclusion

This programme of research explored and identified the key strengths, shortcomings, and opportunities for strengthening PV performance and policy implementation in Kuwait, which not only contributes to the development of solid evidence base in this area of research but also can inform PV development in other Arab countries with nascent PV systems. Overall, the research findings suggest that despite the recent
progress, Kuwait still requires improvement both in terms of its approach to PV policy implementation and its PV system performance. This programme of research helped highlight the different areas which require further development to ensure the development of a robust national PV system capable of ensuring patient safety.

The findings of this programme of research highlight the need for applying a holistic approach that takes into account the resources and infrastructure available when addressing the policy and programmatic gaps in each country. The lessons learned from studying Kuwait along with Jordan and Oman can help guide both the development and implementation of PV systems and policy in other countries with nascent PV systems and move countries in the region closer towards their shared goal of harmonisation based on the Arab GVP guideline. Additionally, the findings demonstrated that more efforts are needed in coordinating regional efforts so that experience and expertise from advanced systems can be utilised in bolstering nascent systems. The Arab GVP guideline, with its aim of unifying PV procedures and activities among Arab countries, offers an opportunity to facilitate such efforts. However, there is a need for the Arab League to take a more proactive role as a central organising force for this goal to be realised.
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Appendix I: UREC study approval

The University of Manchester

Appendix I: UREC study approval

[Table]

This appendix is effective for a period of five years however please note that it is only valid for the specifications of the research project as outlined in the approved documentation set. If the project continues beyond the five year period or if you wish to propose any changes to the methodology or any other specifics within the project, an application to send an amendment must be submitted for review. Failure to do so could invalidate the licence and constitute research misconduct.

You are reminded that, in accordance with University policy, any data carrying personal identification must be encrypted when not held on a secure university computer or kept securely in a location which is accessible only to those involved with the research.

Reporting Requirements:
You are required to report in the following:
1. Annexure

Page 1 of 2

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2. Breaches and adverse events
3. Notification of progress/exit of the study

Feedback

It is our aim to provide a timely and efficient service that ensures transparent, professional and proportionate ethical review of research with consistent outcomes, which is supported by clear, accessible guidance and training for applicants and committees. In order to assist us with our aim, we would be grateful if you would give your view of the service that you have received from us by completing a UREC Feedback Form. Instructions for completing this can be found in your approval email.

We wish you every success with the research.

Yours sincerely,

[Signature]

Ms Lubica Stanikova
Secretary to University Research Ethics Committee 5
Appendix II: UREC amendment approval – Widening participant inclusion criteria

**Please ensure you read the contents of this message. This email has been sent via the Ethical Review Manager (ERM) system on behalf of the University of Manchester.**

Dear Mr. Hemza Gerashi,

Thank you for submitting your amendment request on 26/03/2019 13:15 for project 2019-3900-9911, entitled Arab GVP guideline implementation which has now been approved. Your documentation has been suitably updated to reflect the proposed changes. Please ensure you use this documentation.

Please note that if you have submitted revised supporting documents to accompany your amendment request, the approved versions of these are listed in a table below:

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We wish you every success with the research.

Best wishes,

Ms. Lubica Stasinkova

Secretary to University Research Ethics Committee S
Appendix III: UREC amendment approval – Survey distribution

APPROVED UREC Amendment Ref: 2021-3990-20131 (Automatic Email from the UoM Ethical Review Manager (ERM) system)
donotreply@infonetica.net <donotreply@infonetica.net>
Tue 20/07/2021 14:19 PM
To: Douglas Sterke <douglas.sterke@manchester.ac.uk>; Ellen Schafferle <ellen.schafferle@manchester.ac.uk>; Hannu Garasi <hannu.garasi@postgrad.man.ac.uk>
Cc: University Research Ethics Committee 5 <urec.5@manchester.ac.uk>

**Please ensure you read the contents of this message. This email has been sent via the Ethical Review Manager (ERM) system on behalf of the University of Manchester.**

Dear Mr Hannu Garasi,

Thank you for submitting your amendment request on 20/07/2021 14:19 for project 2021-3990-20131; entitled: Arab GVP guideline implementation which has now been approved. Your documentation has been suitably updated to reflect the proposed changes. Please ensure you use this documentation.

Please note that if you have submitted revised supporting documents to accompany your amendment request, the approved versions of these are listed in a table below.

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Please ensure you read the information on the Research Ethics website in relation to data collection in the COVID environment as well as the guidance issued by the University in relation to face-to-face (in person) data collection both on and off campus.

A word document version of this guidance is also available.

We wish you every success with the research.

Best wishes,

Miss Kate Harwsey

Secretary to University Research Ethics Committee 5
Appendix IV: JFDA letter requesting permission to conduct study
Dear Director-General of Jordan Food and Drug Administration-The Hashemite Kingdom of Jordan

Greetings,

Subject: Request Approval to conduct a Study in the Administration

It gives me great pleasure to extend to you my greetings and appreciation. I would seek your precious approval for visiting your notable administration in order to make interviews and closely review the work nature within Rational Use and Pharmacovigilance Unit, Jordan Food and Drug Administration in your country as I am preparing to collect the required information for writing my doctoral thesis on Pharmacovigilance. Considering that your country is among the countries that are advanced in this field, I have decided to conduct a study for reviewing your vast experience on this significant subject. I am sure that you will be considering my request with great interest and I wish that my visit will be approved. It will provide you with the findings of this study once it is done. Knowing that there is an attached document showing study-related information.

