THE VALUE OF PATIENT REPORTING OF ADVERSE DRUG REACTIONS TO PHARMACOVIGILANCE SYSTEMS

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ACADEMIC DISSERTATION

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ABSTRACT

Patient reporting of adverse drug reactions (ADRs) has become an important element of pharmacovigilance. The aim of this thesis was to research the value of patient reporting of ADRs to pharmacovigilance systems. The study consists of 4 original studies, of which study I and II are interrelated. Study I identified which are the clinical and subjective aspects of adverse drug reactions (ADRs) that patients provide. A literature review covered peer-reviewed literature published in English until January 2015, a total of 34 studies. Main results supported patient reporting having the advantages of bringing novel information about ADRs. Patients provide a more detailed description of ADRs, and report about different medicines, system organ classes and effects, when compared with health care providers (HCPs). In addition, patients describe the severity and impact of ADRs on daily life, complementing information derived from HCPs. Patient reporting is still relatively rare in most countries. This study concluded that patient reporting adds new information, and perspective about ADRs in a way otherwise unavailable.

The opinions and experiences of different stakeholders on the role of direct patient reporting were explored through a series of qualitative interviews in selected countries (Study II). Participants from countries introducing patient reporting recently expressed a more negative attitude. All participants highlighted the need for additional resources, both human and financial, to address patient reporting and associated advantages. The findings identified perceived barriers and facilitators of patient reporting, such as the engagement of patients, use of information and dissemination of patient reporting.

Study III analyzed the correlation between several sociodemographic and economic factors and direct patient reporting rate in diverse countries. The study was based on the hypothesis that a higher human development index is related with a higher reporting rate and patient involvement in their health status. Health investment indicators, such as per capita public health expenditure, hospital bed density and under five mortality rate categories were the relevant factors to discriminate countries that have higher patient reporting rates. Although general, these results point that to reach better patient involvement in the pharmacovigilance system it is preferable to invest in public health education rather than to have more sophisticated pharmacovigilance systems designed to capture all patients’ inputs.

Study IV aimed to assess the degree of variation of language used by HCPs when describing ADRs, and to compare it with the corresponding Medical Dictionary of Regulatory Activities (MedDRA) codes. The study concluded that lexical and semantic distances between spontaneous reports and coded terms by MedDRA exist, as well as between different groups of HCPs. These differences may interfere with the strength of a generated safety signal, which places more value into having additional source of ADRs information e.g. from the patients. In this context, HCPs can be seen as bench-markers, while assessing the pharmacovigilance system maturity.
ACKNOWLEDGEMENTS

My journey with this project started in 2013. It has been a long, fulfilling journey of almost 5 years that has allowed me to grow tremendously as a person and as a scientist. I was able to explore the amazingly interesting area of Pharmacovigilance, the one that captured my attention ever since the first patient reported an adverse drug reaction to me while I was working in a community pharmacy. I still remember which reaction it was and how much it had impacted this person’s life. In the meantime, this work has been an integral part of my own personal development, travelling with me from Lisbon to Zurich and eventually Helsinki.

This project would not have happened if it wasn’t for Professor Afonso Cavaco’s challenge back in 2013. I am very grateful for all his teaching, his dedication and time spent with me. With him I learned the value of being detail-oriented and to how to do independent research; in fact, I’ve learned the meaning of being a PhD student, of hard-work, of thinking outside of the box. I will fondly remember all those long sessions at his office and the huge amount of brainstorming we did. With Professor Afonso I knew I could always count with support, for everything. And his humour, which always made me laugh. Professor Afonso, I thank you for everything.

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I publicly said that I had the best possible supervisors a PhD student can have, and I will reaffirm it here. It has always been a pleasure working together with such great scientists, tutors – and friends.

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LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications:


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DEFINITIONS OF KEY CONCEPTS

**Adverse event (AE)**
Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. The event can be an unfavorable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered to be to the medicinal product (European Medicines Agency 2012).

**Adverse reaction; synonyms: Adverse drug reaction (ADR), Suspected adverse (drug) reaction, Adverse effect, Undesirable effect**
An adverse drug reaction is defined as a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function (World Health Organization 2002). In the European Union, the definition of adverse drug reaction includes the use of the product within or outside the terms of the marketing authorisation or from occupational exposure. Conditions of use outside the marketing authorisation include off-label use, overdose, misuse, abuse and medication errors (European Medicines Agency 2012).

**Clinical trial**
A clinical trial means a clinical study which fulfils any of the following conditions: (a) the assignment of the subject to a particular therapeutic strategy is decided in advance and does not fall within normal clinical practice of the Member State concerned; (b) the decision to prescribe the investigational medicinal products is taken together with the decision to include the subject in the clinical study; or (c) diagnostic or monitoring procedures in addition to normal clinical practice are applied to the subjects (European Medicines Agency 2012).

**Consumer**
For the purposes of reporting cases of suspected adverse drug reactions, a person who is not a healthcare professional such as a patient, lawyer, friend or relative/parent/child of a patient (European Medicines Agency 2012).

**Drug safety**
Drug safety is the main aspect of medicinal therapy that can play a major role in deciding which drug should be given to a patient (Alshammari 2016).

**Healthcare professional (HCP)**
For the purposes of reporting suspected adverse drug reactions, healthcare professionals are defined as medically qualified persons, such as physicians, dentists, pharmacists, nurses and coroners (European Medicines Agency 2012).
**Medication error (ME)**
A medication error is an unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the patient (European Medicines Agency 2012).

**National pharmacovigilance centre**
A single, governmentally recognized centre (or integrated system) within a country with the clinical and scientific expertise to collect, collate, analyse and give advice on all information related to drug safety (World Health Organization 2002).

**Pharmacoepidemiology**
The study of the use and effects of drugs in large numbers of people. Applies epidemiological methods to studies of the clinical use of drugs in populations (Montastruc et al. 2015).

**Pharmacovigilance**
According to the World Health Organization, pharmacovigilance is defined as “the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problems” (World Health Organization 2002).

**Risk management system**
A set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to a medicinal product, including the assessment of the effectiveness of those activities and interventions (European Medicines Agency 2012).

**Serious adverse drug reaction**
An adverse reaction which results in death, is life-threatening, requires in-patient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect (European Medicines Agency 2012).

**Signal**
A signal can be defined as information arising from one or multiple sources, including observations and experiments, which suggests a new potentially causal association, or a new aspect of a known association between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action (European Medicines Agency 2012).