Best regards,

(Signed)

HAMZA YOUSUF GARASHI
Ph.D. Student, University of Manchester -United Kingdom.
Appendix V: Oman DGPA&DC letter requesting permission to conduct study
Dear Director-General of Directorate General of Pharmaceutical Affairs and Drug Control-Sultanate Oman

Greetings,

**Subject: Request Approval to conduct a Study in the Administration**

It gives me great pleasure to extend to you my greetings and appreciation. I would seek your precious approval for visiting your notable administration in order to make interviews and closely review the work nature within Pharmacovigilance and Drug Information Department of the General Directorate of Pharmaceutical Affairs and Drug Control in your country as I am preparing to collect the required information for writing my doctoral thesis on Pharmacovigilance. Considering that your country is among the countries that are advanced in this field, I have decided to conduct a study for reviewing your vast experience on this significant subject. I am sure that you will be considering my request with great interest and I wish that my visit will be approved. It will provide you with the findings of this study once it is done. Knowing that there is an attached document showing study-related information.

Best regards,

(Signed)

HAMZA YOUSUF GARASHI

Ph.D. Student, University of Manchester -United Kingdom
Appendix VI: KDFCA letter requesting permission to conduct study
Dear Director-General of Drug and Food Control Administration

Greetings,

Subject: Request Approval to conduct a Study in the Administration

It gives me great pleasure to extend to you my greetings and appreciation. I would seek your precious approval for visiting your notable administration in order to make interviews and closely review the work nature within Quality Assurance Unit of Drug and Food Control Administration. I am preparing to collect the required information for writing my doctoral thesis on Pharmacovigilance and considering that Drug Control Administration is among the significant administrations in the field of controlling and ensuring the safety of medicines. I have decided to conduct a study for reviewing your vast experience on this significant subject. I am sure that you will be considering my request with great interest and I wish that my visit will be approved. It will provide you with the findings of this study once it is done. Knowing that there is an attached document showing study-related information.

Best regards,

(Signed)
HAMZA YOUSUF GARASHI
Ph.D. Student, University of Manchester -United Kingdom
Appendix VII: JFDA approval to conduct study

Dear colleague,
referred to your letter dated 27/5/2018, you are welcome to visit JFDA/RDU department to start your survey, you can contact me to arrange for your visit.

Head Of Jordan Pharmacovigilance And Rationale Drug Use Department
Jordan Food And Drug Administration
E-Mail: Nidaa.bawaresh@jfda.jo
Mobile no.: +962-795038998
Appendix VIII: Oman DGPA&DC approval to conduct study
Dear Mr. HAMZA YOUSUF GARASHI

Greetings,

Subject: Request Approval to Conduct a Study in the Directorate

With reference to the above subject, I would like to inform you that we have accepted your request to visit the Directorate and closely review the work nature within Pharmacovigilance and Drug Information Department. Please contact the Director of this Department, Mr. HUSAIN AL-RAMEMI (husain74@hotmail.co.uk) for coordination thereof.

Best regards,

Dr. / MOHAMMAD BIN HIMDAN AL-RABEE
General Manager
Appendix IX: KDFCA approval to conduct study

Hamza Garachi

From: Sara Al Maqseed <sara.almaqseed@mon.gov.kw>
Sent: 16 June 2018 16:25
To: Hamza Garachi
Subject: Re: Study Approval Request

Follow Up Flag: Follow up
Flag Status: Flagged

Dear Mr. Garachi,

I'm here to let you know that would be my pleasure to provide you with all the support you require in collecting your data as best possible.

Best of luck
Sarah
Ph. Sara J. AL-Maqseed
Registration and Release Superintendent
Pharm. & Herbal Medicines Reg. & Control Admin.
Kuwait MOH

From: Hamza Garachi <hamza.garachi@postgrad.manchester.ac.uk>
Sent: Wednesday, June 13, 2018 1:34 AM
To: Sara Al Maqseed
Subject: Study Approval Request

Dear Ph. Al-Maqseed,

As per our telephone conversation please find attached to this message a letter requesting approval to conduct my study at the Pharmaceutical and Herbal Medicines Registration and Control Administration, Kuwait. Also attached are a copy of the study information sheet as well as a letter indicating that I am a student enrolled in the PhD program at the University of Manchester.

Your assistance is highly appreciated.

Regards,

Hamza Garachi
Appendix X: Narrative literature review (Study One) – Search strategy

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Appendix XI: Narrative literature review (Study One) – Study quality appraisal scores

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<th>Introduction and Aims</th>
<th>Method and Data</th>
<th>Sampling</th>
<th>Data Analysis</th>
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<td><strong>3.67</strong></td>
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<td><strong>0.48</strong></td>
<td><strong>0.68</strong></td>
<td><strong>0.86</strong></td>
<td><strong>0.62</strong></td>
<td><strong>0.54</strong></td>
<td><strong>0.59</strong></td>
<td><strong>0.48</strong></td>
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Appendix XII: Participant background information questionnaire

A strategy for the implementation of the ‘guideline on good pharmacovigilance practices (GVP) for Arab countries’ in countries with nascent pharmacovigilance systems

Questionnaire

1. Educational background:
   A) Pharmacy   B) Medicine   C) Other (please specify):

2. Educational level
   A) Bachelor’s   B) Master’s   C) PhD

3. Number of years employed in current organization:
   years

4. Position currently employed in within the organisation:

5. Number of years working in current position within the organisation:
   years

6. Number of years of experience working in pharmacovigilance:
   years

7. Age:  years


Thank you for taking the time to fill out this questionnaire, your help towards the completion of this research project is highly appreciated.
Appendix XIII: Interview topic guide

A strategy for the implementation of the “Guideline on good pharmacovigilance practices (GVP) for Arab countries” in countries with nascent pharmacovigilance systems

Interview Schedule

Introduction

I’d like to take this opportunity to thank you for taking the time to participate in this study about the development of a strategy for the implementation of the ‘guideline on good pharmacovigilance practices (GVP) for Arab countries’. My name is Hanna Ganszli, and I am a PhD student at the University of Manchester.