**Spontaneous reporting system (SRS)**
According to the World Health Organization, it is a “system whereby case reports of adverse drug events are voluntarily submitted to the national regulatory authority” (World Health Organization 2002).
**Spontaneous report (SR)**
An unsolicited communication by a healthcare professional or consumer to a company, regulatory authority or other organisation (e.g. the World Health Organization, a national/regional centre, a poison control centre) that describes one or more adverse reactions in a patient who was given one or more medicinal products and that does not derive from a study or any organised data collection scheme (European Medicines Agency 2012).
## ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>ADE</td>
<td>Adverse drug event</td>
</tr>
<tr>
<td>ADR</td>
<td>Adverse drug reaction</td>
</tr>
<tr>
<td>AE</td>
<td>Adverse event</td>
</tr>
<tr>
<td>AIDS</td>
<td>Acquired immune deficiency syndrome</td>
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<td>CEM</td>
<td>Cohort Event Monitoring</td>
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<tr>
<td>CHMP</td>
<td>Committee for Human Medicinal Products</td>
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<tr>
<td>DHPC</td>
<td>Direct Healthcare Professional Communication</td>
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<tr>
<td>EMA</td>
<td>European Medicines Agency</td>
</tr>
<tr>
<td>EU</td>
<td>European Union</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>HCP</td>
<td>Healthcare professional</td>
</tr>
<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
</tr>
<tr>
<td>MAH</td>
<td>Marketing Authorisation holder</td>
</tr>
<tr>
<td>MedDRA</td>
<td>Medical Dictionary for Regulatory Activities</td>
</tr>
<tr>
<td>NCA</td>
<td>National competent Authority</td>
</tr>
<tr>
<td>NME</td>
<td>New molecular entity</td>
</tr>
<tr>
<td>PRAC</td>
<td>Pharmacovigilance Risk Assessment Committee</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomised controlled trial</td>
</tr>
<tr>
<td>RMP</td>
<td>Risk management plan</td>
</tr>
<tr>
<td>SR</td>
<td>Spontaneous reporting</td>
</tr>
<tr>
<td>SRS</td>
<td>Spontaneous reporting system</td>
</tr>
<tr>
<td>TSR</td>
<td>Targeted spontaneous reporting</td>
</tr>
<tr>
<td>UK</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>USA</td>
<td>United States of America</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
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<tr>
<td>WHO-UMC</td>
<td>Uppsala Monitoring Centre</td>
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INTRODUCTION

Pharmaceutical development has been one of the greatest societal advancements of the past decades. The investment in the development of medicines has drastically improved global health and contributed to the prosperity of society (Daniel et al. 2015). The contribution of new medicines to prevent and treat common or complex diseases, as well as enhance existing treatments, has improved the life expectancy and resulted in a better quality of life of patients.

However, as illustrated by the thalidomide catastrophe in the 1960s, unexpected and serious adverse drug reactions (ADRs) are many times only identified in the post-marketing phase (Ridings 2013). The goal of pharmacovigilance is to uncover, report and address ADRs at the time of approval and throughout a medicine’s lifecycle. The aims of pharmacovigilance are to enhance patient care and patient safety in relation to the use of medicines; and to support public health programmes by providing reliable, balanced information for the effective assessment of the risk-benefit profile of medicines (World Health Organization 2002).

Pharmacovigilance has grown remarkably in the past few decades. Since its creation in the 1960s, the spontaneous reporting system (SRS) has been the basis of pharmacovigilance, with reporting mostly done by healthcare professionals (HCPs) (Pal et al. 2013). Despite the focus of pharmacovigilance being in patients, for many decades their contribution was not valued (van Grootheest et al. 2003). Crucial questions were asked, such as whether patient reports could quantitatively increase the number of reports or provide enough valid information that could lead to a timely detection of safety signals. Overtime, evidence started to build on the benefits of patient reporting (Blenkinsopp et al. 2007; de Langen et al. 2008). Currently, patients are known to provide reliable and balanced information that can be used in the monitoring of medicines and effective assessment of their risks and benefits (Baird et al. 2014). This information can be used by HCPs and patients, increasing the safe and effective use of medicines. Nevertheless, questions remain about how to garner the full-potential of patients. To make the most of the information from patients, it is necessary to assess and determine its value to pharmacovigilance, investigate how the information is used and explore common limitations to both HCPs and patients.
REVIEW OF THE LITERATURE

1.1 ADVERSE DRUG REACTIONS

The WHO defined an adverse drug reaction (ADR) as “a response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological functions” (World Health Organization 2002). As proposed by Edwards and Aronson, ADRs can be classified into six types (Table 1) (Edwards & Aronson 2000). Although this is an attempt to classify the most common reactions, it is not always possible to classify an ADR due to the bizarre clinical nature (Edwards & Aronson 2000).

Table 1. Classification of adverse drug reactions (adapted from Edwards and Aronson 2000).

| Type of reaction                  | Features                                      | Examples                                                      |
|----------------------------------|-----------------------------------------------|                                                               |
| A: Dose-related                  | Common                                        | Toxic effects:                                               |
|                                  | Related to a pharmacological action of a medicine | - Digoxin toxicity; serotonin syndrome with SSRIs             |
|                                  | Predictable                                   | - Side effects                                              |
|                                  | Low mortality                                 | Anticholinergic effects of tryclicic antidepressants          |
| B: Non-dose related              | Uncommon                                      | Immunological reactions:                                    |
|                                  | Not related to pharmacological action of a medicine | - Penicillin hypersensitivity                               |
|                                  | Unpredictable                                 | - Idiosyncratic reactions:                                  |
|                                  | High mortality                                | - Acute porphyria                                           |
|                                  |                                              | - Malignant hyperthermia                                    |
|                                  |                                              | - Pseudoallergy (e.g. ampicillin rash)                      |
| C: Dose-related and time-related | Uncommon                                      | Hypothalamic-pituitary-adrenal axis suppression by corticoids |
|                                  | Related to the cumulative dose                |                                                               |
| D: Time-related                  | Uncommon                                      | Teratogenesis (e.g. vaginal carcinoma with diethistilbostrol) |
|                                  | Usually dose-related                          | Carcinogenesis                                               |
|                                  | Occurs or becomes apparent sometime after use | Tardive dyskinesia                                          |
| E: Withdrawal                    | Uncommon                                      | Opiate withdrawal syndrome                                   |
|                                  | Occurs soon after withdrawal of medicine      | Myocardial ischaemia (beta-blocker withdrawal)               |
| F: Unexpected failure of therapy | Common                                        | Inadequate dosage of oral contraceptive, particularly when used with specific enzyme inducers |
|                                  | Dose-related                                  |                                                               |
|                                  | Often caused by drug interactions             |                                                               |
SSRI: serotonin-selective reuptake inhibitors

In the European Union (EU), the ADR definition changed with the new pharmacovigilance legislation of 2010 (Härmark et al. 2016). It now includes ADRs occurring outside the terms of the marketing authorisation or from occupational exposure. Conditions of use outside the marketing authorisation include off-label use, overdose, misuse, abuse and medication errors (European Commission 2000; European Medicines Agency 2017).

In an ADR, there is a causal link between the medicine and the reaction (Edwards 2017). This is distinct from an adverse drug event (ADE), in which the adverse outcome may or may not be caused by the medicine itself (Edwards & Aronson 2000). This definition is important in clinical trials, as not all events are medicine-related (Edwards & Aronson 2000).

ADRs can be also classified in “unexpected ADRs” and “serious ADRs” (Edwards & Aronson 2000). The term “unexpected” is employed when the nature or severity of the reaction is not consistent with the description of the labelling of the medicinal product, while “serious ADRs” refers to reactions that result in death, are life-threatening, require patient hospitalisation or the prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, is a congenital anomaly/birth defect or a cancer (Montastruc et al. 2015).

1.2 EPIDEMIOLOGY OF ADVERSE DRUG REACTIONS

ADRs are among the leading causes of morbidity and mortality (Bouvy et al. 2015). They can lead to discontinuation of therapy, originating even more negative health outcomes. ADRs can occur in different settings (Figure 1). A recent study involving EU-countries, Norway, Iceland and Switzerland pointed that 3.5% of hospital admissions were caused by ADRs and 10.1% of patients experienced an ADR during their hospital stay (Bouvy et al. 2015). In ambulatory care setting, the prevalence of ADRs can reach 16.5% (Thomsen et al. 2007; Taché et al. 2011). While hospitalized patients are under close medical monitoring, community dwellers are not. If not for a serious ADR, it is more difficult to follow a patient and ascertain the presence of an ADR (Yu et al. 2015).