The purpose of this interview is to explore your views concerning this subject. As part of the interview, you will be asked questions relating to pharmacovigilance in your country. These questions will explore topics relating to the pharmacovigilance system in place, the implementation of pharmacovigilance as a policy, and finally, the implementation of the GVP for Arab countries.

It is worth noting that this is an open discussion and at each, you are not expected to know the answer to all the questions asked. The objective is for you to express your views irrespective of whether they are positive or negative, as both are considered to be informative and useful for the study. There are no right or wrong answers.

The discussion will be audio recorded to ensure that no important or relevant information is missed. You can rest assured that complete confidentiality will be maintained and that no names will be used in future reports or publications.

Topics:

1- Pharmacovigilance structure and function issues:

In this first part of our interview, I would like to ask you a number of questions which will allow me to map the pharmacovigilance systems currently in place in your country.

a. Question(s) exploring the structure and function of the pharmacovigilance department or centre
additional monitoring and/or additional risk minimisation

b. Question(s) exploring the structure and function of the country’s pharmacovigilance system

i. Main organisations/individuals involved/operating as part of the system

ii. Reporting – who reports (physicians, patients, pharmacists, other healthcare professionals, companies), what is reported (type of product e.g. medicines, herbs, supplements, etc., new products only or all products, ADEs or ADRs or both, severity of reaction), what is done with reports e.g. causality assessment, signal detection, statistical analysis

iii. Existence of peripheral centres – location, interconnectivity and coordination with each other and the main centre, safety communication strategy with stakeholders, advisory committees

iv. Existence of PV advisory committee – representation, decision making process, frequency of meeting

v. Existence of dedicated budget for PV

c. Question(s) identifying the legal aspects related to the country’s pharmacovigilance system

i. Legal basis for pharmacovigilance – law in the country controlling practice, part of country’s medicines policy

ii. Guidelines being followed – existence of local guideline?

2. Strengths and weaknesses of pharmacovigilance department/centre and system

In the next couple of questions, I would like to explore your views on the points of strength and weakness of the pharmacovigilance department/centre and the pharmacovigilance system currently in place in your country.
2. Question(s) exploring participants’ opinions on the strengths of the pharmacovigilance department/centre as well as the country’s pharmacovigilance system – why and/or how?

b. Question(s) exploring participants’ opinions on the weaknesses of the pharmacovigilance department/centre as well as the country’s pharmacovigilance system – why and/or how?

3. Implementation process of country’s pharmacovigilance policy

I would like to shift the focus in the next few questions towards exploring your views of your country’s pharmacovigilance policy the process it underwent when it was implemented, as well as what you see as the main facilitators and barriers to this process.

a. Questions exploring the participants’ opinions on country’s pharmacovigilance policy and its goals – extent of agreement and understanding

b. Question(s) investigating the participants’ views on the implementation process of the country’s pharmacovigilance policy including resources provided for implementation – important milestones: when and what occurred? Who was involved? Why were these steps taken? How were decisions taken? Any transposition of the GVP into local regulations? If so how?

c. Question(s) exploring the participants’ views on the facilitators of the implementation process of the country’s pharmacovigilance policy – why and how

d. Question(s) exploring the participants’ views on the barriers to the implementation process of the country’s pharmacovigilance policy – why and how

4. Implementation process of ‘guideline on good pharmacovigilance practices for Arab countries’

In the final part of our interview, I would like to ask you a number of questions which will allow me to understand how the GVP for Arab countries was implemented as well as your views on the facilitators and barriers to the implementation process.

a. Question(s) exploring the participants’ opinions on the ‘guideline on good pharmacovigilance practices in Arab countries’ as a policy and its goals – extent of agreement and understanding
b. Question(s) investigating the participants’ views on the implementation process of the ‘guideline on good pharmacovigilance practices in Arab countries’ within their country – Important milestones: when and what occurred? What resources provided? Are resources provided adequate? Who was involved in the process? What aspects of the guideline were adopted and why?

c. Question(s) exploring the participants’ views on the facilitators of the implementation process of the ‘guideline on good pharmacovigilance practices in Arab countries’ within their country – also ask why and how

d. Question(s) exploring the participants’ views on the barriers to the implementation process of the ‘guideline on good pharmacovigilance practices in Arab countries’ within their country – also ask why and how

Additional questions

The purpose of this discussion was to gather information on the pharmacovigilance system in your country and how it functions, in addition to your views on the implementation process. The main reason for this was to come up with recommendations how best to implement a pharmacovigilance policy in general, and the ‘guideline on GVP for Arab countries’ in particular.

1. What recommendations would you give to Kuwait regarding the implementation of pharmacovigilance?

2. Is there anything anyone would like to add that you believe was not covered during this discussion?

3. Is there anyone that you think that I should interview as part of this study?
Appendix XIV: Questionnaire – PV system strengths and weaknesses in Jordan, Oman, and Kuwait

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<th>Respondent Comments</th>
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<tr>
<td>2. Current total number of reports in the national database</td>
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<tr>
<td>3. Percentage of total annual reports acknowledged and/or issued feedback</td>
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<tr>
<td>4. Percentage of total reports subjected to causality assessment in the previous calendar year</td>
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| 5. Percentage of total annual reports satisfactorily completed and submitted to the national pharmacovigilance centre in the previous calendar year  
  Subset indicator: of the reports satisfactorily completed and submitted to the national pharmacovigilance centre, percentage of reports committed to the WHO database |         |                     |
<p>| 6. Percentage of reports of therapeutic ineffectiveness received in previous calendar year |         |                     |
| 7. Percentage of reports on medication errors reported                                |         |                     |</p>
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<td>in the previous year</td>
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<tr>
<td>8. Percentage of registered pharmaceutical companies having a functional pharmacovigilance system</td>
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<td>9. Number of active surveillance activities initiated, ongoing or completed during the past five calendar years</td>
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**Core Outcome/Impact Indicators**