Special populations, such as paediatric and geriatric patients, are especially vulnerable regarding rational pharmacotherapy. In hospitalized children, the ADR incidence rate was estimated to be 9.5% (Impicciatore et al. 2001; Clavenna & Bonati 2009), while the incidence in outpatients was around 1.5% (Aagaard et al. 2010). A recent study from China suggested that 2.2% of all ADRs were severe and 0.3% were fatal (Li et al. 2014). Paediatric patients are also more exposed to off-label use of medicines (Verhamme & Sturkenboom 2011). In a study at a hospital setting around 30% of all prescriptions for children did not have paediatric indication (Neubert et al. 2004).

Similarly, older patients are most at risk of ADRs due to the increased use of medication and the changes in physiology caused by older age/aging (Lehnert et al. 2011; Davies & O’Mahony 2015). Many studies have shown the correlation
between age and the number of ADRs, although this is a complex issue (Lehnert et al. 2011). Two systematic reviews have suggested that the hospital admission rate of patients ≥65 years to be of 10% and 11%, respectively (Kongkaew et al. 2008; Pont et al. 2014). A study linked ADRs to 0.75% of all annual emergency department visits in a populous Canadian province by patients aged >66 years, leading approximately 21.6% of them to be hospitalized (Wu et al. 2012).

ADRs constitute a severe burden for hospitalized patients (Lehnert et al. 2011; Wu et al. 2012). In a seminal meta-analysis, Lazarou et al. demonstrated that ADRs cause an overall fatality of 0.32%, making it between the fourth and sixth cause of death in the USA (Lazarou et al. 1998). It is estimated that up to 0.49% of hospital admissions in EU-countries, including Norway, Iceland and Switzerland result in a fatal outcome (Bouvy et al. 2015). This rate could mean nearly 419,000 ADR-related deaths per year (Bouvy et al. 2015). Previous estimates pointed to numbers of 197,000 ADR-related deaths per year in the EU alone (European Commission 2008).

**Figure 1** Different settings in which ADRs can occur (Bouvy et al. 2015).

### 1.3 BURDEN ASSOCIATED WITH ADVERSE DRUG REACTIONS

ADRs represent a heavy burden which is complex and multifactorial (Lehnert et al. 2011; Batel-Marques et al. 2016). There are two main costs associated with ADRs: cost of treating illnesses induced by medicines and cost of avoiding them (Lundkvist & Jonsson 2004). Often patients suffering from ADRs will get prescribed new medicines to treat them. The iatrogenic use potentially creates new pharmacotherapy problems and increased health resource utilization (Hohl et al. 2011). Furthermore, many patients suffering from ADRs will not get hospitalized yet need to get treated (Taché et al. 2011).
The direct and indirect costs resulting from ADRs are difficult to estimate (Lundkvist & Jonsson 2004). In the EU, it has been estimated that the annual total costs with ADRs are as high as €79 billion, both for in- and out-patients (Bouvy et al. 2015). A study from Germany extrapolated ADR-related costs with in-patients to be around €2.245 billion per year to the health system in Germany alone (Meier et al. 2015). Despite estimates concerning in-patients, it remains difficult to assess the public health burden that ADRs pose to community dwellers (Lundkvist & Jonsson 2004; Taché et al. 2011; Wu et al. 2012). The real associated costs are expected to be high, both at hospital and community settings and set to increase further as medication use increases due to an aging population (Pont et al. 2014; Davies & O’Mahony 2015; Batel-Marques et al. 2016).

1.4 CAUSALITY ASSESSMENT AND SAFETY SIGNAL

1.4.1 CAUSALITY ASSESSMENT

An important task in pharmacovigilance relates to causality assessment of suspected ADRs (Miremont-Salamé et al. 2016). Causality assessment is directly related to signal detection and aims at determining the probability that a specific medicine is responsible for the adverse drug event (Rehan et al. 2009). Pharmacovigilance deals with rare outcomes of medicines which are harmful to varying degrees and frequency (Edwards 2012). Identifying the causes of the adverse outcome and its implications on the use of the medicinal product has repercussions on the risk-benefit ratio evaluation (Arnardottir et al. 2011; Alves et al. 2013, 2014; Durrieu et al. 2016).

Causation is a complex process, whereby an expert expresses a judgment about possible drug causation by considering all available data relevant to a suspected ADR, estimates its relative importance and assigns weights to deduce the probability of the role of the drug in the untoward event (Agbabiaka et al. 2008). There may be several causes justifying the drug effect and these must be evaluated in each situation (Edwards 2017).

An inherent problem with causality assessment concerns the fact that ADRs are rarely specific to a medicine (Edwards 2012; Miremont-Salamé et al. 2016). Pharmacovigilance develops hypotheses that warrant further investigation. Clinical judgement remains the first and indispensable step to identify and assess an ADR, particularly if it is serious (Miremont-Salamé et al. 2016). It has been mentioned that patients cannot properly perform causality assessment and that due to their lack of judgement they would create “noise” and prove a drain on surveillance systems (van Grootheest et al. 2003; Krska et al. 2011). However, just like with HCPs, being certain about the causality is not a prerequisite to submit an ADR report. Research has shown that patients feel knowledgeable about medicines’ risks, being able to identify suspected ADRs adequately and describe processes of assessing causality that mirror those of standard algorithms designed for use by HCPs (Krska et al. 2011; Krska & Morecroft 2013) However, questions remain about how patients identify suspect
ADRs and their ability to distinguish between ADRs and other symptoms (Rolfes et al. 2017).

1.4.2 SAFETY SIGNAL MANAGEMENT

Signal detection aims to capture, as soon as possible, any possibly unexpected drug hazard which may either be derived from new ADRs or a change of frequency of ADRs that are already known (Pontes et al. 2014). Suspected signals should be followed up with deeper investigation, such as formal pharmacoepidemiological studies (Gould et al. 2015).

As proposed by Hauben and Aronson (2009), a safety signal is defined as: “information that arises from one or multiple sources (including observations and experiments), which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, which would command regulatory, societal or clinical attention, and is judged to be of sufficient likelihood to justify verificatory and, when necessary, remedial actions”. Signal management is a process that covers the evaluation of the data supporting the detection of a signal, going through the evidence to confirm, analyse, prioritize and assess the actions needed to address it, as well as tracking the steps taken (Monaco et al. 2017; Delannois et al. 2018). The initial analysis of the suspected signal depends on the quality and quantity of information contained in the report (Hauben & Aronson 2009). The value of individual ADR reports is directly proportional to the amount of clinically relevant information they include (Durrieu et al. 2016). If the reports offer few or no clinical data then the ability to establish a relationship between a drug and a suspected ADR is compromised (Bandekar et al. 2010; Durrieu et al. 2016; Monaco et al. 2017). One of the concerns regarding patient reporting was related to the quality of the information provided, taking into account the lack of medical training and supposed lack of causality assessment (World Health Organization 2002; Anderson et al. 2011). However, over the years, several studies have demonstrated the continued patients’ contribution to signal detection (Hazell et al. 2013; van Hunsel et al. 2017; Watson et al. 2018). This will be further addressed in Chapter 2.

1.5 RISK MANAGEMENT

1.5.1 THEORETICAL CONTEXT

As highlighted in previous chapters, all medicines entail a certain amount of risk and hence the need to minimise these (Hartford et al. 2006). What leads a physician to prescribe and a patient to take the medicine is the expectation that the benefit will outweigh the risk, thus achieving a cure for the condition the medicine is labelled for. There are levels of risk that we are willing to take: in order for a medicine with a low perceived benefit to be acceptable, such as a cough syrup, it has to be a low risk. Similarly, for a medicine with much greater benefits, for example treatment of cancer or Human Immunodeficiency Virus/Acquired
Immunodeficiency Syndrome (HIV/AIDS), the acceptable risks can be much higher (Breckenridge 2003). In an analogous way, the regulation of medicines is based on an assessment of risks and benefits (Figure 2).

![Risk-benefit relationship for drugs](Breckenridge 2003)

Figure 2 Risk-benefit relationship for drugs (Breckenridge 2003).

Strategies to manage the risks in a coordinated fashion allow for the identification, assessment and prioritization of risks. Applied to medicines it means ensuring that the uncertainty of ADRs is controlled and that the product’s demonstrated benefits outweigh its inherent risks (ICH Expert Working Group 2005).

According to the International Organization for Standardization’s (ISO) Standard 31000, risk is defined as “the effect of uncertainty on objective and is often characterized by reference to potential events and consequences, or a combination of these” (ICH Expert Working Group 2005). For the risk related to a medicinal product, EU Directive 83/2010/EC defines it as any risk relating to the quality, safety or efficacy of the medicinal product regarding patients’ health or public health, or any risk of undesirable effects on the environment (European Commission 2000).

1.5.2 THE “SWISS CHEESE” MODEL

The provision of healthcare always involves human decision-making and delivery, i.e., processes that are inherently subject to error (Reason 2000). Systems must be designed in a way as to prevent errors from happening and resulting in harm to patients (Reason 2000). The occurrence of harm is the result of an interaction between the activities, procedures, and the objects, such as medicinal products and equipment. Healthcare delivery is performed in organizations like hospitals and clinics by professionals such as physicians,
nurses and pharmacists subject to known patterns of human behaviour. Patients, being human beings, also present well-known cognitive and behavioural limitations (Perneger 2005).

James Reason proposed the image of the “Swiss cheese” to illustrate the occurrence of system failures (Reason 2000) (Figure 3). This theory postulated that every step in a process has the potential for failure to a varying degree. Reason’s analogy portrays the Swiss cheese as a series of slices with its characteristic holes. The series of slices acts as a defence against the impact of the holes (Perneger 2005).

Active failures are committed by people in direct contact with the patient or system and are difficult to foresee. Latent conditions are inherent to the design of the system; these conditions can be identified and corrected before the failure occurs. The holes are in constant formation, and when by chance all align the harm can pass and harm the patient. In other words, the slices illustrate risk management working against ineffective controls that may arise through the holes (Reason 2000). This theory is frequently referred and accepted by safety professionals. It has established itself as a reference for the aetiology, investigation or prevention of accidents in aviation, government, insurance and finance, healthcare, nuclear, marine, oil among other domains (Reason 2000). In this theory defences, barriers, and safeguards occupy a key position in the system approach. High-technology systems have many defensive layers: some are engineered (alarms, physical barriers, automatic shutdowns), others rely on people (surgeons, anaesthetists, pilots, control room operators), and others depend on procedures and administrative controls (Perneger 2005). These barriers are mostly effective but there are always weaknesses. In an ideal world each defensive layer would be intact. In reality, they are more like slices of Swiss cheese, having many holes—although, unlike in the cheese, these holes are continually opening, shutting, and shifting their location. The presence of holes in any one “slice” does not normally cause a bad outcome. Usually this can happen only when the holes in many layers momentarily line up to permit a trajectory of accident opportunity—bringing hazards into damaging contact with victims.
1.5.3 RISK MANAGEMENT OF MEDICINES

Concerning medicines, risk management and minimization plans, as well as post-approval studies, are based on risks not identified in the pre-approval phases and that need to be further characterized or minimized in the post-marketing environment (Dieck & Sharrar 2013). Many ADRs only become apparent during the post-approval period when larger patient populations are exposed to the medicinal product during normal clinical practice (Schick et al. 2017).

From a regulatory perspective, risk management means the detection and assessment of risks, the development and selection of measures to reduce risk, and monitoring of the effectiveness of risk control; all aspects of pharmacovigilance are intended to minimize risk associated with use of medicinal substances (Arlett & Kurz 2011; Dieck & Sharrar 2013; Arlett et al. 2014). Regulatory agencies have issued guidance that addresses these issues through pharmacovigilance, signal detection, observational studies and registries (Dieck & Sharrar 2013). In the EU, the risk management approach is guided by both the need to find unexpected hazards and by gathering positive evidence of safety (Raine 2012; Arlett et al. 2014; Santoro et al. 2017). Drug development and pharmacotherapy are components of integrated pharmaceutical medicine. The term ‘drug safety’ can be used when evaluating adverse events during clinical trials, and when evaluating adverse drug reactions to a correctly prescribed, dispensed and administered drug. In the context of post-marketing surveillance, ‘drug safety’ is many times associated with pharmacovigilance (Alshammari 2016). The term ‘medication safety’ refers to the evaluation of medication errors that occur at the prescribing, dispensing and/or administration level; endeavours
to educate clinicians and patients about the correct use of a particular drug; and the design and implementation of safety systems and educational programmes to minimise these errors (Mitchell 2008). Drug safety and medication safety are subsets of patient safety. Patient safety has been defined as “the prevention of harm to patients” (Mitchell 2008). Emphasis is placed on the system of care delivery that (1) prevents errors; (2) learns from the errors that do occur; and (3) is built on a culture of safety that involves health care professionals, organizations, and patients (Mitchell 2008). These initiatives span a broad range of activities within the lifecycle development of a medicine.

1.5.3.1 BENEFIT-RISK ASSESSMENT

The assessment of the benefit-risk in the context of a new drug application is a central element of the scientific evaluation for a marketing authorization application (Mt-Isa et al. 2016). The assessment requires evaluation of all relevant data and the use of judgment and arguments to establish as objectively as possible a sufficient level of confidence that a set level of quality, efficacy and safety have been demonstrated for the medicinal product (Moseley 2004). In this context, risk is represented by unintended ADRs. Benefit is represented by the health gain realised by the intended mechanism of action of the medicine (Mt-Isa et al. 2016).