1. Number of signals detected in the past 5 years by the pharmacovigilance centre
2. Number of regulatory actions taken in the preceding year as a consequence of national pharmacovigilance activities includes:
   a. number of product label changes (variation)
   b. number of safety warnings on medicines to: (i) health professionals, (ii) general public
   c. number of withdrawals of medicines
   d. number of other restrictions on use of medicines
3. Number of medicine-related hospital admissions per 1000 admissions
4. Number of medicine-related deaths per 1000 persons served by the hospital per year
5. Number of medicine-related deaths per 100,000 persons in the population
6. Average cost (US$) of treatment of medicine-related illness
7. Average duration (days) of medicine-related extension of hospital stay
8. Average cost (US$) of medicine-related hospitalization
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<td><strong>Complimentary Process Indicators</strong></td>
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<tr>
<td>1. Percentage of healthcare facilities with a functional pharmacovigilance unit (i.e. submitting ≥ 10 reports to the pharmacovigilance centre) in the previous year</td>
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<tr>
<td>2. Percentage of total reports sent in the previous year by the different stakeholders includes:</td>
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<tr>
<td>a. medical doctors</td>
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<tr>
<td>b. dentists</td>
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<tr>
<td>c. pharmacists</td>
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<tr>
<td>d. nurses or midwives</td>
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<tr>
<td>e. the general public</td>
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</tr>
<tr>
<td>3. Total number of reports received per million population per year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Average number of reports per number of healthcare providers per year includes:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. medical doctors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>b. dentists</td>
<td></td>
<td></td>
</tr>
<tr>
<td>c. pharmacists</td>
<td></td>
<td></td>
</tr>
<tr>
<td>d. nurses or midwives</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Percentage of health-care providers aware of and knowledgeable about ADRs per facility</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Percentage of patients leaving a health facility aware of ADRs in general</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Number of face-to-face training sessions in pharmacovigilance organized in the previous year for:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assessment Indicators</td>
<td>Answers</td>
<td>Respondent Comments</td>
</tr>
<tr>
<td>-----------------------</td>
<td>---------</td>
<td>---------------------</td>
</tr>
</tbody>
</table>
| c. health professionals  
  d. the general public | | |
| 8. Number of individuals who received face-to-face training in pharmacovigilance in the previous year:  
  c. healthcare professionals  
  d. the general public | | |
| 9. Total number of national reports for a specific product per volume of sales of that product in the country (product specific) from the industry | | |
| 10. Number of registered products with a pharmacovigilance plan and/or a risk management strategy among the marketing authorization holders in the country  
  Subset Indicator: Percentage of registered products with a pharmacovigilance plan and/or a risk management strategy from the market authorization holders in the country | | |
| 11. Percentage of market authorization holders who submit periodic safety update reports to the regulatory authority as stipulated in the country | | |
| 12. Number of products voluntarily withdrawn by market authorization holders because of safety concerns in the previous year  
  Subset Indicator: Number of summaries of product characteristics (SPCs) updated by market authorization holders (MAHs) because of safety concerns in the previous year | | |
| 13. Number of reports from each registered pharmaceutical company received by the | | |
### Assessment Indicators

| Pharmacovigilance centre in the previous year |  |
| Complimentary Outcome/Impact Indicators |  |

1. Percentage of preventable ADRs reported in the previous year out of the total number of ADRs reported

2. Number of medicines-related congenital malformations per 100,000 births

3. Number of medicines found to be possibly associated with congenital malformations in the past 5 years

4. Percentage of medicines in the pharmaceutical market that are counterfeit/substandard

5. Number of patients affected by a medication error in hospital per 1000 admissions in the previous year

6. Average work or schooldays lost due to drug-related problems

7. Cost savings (US$) attributed to pharmacovigilance activities

8. Health budget impact (annual and over time) attributed to pharmacovigilance activity

9. Average number of medicines per prescription

10. Percentage of prescriptions with medicines exceeding manufacturer’s recommended dose

11. Percentage of prescription forms prescribing medicines with potential for interaction

12. Percentage of patients receiving information on the use of their medicines and on potential ADRs associated with those medicines
Subject: Invitation to participate in the research project titled: A strategy for the implementation of the ‘guideline on good pharmacovigilance practice (GVP) for Arab countries’ in countries with nascent pharmacovigilance systems.

Dear Sir/Madam,

This is a letter of invitation to consider participating in a study I am conducting as part of my Doctoral degree in Pharmacy Practice at the University of Manchester/UK under the supervision of Prof Ellen Sachse and Dr Douglas Steinke. This study aims to explore the implementation of pharmacovigilance as a policy as well as the ‘guideline on GVP for Arab countries’ in Kuwait, in addition to a select group of countries within the Arab World. To achieve this, I am planning to conduct some interviews with key officials as well as collect related documents at Y (name of the organization) in Y (country name).

Please note that the study has the approval of your organization (name of organization) that is happy for its employees to take part. Before you decide to take part in this study, it is important for you to understand why the project is being conducted and what it will involve. Please take time to carefully read the attached Participant Information Sheet and discuss it with others if you wish before making your decision on whether or not to participate in the study.

Please note that participation in the study is completely voluntary. If you decide to take part, then please contact me directly via the following email:

hamza.zarabi@nostra.manchester.ac.uk

If you have any enquiries about the study, then please do not hesitate to contact me through the following contact information:

Hamza Zarabi, e-mail: hamza.zarabi@nostra.manchester.ac.uk Tel: 444 161 275 7493

I would like to assure you that this study has been reviewed and received ethics committee approval through the Research Ethics Review Board at the University of Manchester.

I very much look forward to speaking with you and thank you in advance for your assistance in this project.