Evaluation of the balance between benefits and risks of drugs is fundamental (Arlett et al. 2014). Regulators in turn must make decisions about benefits and risks of medicines based on trials conducted prior to licensing (Arlett et al. 2014). Thereafter, there is the need to monitor them after marketing approval so that information made available to HCPs and the public can be updated in the light of emerging benefit-risk information (Pignatti et al. 2015; Mt-Isa et al. 2016). As described previously, many of the initial safety concerns are evaluated over the lifecycle of the medicine (Figure 4). Considerations about the safety profile of medicines might be changed over the course of their use in clinical practice, thus impacting their risk-benefit balance (Evans & Leufkens 2014). This requires proactive drug safety data analysis, as well as integration of methods exploring real-world conditions (Guo et al. 2010). Expanding the pool of potential reporters to patients can lead to a faster, more detailed identification of new safety concerns (Härmark et al. 2016). Patient input about suspected ADRs may provide convincing evidence of causality of an effect on their own (Evans & Leufkens 2014).
1.6 THE SCIENCE OF PHARMACOVIGILANCE

1.6.1 PHARMACOVIGILANCE: DEFINITIONS, SCOPE AND PUBLIC HEALTH IMPACT

Pharmacovigilance has been defined by the WHO as “the science and activity relating to the detection, assessment, understanding and prevention of adverse effects or any other possible medicine-related problems” (World Health Organization 2002). Given that the focus of pharmacovigilance is on the health and safety of populations rather than that of individuals, it can be classified as a public health activity (Callréus 2013). The scope of pharmacovigilance has developed considerably in recent times (Pitts et al. 2016). It moved from the uncovering, reporting and appraisal of ADRs in already approved and marketed medicines to dealing with a wider range of issues related to medicines use (as shown in Figure 5) (Dal Pan 2014). Currently, pharmacovigilance can be described as the systematic monitoring of the process of premarket review and post-market surveillance, which includes the use of medicines in every day practice (Pitts et al. 2016).
According to the World Health Organization (2014) the current declared aims of pharmacovigilance are the following:

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

**1.6.2 PUBLIC HEALTH IMPACT OF PHARMACOVIGILANCE**

Pharmacovigilance plays an important role in public health. According to the WHO, public health is defined as the organized efforts of society to protect, promote and restore people’s health (Pal et al. 2013). Pharmacovigilance programs are thus an essential component of national healthcare systems (Babigumira et al. 2014).

As described in Chapter 1.2, ADRs represent a heavy burden to health systems. Pharmacovigilance, as a part of a well-functioning health care system, can help improve population health by identifying and reducing medicines-related problems and harm (Babigumira et al. 2014). However, not all countries have the same level of pharmacovigilance activity strength (Aagaard et al. 2012). High-income countries have a higher medication consumption, but as well greater resources to survey the safety of medicines. Health systems in low and middle-income countries have several weaknesses (Babigumira et al. 2014). These countries have problems like inadequate and overly centralized planning systems, weak drug policies and supply systems, and shortage and poor
distribution of qualified staff (Mills 2014). With a growing global health spending, both high and low and middle income countries will have a higher consumption of medicines (Jakovljevic & Getzen 2016). Likewise, with the acceleration of globalization and health gains in the developing world there will be a need to monitor the safety of medicines in new sets of populations (Gunawardena et al. 2008; Olsson et al. 2010). The introduction of patient reporting of ADRs can thus be seen as an opportunity to provide better monitoring of medicines.

1.7 LANDMARK CASES SINCE THALIDOMIDE CATASTROPHE IN EARLY 1960s AND ITS IMPACT ON PHARMACOVIGILANCE

1.7.1 THALIDOMIDE (EARLY 1960s)

Modern pharmacovigilance arose from the advent of the thalidomide disaster in the early 1960s (Emanuel et al. 2012). Thalidomide (marketed as Distaval®, Softenon® or Contergan®) was developed by the German pharmaceutical company Grünenthal as a sedative and to treat morning sickness in pregnant women (Kim & Scialli 2011). It was introduced in the market in the late 1950s, although it was not introduced at the time in the US market (Botting 2002; Vargesson 2015). In 1961, the Australian physician McBride wrote to The Lancet describing an increase of congenital abnormalities in babies delivered from women who had taken the drug (Mcbride 1961). Most of the children were born with phocomelia, and other effects later attributed to thalidomide, including congenital heart disease, malformations of the inner and outer ear, and ocular abnormalities (Vargesson 2015). By the time of its withdrawal at the end of 1961, it was estimated that more than 10,000 children had been born with deformities (Emanuel et al. 2012). Thalidomide became the largest man-made medical disaster in history (Vargesson 2015).

The thalidomide scandal was not only a wake-up call to improve drug testing and increase the requirements for safety of medicines, but it also made clear that a system for monitoring post-market drug safety was required (Weigmann 2016). It also completely changed the way new drugs are developed, tested and introduced in the market (Emanuel et al. 2012; Vargesson 2015). New criteria about market authorization were devised, as well as new safety and quality standards (Greene & Podolsky 2012). A post-marketing safety surveillance system to help prevent similar tragedies from occurring in the future was set up (Olsson 1998; Pal et al. 2013). This marked the start of the spontaneous reporting system in several countries, through which physicians (and later other healthcare professionals) could voluntarily report suspected ADRs (Pal et al. 2013). The thalidomide catastrophe also created a demand for access to balanced drug information to prescribers and other HCPs, as well as medicine users and the public, in knowing the benefits and risks of medicines they are prescribed and they are taking.
1.7.2 ROFECOXIB (EARLY 2000s)

Effects of non-steroidal anti-inflammatory drugs (NSAIDs) are mediated by cyclo-oxygenases (COXs) resulting in decreased production of prostanoids (Weaver 2001). Due to the gastrointestinal toxicity associated with COX-1 inhibitors, new molecules where developed to produce a safer and more selective analgesic and anti-inflammatory response. Celecoxib, the first selective COX-2 inhibitor came to the market in 1998, soon followed by other molecules (Silverstein et al. 2000; Nissen 2012). Rofecoxib (Vioxx®) was developed by the American manufacturer Merck (Dai et al. 2005). Both celecoxib and rofecoxib gained widespread acceptance among prescribers due to two studies published at the time, the gastrointestinal toxicity with celecoxib versus non-steroidal anti-inflammatory drugs for osteroarthritis and rheumatoid arthritis (CLASS) and the Vioxx Gastrointestinal Outcomes Research (VIGOR) studies (Bombardier et al. 2000; Silverstein et al. 2000; Dai et al. 2005). As an example, within five months of the launch of rofecoxib, more than 42,000 patients had been prescribed the drug in England, even though newly marketed drugs carry a black triangle warning indicating an incomplete safety profile (Layton et al. 2003).

Rofecoxib was first approved for the treatment of pain associated with osteoarthritis as an effective, safer alternative to traditional NSAIDs (Krumholz et al. 2007). Since early development of rofecoxib, concerns emerged about the drug’s potential to adversely affect the cardiovascular system by altering the ratio of prostacyclin to thromboxane, which acts in opposition, balancing the blood flow and clotting (Wahab et al. 2014; Grosser 2006; Rawson et al. 2005).

Merck initiated the VIGOR trial in 1999 in order to expand the indications of rofecoxib (Nissen 2012). Involving over 8,000 patients, it compared the gastrointestinal toxicity of rofecoxib against naproxen, not focusing on the cardiovascular risk of the molecule (Bombardier 2002). The trial showed that rofecoxib was not more effective than naproxen in relieving symptoms of pain, but it did halve the risk of gastrointestinal events (Bombardier et al. 2000). However, it also showed that the risk of serious cardiovascular adverse events including myocardial infarction was 79% higher in the rofecoxib group (Bombardier et al. 2000; Krumholz et al. 2007; Nissen 2012). This safety issue received little public attention at the time (Mukherjee et al. 2005). Merck covered the risks related to cardiovascular events in their data analysis and went ahead with an aggressive promotion of the medicine, as well as pursuing the expansion of the indications for rofecoxib. For that, it conducted additional trials (Krumholz et al. 2007). In the analysis of the adenomatous polyp prevention on Vioxx (APPROVe) study, the increased cardiovascular risk compared with placebo was evident and the company could not refuse it (Krumholz et al. 2007; Nissen 2012). This lead Merck to withdraw the drug from world markets. At the time of the withdrawal, over 100 million prescriptions for rofecoxib had been written and over 20 million patients had received this drug in the USA alone (Nissen 2012; Wahab et al. 2014).
The rofecoxib scandal brought to light many of the shortfalls in pharmacovigilance: opaque clinical trials, without disclosure of key information to regulators (Duijnhoven et al. 2013); complacency of regulators regarding the quality of the data and a passive approach to the safety aspects; over-reliance in spontaneous reporting to identify serious ADRs; and a lack of transparency about drug regulation in general (Krumholz et al. 2007; Nissen 2012; Wahab et al. 2014). The Vioxx scandal was a call to make pharmacovigilance more robust (Edwards 2005). It started the process of changing pharmacovigilance regulation to its current format e.g. in the EU and US.

1.7.3 THIAZOLIDINEDIONES (LATE 1990s AND BEGINNING OF 2000s)

Thiazolidinediones are a class of glucose-lowering medicines for Type II diabetes developed in the late 1990s (Tuccori et al. 2016). They are agonists for the peroxisome-activated receptor γ (PPAR-γ). PPAR-γ receptors are ligand-activated nuclear transcription factors that modulate gene expression, lowering blood glucose primarily by increasing insulin sensitivity in peripheral tissues (A.Wahab et al. 2014).

At the time of approval of rosiglitazone (Avandia®), there were concerns about the other available thiazolidinedione in the market, troglitazone (Rezulin®). This molecule caused rare but serious hepatic damage and was eventually withdrawn from the market (Jaeschke 2007). When pharmaceutical companies presented new alternatives in the form of rosiglitazone and pioglitazone that did not appear to cause this type of ADRs, regulators were fast in approving them (Psaty & Furberg 2007). Rosiglitazone was approved by the US Food and Drug Administration (FDA) in 1999 and by the European Medicines Agency (EMA) in 2000 (Pouwels & van Grootheest 2012).

After market introduction, rosiglitazone became widely popular, capturing a major share of the diabetes market (Nissen & Wolski 2010). Already at the time of approval, concerns were expressed by the FDA regarding an increase in the risk of heart failure and fluid retention (Pouwels & van Grootheest 2012). These concerns were also expressed by the EMA and in the authorization granted it was stated that rosiglitazone should not be prescribed to patients with a history of heart failure. Both agencies requested further studies to evaluate the risk of cardiovascular events (Nissen & Wolski 2010). After the regulatory approval of rosiglitazone, evidence started building about its cardiovascular safety profile. Two years after its launch, spontaneous reports associated rosiglitazone with fluid retention and congestive heart failure (Nissen 2010).

In 2007, a meta-analysis of 42 studies was published (Pouwels & van Grootheest 2012). This study found that rosiglitazone was statistically associated with an increased risk of myocardial infarction and death from cardiovascular causes (Nissen & Wolski 2010). With an accumulation of evidence on the cardiovascular risk of rosiglitazone, the EMA decided in 2008 to suspend the market authorization. The FDA opted for the implementation of restriction
measures for the use of this medicine (Pouwels & van Grootheest 2012). Currently, only pioglitazone is marketed.

The issues with rosiglitazone followed on the limitations identified for the rofecoxib scandal. The cardiovascular safety of the molecule revealed itself fully when introduced in current clinical practice. This pointed to the need of more transparent clinical trials, the use of pharmacoepidemiological methods to follow-up on identified risks during pre-clinical development and a stronger safety monitoring of the molecule during its clinical use in a more systematic way (Dolgin 2010; Pouwels & van Grootheest 2012). These considerations were taken up with the approval of the EU pharmacovigilance legislation in 2010 (Borg et al. 2011; Santoro et al. 2017).

1.7.4 BENFLUOREX

Benfluorex (Mediator®) is an amphetamine derivative that stimulates the release of dopamine, noradrenalin and serotonin, inhibiting their reuptake (Frachon et al. 2011). Due to this mechanism of action, it inhibits the sensation of hunger and has an action on the metabolism of lipids and carbohydrates. It was used as an anorectic and hypolipidemic substance, having been introduced in the market in 1976 (Boutet et al. 2009). Benfluorex was indicated as an adjuvant therapy of overweight diabetics, in combination with an appropriate diet (Fournier & Zureik 2012). Despite its anorexic properties, it was not authorized as an appetite suppressant, but it was used off-label for this purpose (Benkimoun 2010). It was authorised in several European countries, although by the time of withdrawal only France, Cyprus and Portugal had the product marketed (Le Ven et al. 2016). Despite the similarity of benfluorex with two earlier withdrawn obesity drugs, fenfluramine and dexfenfluramine, and some concerns with its use, it was kept in the market for more than 30 years (Frachon et al. 2011).

At the end of 2009, the results of a pharmacovigilance survey, combining the preliminary data from three studies (the retrospective case-control study performed in a Brest hospital, the REGULATE trial and the data from the French National Insurance Fund) and from a recent publication from Boutet and colleagues, showed that patients treated with benfluorex had a risk of cardiac valve diseases and pulmonary hypertension (PHT) (Boutet et al. 2009; Frachon et al. 2010; Szymanski et al. 2014). This prompted the French regulatory agency to withdraw Benfluorex and informed its European partners, leading the EMA to re-evaluate the medicine. It was observed that these ADRs could happen after an average of 328 days of benfluorex exposure, with data on drug utilization referring for more than 3 years of patient use (Frachon et al. 2010). This led the agency to conclude that the risk of developing these conditions could not be excluded, which meant that the benefit-risk of benfluorex during normal clinical practice was now negative (Mullard 2011).

This event with benfluorex highlighted the risks of off-label use, and the need to strengthen spontaneous reporting and conduct post-marketing surveillance studies, with the need to develop better methods for picking out faint
safety signals from a large volume of data (Benkimoun 2010; Degrassat-Théas et al. 2015). In October 2012, the EU pharmacovigilance legislation was amend following the withdrawal of benfluorex from the market (Degrassat-Théas et al. 2015). It also points out that something is missing in the ADR monitoring and in results of post-marketing surveillance studies (Benkimoun 2010).

1.7.5 SUMMARY

The thalidomide catastrophe marked a tipping point in drug safety (Ridings 2013). It changed the regulatory environment regarding market introduction of medicines. One of the most important changes was the development of a system to monitor the safety of drugs in the post-marketing phase, the spontaneous reporting system (SRS) (Pal et al. 2013). However, apart from some countries, patient reporting was not accepted (van Hunsel et al. 2012). Therefore, postmarketing reporting of ADRs during real-world clinical use is an important factor in identifying new, rare and serious ADRs with potential to affect the benefit-risk balance of the product (Lane et al. 2018). While the SRS is an effective method of identifying safety signals, it has some limitations (to be further expanded in the next chapters). This was put into evidence after the rofecoxib and rosiglitazone scandals. It was suggested that high-quality evidence is necessary to improve the quality and efficacy of public health interventions (Lane et al. 2018). The accumulation of indications that pharmacovigilance should change led to the new EU legislation (explained in the next chapter). With the EU legislation change in 2012, there was hope that gathering more robust evidence would lead to quicker regulatory actions (Arlett & Kurz 2011). In fact, as shown after the benfluorex case, there is a need for constant improvement and redoubled vigilance (Degrassat-Théas et al. 2015). One source to provide greater robustness to the system is precisely patient reporting (Härmark et al. 2016). This is going to be further explained in Chapter 2.