Sincerely,

Hamza Zarabi, MPharm, MSc, MBA
PhD student at Centre for Pharmacy Workforce Studies (CPWS)
Division of Pharmacy & Optometry
School of Health Sciences
Faculty of Biology, Medicine and Health
University of Manchester
Manchester M13 9PT, UK

Version 1; Date 5/10/2018
Appendix XVI: Interview participant information sheet

A strategy for the implementation of the ‘guideline on good pharmacovigilance practices (GVP) for Arab countries’ in countries with nascent pharmacovigilance systems: The case of Kuwait

Participant Information Sheet

You are being invited to take part in a research study which explores the implementation of a pharmacovigilance policy and the ‘guideline on good pharmacovigilance practices (GVP) for Arab countries’. The countries included in this study are Kuwait, Oman and Jordan. Before you decide if you would like to take part, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Please ask if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part. Thank you for reading this.

About the research

Who will conduct the research?

Hanan Gershi (Researcher/PhD student), under the supervision of Prof. Ellen Schafhautle and Dr. Douglas Steynke of the Division of Pharmacy and Optometry, School of Health Sciences, University of Manchester.

What is the purpose of the research?

The development and design of a strategy for the implementation of the ‘guideline on GVP for Arab countries’ in Kuwait and provide recommendations to other countries in the region with pharmacovigilance systems that are in the development stage.

You have been asked to take part in the study based on the fact that you are either currently or have previously worked for/in a stakeholder organisation within pharmacovigilance, such as the National Drug Authority, National Pharmacovigilance Centre, or within the pharmaceutical industry. Furthermore, you are considered to have a wealth of experience and insight relating to the aims of this research given your direct involvement in the practice of pharmacovigilance and/or the implementation of its policy and or guidelines within one of the three countries under investigation. It is anticipated that between 12 and 20 participants per country will be recruited for the purpose of the study.

Will the outcomes of the research be published?

In addition to being published as part of a PhD thesis, the findings of the research are expected to be published in peer-reviewed academic journals and presented at conferences. Furthermore, you will be given a summary report of the research findings.
Who has reviewed the research project?

The project has been reviewed by the University of Manchester University Research Ethics Committee (UREC) 5, in addition to the researcher’s supervisors Prof. Ellen Schilhause and Dr. Douglas Steinae.

Who is funding the research project?

The PhD project is being funded by the government of the State of Kuwait.

What would my involvement be?

What would I be asked to do if I took part?

If you decide to take part you will be asked to complete a brief background information questionnaire, which asks about the number of years you have been employed in your current organization, your current position, and experience in pharmacovigilance. You will also be asked to take part in a one-to-one interview, with the researcher, Hanaa Gusfali, who will ask questions related to pharmacovigilance and its implementation in your country. These will be conducted in person or, in the case where this is not possible, via Skype® or telephone. The interview will be digitally audio-recorded, with your consent, onto an encrypted device and professionally transcribed, either by the researcher, or a university-approved transcriber. You may also be asked to participate in a follow-up interview, which will also be audio recorded and transcribed, if deemed necessary by the research team in order to ask additional questions or to clarify responses given during the initial interview.

Interviews will be conducted across different locations across the Arab World, mainly Kuwait, Oman, and Jordan. They will be held on the premises of the National Drug Authorities or National Pharmacovigilance Centres of these countries, if you are currently employed at one of these organizations. In the case that you are not, then a suitable alternative venue will be arranged. In all cases the researcher will ensure that the necessary steps are taken to ensure that the individual interviews be held in a quiet environment conducive to open, uninterrupted conversations.

There are no direct benefits to participating in this study, but participation does provide you with the opportunity to contribute to recommendations for the improvement in pharmacovigilance practice in countries in the Arab World, and particularly inform policy implementation in Kuwait.

It is unlikely that participation in this research poses any risks, or that we will be discussing topics which you may find upsetting or distressing. Should this be the case, however, the interviewer will offer to temporarily interrupt the audio recording. Should you not wish to continue, the interview can be discontinued.

The duration of the research will be one interview per participant lasting up to 90 minutes, one five-minute questionnaire, in addition to the time involved in reading this document, considering whether to participate in the study, and consenting.
Will I be compensated for taking part?

There will be no compensation given for participating in the research.

What happens if I do not want to take part or if I change my mind?

It is up to you to decide whether or not to take part and your participation in the study is completely voluntary. In the case where you decide that you want to take part in the study, it is requested that you contact the researcher (Hamza Garashi) directly using the contact details provided to you by the contact person. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you agree to participate in the study you are still free to withdraw at any time without giving a reason and without detriment to yourself. However, it will not be possible to remove your data from the project once it has been anonymised as we will not be able to identify your specific data. This does not affect your data protection rights. If you decide not to take part you do not need to do anything further.

You are free to decline the interview(s) (initial and follow-up) from being audio recorded. In addition, you should feel comfortable with the recording process at all times and are free to request that recording be stopped at any time during the interview.

Data Protection and Confidentiality

What information will you collect about me?

In order to participate in this research project we will need to collect information that could identify you, called “personal identifiable information”. Specifically we will need to collect:

1- Name  
2- Gender  
3- Age  
4- Telephone number (personal or work)  
5- Email address (personal or work)  
6- Job title/role

In addition to the above information, the one-to-one interview (initial and follow-up) with the researcher will be digitally audio-recorded onto an encrypted device.

Under what legal basis are you collecting this information?

We are collecting and storing this personal identifiable information in accordance with data protection law which protect your rights. These state that we must have a legal basis (specific reason) for collecting your data. For this study, the specific reason is that it is “a public interest task” and “a process necessary for research purposes.”

What are your rights in relation to the information you will collect about me?

You have a number of rights under data protection law regarding your personal information. For example you can request a copy of the information we hold about you, including audio recordings.

If you would like to know more about your different rights or the way we use your personal information to ensure we follow the law please consult our Privacy Notice for Research.
Will my participation in the study be confidential and my personal identifiable information be protected?