1.8 THE 2010 EUROPEAN UNION PHARMACOVIGILANCE LEGISLATION

In 2004, the same year rofecoxib was withdrawn from world markets, the European Commission requested an independent assessment of the EU pharmacovigilance system (Fraunhofer Systems and Innovation Research 2006). As explained in previous chapters, the drivers for a change in the legislation came from the need to further strengthen practices and guidance in order to reinforce public safety. Additionally, a rationalization and harmonization of the system was sought, removing duplication of efforts of Member States relating to reporting, review and assessment of activities. Pharmacovigilance activities had become more complex over time, and the current legislative framework did not respond adequately to the challenges (Fraunhofer Systems and Innovation Research 2006).
Based on the recommendations of this assessment (Fraunhofer Systems and Innovation Research 2006), a consultation was launched in 2006 with the aim of collecting the views of stakeholders in the pharmacovigilance process, including comments on what were strengths and weaknesses of the system and how could these be improved. The outcome of this process led to amendments to Directive 2001/83/EC, Regulation (EC) 726/2004 and in Commission guidance (Volume 9A of Eudralex) on the pharmacovigilance-specific regulation. The aim of these landmark changes was to achieve a framework for the management of risks associated with medicinal products, including innovative medicines such as advanced therapy medicinal products (Borg et al. 2011; Santoro et al. 2017).

### 1.8.1 KEY DELIVERABLES

The pharmacovigilance legislation was approved in 2010 and came into effect in July 2012. The two pivotal legislative pieces are Directive 2010/84/EC and Regulation (EC) 1235/2012. The Regulation and Directive were supported by Commission Implementing Regulation (EU) No 520/2012 published in June 2012. The goals of the legislation are to enhance better collection of data on medicines and their safety; to deliver a rapid and robust assessment of issues related to drug safety; enhance regulatory processes; engage patients; and increase the levels of transparency on drug safety regulation (Borg et al. 2011).

### 1.8.2 REGULATORY DECISION-MAKING PROCESS

One of the major aims of the amendments to the legislation was intended to rationalise and streamline the pharmacovigilance process in the EU (Borg et al. 2011). The Directive and Regulation introduced several measures to simplify the EU pharmacovigilance procedures both to regulators and pharmaceutical companies. Further to that, the roles, responsibilities and obligations between the European Medicines Agency (EMA) and Member States were better defined (Borg et al. 2015).

The amendments impacted the requirements for marketing authorisation for medicinal products (Borg et al. 2011). In the EU market, the EMA evaluates all modifications to key safety profiles, as well as suspensions and revocations. This is irrespective of the authorisation route for the medicinal products, either through national or centralised procedure. In the field of simplification and reduction of procedural burden, the legislation introduced several measures. These included the electronic submission of Periodic Safety Update Reports (PSUR) by the marketing authorization holder (MAH), the creation of a repository at the EMA for PSURs, and the possibility for the MAHs not to submit PSURs when requesting marketing authorisation for generic products (Borg et al. 2011). The role of the EMA has been further developed, especially on the management of EudraVigilance (Postigo et al. 2018). The legislation also established uniform criteria and procedures to be adopted throughout the EU, with standard format and content for the electronic transmission of reports and information.
The new legislation introduced a new layer of documentation that is used to govern the whole pharmacovigilance process (Borg et al. 2011). These are now present in the several modules of the Good Pharmacovigilance Practices (GVP), which started being released in 2012 (Borg et al. 2015). The GVPs constitute a set of measures drawn up to facilitate the performance of pharmacovigilance across the EU.

### 1.8.3 Pharmacovigilance Risk Assessment Committee (PRAC)

The Pharmacovigilance Risk Assessment Committee (PRAC) was set up in July 2012, succeeding the Pharmacovigilance Working Party (PhVWP) of the Committee for Medicinal Products for Human Use (CHMP). The PRAC was established to ensure the availability of the necessary expertise and resources for pharmacovigilance assessments by the EU and to monitor the effectiveness of risk management systems (Arlett et al. 2014). Meeting every month, it is now one of the seven scientific committees established within the EMA (Pacurariu et al. 2014; Santoro et al. 2017). This committee is composed by representatives of all EU Member-States, as well as from Iceland and Norway, independent scientific experts, HCPs representatives, and patient organization representatives (Santoro et al. 2017). The PRAC is responsible for assessing and monitoring safety issues for human medicines. Its main tasks involve the assessment of pharmacovigilance data submitted during all pre- and post-authorization phases, such as the assessment of PSURs; consultation and recommendations on initial or additional safety monitoring, through the review and agreement of risk management plans, or post-authorization safety studies (PASS) and respective protocols; imposition of new safety measures to protect patients; and establishing a list of medicinal products subject to additional monitoring (European Medicines Agency 2012; Arlett et al. 2014; Borg et al. 2015; Santoro et al. 2017).

### 1.8.4 Regulatory Changes Regarding Market Authorisation

Under the new provisions, all market authorization applications will be required to include a risk management plan (RMP) that gives a detailed description of the risk management system that is to be implemented, regardless of whether the active substances are new or well established (Borg et al. 2015; European Medicines Agency 2017). There is also the requirement of keeping a pharmacovigilance system master file. The risk management system is defined as a set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to a medicinal product, including the assessment of the effectiveness of those activities and interventions. Additionally, RMPs are to be mandatory for all significant changes to existing marketing authorizations, such as a new dose form, route of administration, paediatric indication, or any other significant change in indication. The measures set up in the RMP should be proportionate to the identified and potential risks of a certain medicine (European Medicines Agency 2017).
The new legislation also places more emphasis on post-authorization safety data (Raine 2012). Authorities will evaluate the effectiveness of risk minimization measures through the scrutiny of the proposed risk minimization measures and measurement of other type of observational studies to evaluate key health outcomes. The legislation introduced clarity in the oversight by the authorities of non-interventional studies. Based on a safety concern by the competent authorities, marketing authorization holders (MAHs) can be requested to conduct a PASS at any time during the lifecycle of the medicine (Wise 2015).

1.8.5 ADVERSE DRUG REACTION MONITORING AND SIGNAL MANAGEMENT

The new legislation introduced significant changes in ADR management (Santoro et al. 2017). One of the biggest changes must do with the widening of the legal definition of an ADR. An ADR is now defined as a response to a medicinal product which is noxious and unintended, arising from the use of the medicinal product within or outside of marketing authorization, or from occupational exposure. The use outside of marketing authorization covers off-label use, overdose, misuse, abuse, and medication errors (European Medicines Agency 2017).

To strengthen signal detection, all ADRs must be reported by Member States and MAHs to EudraVigilance (European Commission 2000). This database is to be used as the sole repository for all ADRs arising from clinical trials and from spontaneous reports, whether with EU or non-EU origin (Borg et al. 2011). According to the legislation, signal detection is a task shared by the EMA, national competent authorities and MAHs, who should continuously monitor the data available (Pacurariu et al. 2014).

With the implementation of the legislation, patient reporting has been expanded throughout the EU (Santoro et al. 2017). The EU now mandates Member States to encourage patients to report suspected ADRs directly to regulatory agencies and to enable reporting through web-based formats and alternative means. The new legislation also states that MAHs shall not refuse to consider ADR reports received from patients through appropriate means (Health Action International 2015). This step showed the acceptance among EU legislators of the need to enhance patient engagement in reporting their ADRs. It further emphasized the need for the development of efficient patient reporting systems contributing to signal detection. In addition, the legislation created mechanisms for effective communication with the general public about the risk of medicines (Santoro et al. 2017).