In accordance with data protection law, The University of Manchester is the Data Controller for this project. This means that we are responsible for making sure your personal information is kept secure, confidential and used only in the way you have been told it will be used. All researchers are trained with this in mind, and your data will be looked after in the following way:

Only the study team at The University of Manchester will have access to your personal information. The audio recordings of the interviews will be transcribed verbatim either by the researcher or a University-approved transcribing company which holds a confidentiality agreement with the University. The interview transcripts will be anonymized during the transcription process by removing your name and any other personal identifying information and replaced with a random ID number. Only the research team will have access to the key that links this ID number to your personal information.

Details of your participation will not be divulged to anyone other than the members of the research team. As part of the study maintaining confidentiality, you are asked not to mention the names of colleagues, companies or individuals that you interact with as part of your work during the discussion. In the event that the name of any such persons is mentioned, they will be removed during transcription.

The audio recordings will be downloaded and stored in password-protected format on the University of Manchester’s secure servers until they are transcribed and will be accessible only to the research team. Audio files to be transcribed by the transcribing company will be sent to the company via secure drop box which will immediately destroy them after transcription. Likewise, audio recordings will be destroyed after they have been transcribed and checked for accuracy by the researcher. The anonymised transcript will be stored and backed up in password-protected format on the University of Manchester’s secure servers, as well as on a shared drive on the University’s data management platform and retained for five years. Any paper documents containing identifiable information including the completed questionnaires, consent forms and written notes will be stored securely in locked filing cabinets located in a locked office on the premises of the University of Manchester and will be stored for five years after the publication of the research after which they will be destroyed.

When you agree to take part in this research study, any personal identifying information collected about you will not be shared with any individual(s) or organisation(s) who is not a member of the research team. However, we will only retain these data for the purpose of contacting you to conduct a follow-up interview as part of this study if deemed necessary, as well as sending you a summary of the research findings. None of the information will be used to contact you for future research.

Any discussions taking place during the study are confidential. However, in the interest of ensuring patient safety, there may be circumstances where it may be judged that this confidentiality must be broken. Such a circumstance would be if you tell the researcher something indicating potential professional misconduct, unfitness and/or unprofessional practice that has not been previously reported to the relevant authorities. In such an occurrence, this would initially be discussed with the researcher’s supervisors to assess whether or not there is a need to report this information. If it is deemed that disclosure is necessary, the issue will be discussed with you in the first instance and you will be advised to report to the relevant bodies, or a decision may be made by the research team to disclose to the relevant professional authorities.
Please also note that individuals from The University of Manchester or regulatory authorities may need to look at the data collected for this study to make sure the project is being carried out as planned. This may involve looking at identifiable data. All individuals involved in auditing and monitoring the study will have a strict duty of confidentiality to you as a research participant.

What if I have a complaint?

Contact details for complaints

If you have a complaint that you wish to direct to members of the research team, please contact:

HAMZA GARASHI (PHD STUDENT)  
E-MAIL: HAMZA.GARASHI@POSTGRAD.MANCHESTER.AC.UK  
TEL: +44 161 275 6079

PROF. ELLEN SCHAHEUTLE (SUPERVISOR)  
E-MAIL: ELLEN.SCHAHEUTLE@MANCHESTER.AC.UK  
TEL: +44 161 275 7493

DR. DOUGLAS STEINKE (SUPERVISOR)  
E-MAIL: DOUGLAS.STEINKE@MANCHESTER.AC.UK  
TEL: +44 161 275 2324

If you wish to make a formal complaint to someone independent of the research team or if you are not satisfied with the response you have gained from the researchers in the first instance then please contact:

The Research Governance and Integrity Manager, Research Office, Christie Building, University of Manchester, Oxford Road, Manchester, M13 9PL by emailing research.complaints@manchester.ac.uk or by telephoning +44 161 275 2674.

If you wish to contact us about your data protection rights, please email data.protection@manchester.ac.uk or write to The Information Governance Office, Christie Building, The University of Manchester, Oxford Road, M13 9PL at the University and we will guide you through the process of exercising your rights.

You also have a right to complain to the Information Commissioner’s Office about complaints relating to your personal identifiable information. Tel 0303 123 1133

Contact Details

If you have any queries about the study or if you are interested in taking part then please contact the researcher, HAMZA GARASHI (contact details provided above).
Appendix XVII: Survey participant information sheet

A strategy for the implementation of the ‘guideline on good pharmacovigilance practices (GVP) for Arab countries’ in countries with nascent pharmacovigilance systems: The case of Kuwait

Participant Information Sheet (PIS)

You are being invited to take part in a research study to examine pharmacovigilance systems and policy in select Arab countries with established pharmacovigilance systems to explore and identify the factors affecting their practical implementation to provide recommendations for strengthening PV in Arab countries with nascent PV systems such as Kuwait. Before you decide whether to take part, it is important for you to understand why the research is being conducted and what it will involve. Please take time to read the following information carefully before deciding whether to take part and discuss it with others if you wish. Please ask if there is anything that is not clear or if you would like more information. Thank you for taking the time to read this.

About the research

➢ Who will conduct the research?

Hanna Garashi (Researcher/PhD student), under the supervision of Prof. Ellen Schafheitli and Dr. Douglas Stankne of the Division of Pharmacy and Optometry, School of Health Sciences, University of Manchester.

➢ What is the purpose of the research?

As you recall, you participated in a study which aimed to examine select Arab countries with established pharmacovigilance systems to explore and identify factors affecting their practical implementation to provide recommendations for strengthening pharmacovigilance in Arab countries with systems in the development phase such as Kuwait. Your kind participation provided valuable information that point to differences between the three countries’ level of success in the implementation of pharmacovigilance policy and system being related to system performance. To support these findings, your renewed participation is requested to provide numerical data based on the pharmacovigilance indicators to evaluate and compare the performance of the pharmacovigilance systems in Jordan, Oman, and Kuwait.

You are being asked to participate in this study because you consented to being contacted for the purpose of a follow-up interview during your previous participation as part of the larger study. It is anticipated that between one and six participants per country participants will be recruited for the purpose of the study.

➢ Will the outcomes of the research be published?

The findings from this research are expected to be published in a PhD thesis, as well as academic journals and presented at conferences. Some of the findings from the first round of interviews have already been submitted for publication in a scientific journal.
➢ Who has reviewed the research project?

The project has been reviewed by the University of Manchester University Research Ethics Committee (URECO) 5, in addition to the researcher's supervisors Prof. Ellen Schaffheute and Dr. Douglas Steenke.

➢ Who is funding the research project?

The PhD project is being funded by the government of the State of Kuwait.

What would my involvement be?

➢ What would I be asked to do if I took part?

If you decide to take part you will be asked to take part in a one-to-one interview, with the researcher, Hanan Gurash, who will ask questions related to the performance of your country's pharmacovigilance system based on the WHO Pharmacovigilance Indicators Tool. You will be asked to provide information relating to the system's processes e.g. number of adverse drug reaction reports received, and outcomes e.g. number of signals detected and regulatory actions taken. These will be conducted via Zoom or telephone. The interviews will be digitally audio-recorded, with your consent. You may also be asked to participate in a follow-up interview if deemed necessary by the research team to ask additional questions or to clarify responses given during the initial interview.

Interviews will be conducted with participants from Kuwait, Oman, and Jordan. They will be held remotely with the researchers in Kuwait and you at your place of work or a suitable alternative venue which ensures that the interview can be held in a quiet environment conducive to open, uninterrupted conversations.

There are no direct benefits to participating in this study, but participation does provide you with the opportunity to contribute to recommendations for the improvement in pharmacovigilance practice in countries in the Arab World, and particularly inform policy implementation in Kuwait. Moreover, you will be given a summary report of the research findings.

It is unlikely that participation in this research poses any risks, or that we will be discussing topics which you may find upsetting or distressing. Should this be the case, however, the interviewer will offer to temporarily interrupt the interview. Should you not wish to continue, the interview can be discontinued.

The duration of the research will be one interview per participant lasting up to 120 minutes in addition to the time involved in reading this document, considering whether to participate in the study, and consenting.

➢ Will I be compensated for taking part?

There will be no compensation given for participating in the research.

➢ What happens if I do not want to take part or if I change my mind?

Version 6; Date 23/06/2021
It is up to you to decide whether or not to take part. In the case where you decide that you want to take part in the study, it is requested that you contact the researcher (Hannah Gorashi) directly using the contact details provided to you. If you do decide to take part, you will be given this information sheet to keep and will be asked to sign a consent form. If you decide to take part, you are still free to withdraw at any time without giving a reason and without detriment to yourself. However, it will not be possible to remove your data from the project once it has been anonymised as we will not be able to identify your specific data. This does not affect your data protection rights. If you decide not to take part, you do not need to do anything further.

**Data Protection and Confidentiality**

- **What information will you collect about me?**

In order to participate in this research project, we will need to collect information that could identify you, called “personal identifiable information”. Specifically, we will need to collect:

1. Name
2. Email address (personal or work)
3. Job title/role

In addition to the above information, the one-to-one interviews (initial and follow-up) with the researcher will be digitally audio-recorded.

- **Under what legal basis are you collecting this information?**

We are collecting and storing this personal identifiable information in accordance with UK data protection law which protect your rights. These state that we must have a legal basis (specific reason) for collecting your data. For this study, the specific reason is that it is “a public interest task” and “a process necessary for research purposes”.

- **What are my rights in relation to the information you will collect about me?**

You have a number of rights under data protection law regarding your personal information. For example, you can request a copy of the information we hold about you.

If you would like to know more about your different rights or the way we use your personal information to ensure we follow the law, please consult our Privacy Notice for Research.

- **Will my participation in the study be confidential and my personal identifiable information be protected?**

In accordance with data protection law, The University of Manchester is the Data Controller for this project. This means that we are responsible for making sure your personal information is kept secure, confidential, and used only in the way you have been told it will be used. All researchers are trained with this in mind, and your data will be looked after in the following way.
Only the study team at The University of Manchester will have access to your personal information. Your name and any other personal identifying information will not be included anywhere. Only the research team will have access to your personal information.

Details of your participation will not be divulged to anyone other than the members of the research team. As part of the study maintaining confidentiality, you are asked not to mention the names of colleagues, companies, or individuals that you interact with as part of your work during the discussion. In the case that the name of any such person is mentioned, they will be excluded from the study.

The audio recordings will be downloaded and stored in password-protected format on the University of Manchester’s secure server until the information is entered into Excel and will be accessible only to the research team. Any paper documents containing identifiable information including consent forms and written notes will be stored securely in located in a locked office on the premises of the University of Manchester and will be stored for five years after the publication of the research after which they will be destroyed.

When you agree to take part in this research study, any personal identifying information collected about you will not be shared with any individual(s) or organization(s) who is not a member of the research team. This information will not identify you and will not be combined with other information in a way that could identify you. The information will only be used for the purpose of contacting you to conduct a follow-up interview as part of this study if deemed necessary, as well as sending you a summary of the research findings, and cannot be used to contact you regarding any other matter. None of the information will be used to contact you for future research.

Any discussions taking place during the study are confidential. However, in the interest of ensuring patient safety, there may be circumstances where it may be judged that this confidentiality must be broken. Such a circumstance would be if you tell the researcher something indicating potential professional misconduct, unsafe and/or unethical practice that has not been previously reported to the relevant authorities. In such an occurrence, this would initially be discussed with the researcher’s supervisor to assess whether there is a need to report this information. If it is deemed that disclosure is necessary, the issue will be discussed with you in the first instance and you will be advised to report to the relevant bodies, or a decision may be made by the research team to disclose to the relevant personnel/authorities.

Please also note that individuals from The University of Manchester or regulatory authorities may need to look at the data collected for this study to make sure the project is being carried out as planned. This may involve looking at identifiable data. All individuals involved in auditing and monitoring the study will have a strict duty of confidentiality to you as a research participant.

Your participation in this research will be conducted via Zoom and your personal data may be processed by Zoom. This may mean that your personal data may be transferred to a country outside of the European Economic Area, some of which have not yet been determined by the United Kingdom to have an adequate level of data protection. Appropriate legal mechanisms
to ensure these transfers are compliant with the Data Protection Act 2018 and the UK General Data Protection Regulation are in place. No recordings will made using the above third-party platform.

What if I have a complaint?

> Contact details for complaints

If you have a complaint that you wish to direct to members of the research team, please contact:

E-mail: ellen.schafheutle@manchester.ac.uk

Tel. +44 161 275 7493

Prof. Ellen Schafheutle (Supervisor)

E-mail: douglas.steiaker@manchester.ac.uk

Tel. +44 161 275 2324

Dr. Douglas Steiaker (Supervisor)

If you wish to make a formal complaint to someone independent of the research team or if you are not satisfied with the response you have gained from the researchers in the first instance then please contact:

The Research Ethics Manager, Research Office, Christie Building, The University of Manchester, Oxford Road, Manchester, M13 9PL, by emailing research.complaints@manchester.ac.uk or by telephoning 0161 306 8089.

If you wish to contact us about your data protection rights, please email: dataprotection@manchester.ac.uk or write to The Information Governance Office, Christie Building, The University of Manchester, Oxford Road, M13 9PL at the University and we will guide you through the process of exercising your rights.

You also have a right to complain to the Information Commissioner’s Office about complaints relating to your personal identifiable information. Tel +44 303 123 1113.

Contact Details

If you have any queries about the study or if you are interested in taking part, then please contact the researcher:

E-MAIL: hamza.garashi@postgrad.manchester.ac.uk

TEL. +965 66878102

HAMZA GARASHI (PHD STUDENT)
Appendix XVIII: Interview consent form

Developing the implementation of the ‘Guideline on good pharmacovigilance practices (GVP) for Arab countries’ in countries with nascent pharmacovigilance systems

**Consent Form**

If you are happy to participate please complete and sign the consent form below.

<table>
<thead>
<tr>
<th>Activities</th>
<th>Initials</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 I confirm that I have read the attached information sheet (Version 5, Date 4/2/10) for the above study and have had the opportunity to consider the information and ask questions and had these answered satisfactorily.</td>
<td></td>
</tr>
<tr>
<td>2 I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving a reason and without detriment to myself. I understood that it will not be possible to remove my data from the project once it has been anonymised and forms part of the data set. I agree to take part on this basis.</td>
<td></td>
</tr>
<tr>
<td>3 I agree to the interview being audio-recorded and transcribed (written out in full) by the researcher or a university-approved transcription service provider.</td>
<td></td>
</tr>
<tr>
<td>4 I agree that any data collected may be published in anonymous form in academic books, reports or journals.</td>
<td></td>
</tr>
<tr>
<td>5 I understood that data collected during the study may be leaked at by individuals from The University of Manchester or regulatory authorities, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my data.</td>
<td></td>
</tr>
<tr>
<td>6 I agree that the researchers may retain my contact details in order to provide me with a summary of the findings for this study.</td>
<td></td>
</tr>
<tr>
<td>7 I agree that the researchers may use my contact details in order to contact me for the purpose of conducting a follow-up interview as part of this study if deemed necessary.</td>
<td></td>
</tr>
<tr>
<td>8 I understood that there may be instances where, over the course of the interview, information may be shared which obligates the researcher to treat confidentiality, which have been explained in further detail in the information sheet.</td>
<td></td>
</tr>
<tr>
<td>9 I agree to the transfer of the data collected during the study from Kuwait, Oman, or Jordan to the U.K.</td>
<td></td>
</tr>
<tr>
<td>10 I agree to take part in this study.</td>
<td></td>
</tr>
</tbody>
</table>

**Data Protection**

The personal information we collect and use to conduct this research will be processed in accordance with data protection law as explained in the Participant Information Sheet and the Privacy Notice for Research Participants.

<table>
<thead>
<tr>
<th>Name of Participant</th>
<th>Signature</th>
<th>Date</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Name of person taking consent</th>
<th>Signature</th>
<th>Date</th>
</tr>
</thead>
</table>

This Project Has Been Approved by the University of Manchester’s Research Ethics Committee [1013-3990-7360]

[1 copy for the participant, 1 copy for the research team (original)]

Version 5; Date 4/2/2019

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Appendix XIX: Jordan participants' background information questionnaire results

<table>
<thead>
<tr>
<th>Educational background</th>
<th>Educational level</th>
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Appendix XX: Oman participants' background information questionnaire results

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### Appendix XXI: Kuwait participants' background information questionnaire results

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Appendix XXII: Consolidated criteria for reporting qualitative research (COREQ) checklist

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<td>What did the participants know about the researcher? E.g., personal goals, reasons for doing</td>
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<td>How were participants selected? E.g., purpose, convenience, consecutive, snowball</td>
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<td>How were participants approached? E.g., face-to-face, telephone, mail, email</td>
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<td>Where was the data collected? E.g., home, clinic, workplace</td>
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<td>Was anyone else present besides the participants and researchers?</td>
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<td>Were field notes made during and/or after the interview or focus group?</td>
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<td>Is there a description of diverse cases or discussion of minor themes?</td>
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Once you have completed this checklist, please save a copy and upload it as part of your submission. DO NOT include this checklist as part of the main manuscript document. It must be uploaded as a separate file.