1.8.6 TRANSPARENCY AND COMMUNICATION

One of the goals of the legislation was to increase transparency and increase public trust in the drug regulation process (Santoro et al. 2017). This is due to the demands for more openness and information from different stakeholders in drug regulation, including the public. Transparency became a key
consideration for the EMA in delivering its service to patients and society (Arlett & Kurz 2011).

Marketing authorization documentation is to be publicly available through the EMA or national competent authorities’ webpage, including scientific data and clinical effectiveness details on the product (Santoro et al. 2017). Documents, such as the Summary of Product Characteristics (SmPC), the European Public Assessment report (EPAR), Direct Healthcare Communications Letters (DHPC), or clinical trial reports are also to be made public (Goedecke et al. 2018). The opinions on marketing authorization will be published and any refusals are to be made publicly available as well.

Information on ADRs is available through a webpage created and maintained by the EMA, where key information on drug safety will be published (www.adrreports.eu). Part of the strategy to increase transparency and trust in medicine regulation has also led to holding public hearings during the decision-making process (Borg et al. 2011). Furthermore, the role of HCPs and patients has been strengthened with their inclusion in the works of the scientific committees (Raine 2012).

1.9 PHARMACOVIGILANCE METHODS

Pharmacovigilance activities can be done using various methods, with both passive (such as spontaneous reporting or observational studies) or active approaches (such as simple clinical trials or patient registries) (Härmark & van Grootheest 2008).

Spontaneous ADR reporting is the most widely-used method in pharmacovigilance (Gould et al. 2015; Durrieu et al. 2016). It is an essential component and a major tool of the pharmacovigilance system of any country (Bandekar et al. 2010). As described previously, the development of pharmacovigilance is intimately related with the development of the spontaneous reporting system (Pal et al. 2013). While this method remains indispensable, the need for more active surveillance methods became clear after the rofecoxib and rosiglitazone scandals in the past decade (Edwards 2012; Härmark & van Grootheest 2012). The pharmacovigilance legislation implemented in 2012 in the EU was a step to that direction (as highlighted in Chapter 1.8). The use of more robust and systematic pharmacoepidemiological methods can help counter the weaknesses of spontaneous reporting, such as the determination of the frequency of ADRs, or medicine’s safety compared to a comparator (Gould et al. 2015; Lane et al. 2018). Even though many times regulatory bodies cannot wait for the results of pharmacoepidemiological studies to become available, these are gaining weight in the drug safety regulation (Arlett et al. 2014). In the EU, approximately 10% of safety signals identified by the EMA in 2013 came from observational studies, and their proportion is growing (Pacurariu et al. 2014; Lane et al. 2018). The changing regulatory frame made decision-making more dependent on the assessment of available data coming from a wider pool of information, such as from industry studies, academic studies, studies from public authorities and use
of data from ‘real-life’ health outcomes (Arlett et al. 2014). The use of more robust and systematic pharmacoepidemiological methods can help counter the weaknesses of spontaneous reporting, such as the determination of the frequency of ADRs or its safety compared to a comparator (Verhamme & Sturkenboom 2011). Pharmacoepidemiology studies can help in confirming the clinical benefits and assuring the safety of medicines in the market.

The following chapters will provide a brief overview of methods used in pharmacovigilance.

1.9.1 SPONTANEOUS REPORTING

As described in chapter 1.7, the spontaneous reporting system (SRS) was created soon after the thalidomide disaster (Olsson 1998). Spontaneous reporting is defined as: “An unsolicited communication by a HCP or consumer to a company, regulatory authority or other organisation (e.g. the World Health Organization, a regional centre, a poison control centre) that describes one or more ADRs in a patient who was given one or more medicinal products and that does not derive from a study or any organised data collection scheme” (European Medicines Agency 2017).

Initially, only physicians could report, as it was considered that only a physician could provide the level of high-quality information about ADRs and minimize the risk of reporting known or unrelated associations (van Grootheest et al. 2003; Anderson et al. 2011). Eventually other HCPs, such as pharmacists and nurses were introduced into the SRS, nowadays providing an important contribution to the pharmacovigilance system (Ranganathan et al. 2003; van Grootheest et al. 2004; Rutter et al. 2014). More recently, patients have been allowed to report directly to the authorities as well, e.g., within EU countries (Härmark et al. 2015).

The SRS has been the method that has provided the highest volume of information at the lowest cost, covering all medicines available at the market (Lane et al. 2018; Postigo et al. 2018). International experience has shown that it has led to early detection of safety problems, spurned further investigation of suspected problems and produced regulatory changes to labels and product information (Goedecke et al. 2016). The SRS also has the advantage of enabling medicines to be monitored throughout their lifetime (Pal et al. 2013). The most important function of the SRS is the early identification of signals of new, rare and serious ADRs. It has an important role in generating hypotheses about potential hazards of marketed drugs that require further investigation (Pal et al. 2013).

Despite its proven usefulness, the SRS has several limitations. Reporting is dependent on the initiative and motivation of the reporters, which can lead to biased reporting (Pal et al. 2013). The major limitation can be considered under-reporting of suspected ADRs. Under-reporting can lead to a delay in the discovery of undetected safety problems (Hazell & Shakir 2006). Numerous reasons have been pointed as why HCP do not report ADRs (Lopez-Gonzalez et al. 2009). Factors commonly identified are: reluctance to send reports based on mere
suspicion; lack of time; unawareness of the reporting system; and ignorance of reporting requirements (Lopez-Gonzalez et al. 2009). Other factors are the belief that suspected ADRs are too trivial and too well known to report and fear of involvement in litigation (Varallo et al. 2014).

Due to under-reporting it can be very difficult to assess the risk of specific ADRs associated with the use of drugs based on data obtained only from spontaneous reporting. This can have an impact on the detection of new safety signals (Biagi et al. 2013). To generate a signal, the number of necessary reports will depend on the total number of reports in the database, the total number of ADRs in the database and the number of reports concerning the drug association (Coloma et al. 2013).

Another limitation is that case reports might not contain a complete medical or pharmacological history of patients. Reported data on comorbidities or even on the sex of the patient varies between regions, countries and type of reporter (Biagi et al. 2013). The provision of rich, detailed information about the reactions is of importance for the determination of causality (Hazell & Shakir 2006).

1.9.2 STIMULATED REPORTING

Stimulated reporting refers to the concept that a safety warning by a regulatory agency, such as through a direct healthcare professional communication (DHPC), will result in substantially increased ADR reporting rates (Hoffman et al. 2014). Additional methods have been developed to complement SR, to better identify specific risk factors and high-risk groups, monitor the quantitative aspects of medicine safety, and to characterise ADRs associated with specific medicines and populations (Pal et al. 2013). These methods include, among others, prescription-event monitoring (PEM) in the United Kingdom (Layton et al. 2011), cohort-event monitoring (CEM) or targeted-spontaneous reporting (TSR), the two latter being used mostly in Africa (Bassi et al. 2013; Pal et al. 2013; Suku et al. 2015). The next chapter will provide a brief overview of stimulated reporting methods.

1.9.2.1 PRESCRIPTION-EVENT MONITORING (PEM)

Prescription-Event Monitoring (PEM) is a method developed in the United Kingdom (UK) that is used with small adaptations in a number of countries (Layton et al. 2011). It uses a non-interventional cohort to provide more information on a selected drug or class of drugs (Ferreira 2007). Data collection starts with the identification of patients starting a medication of interest. These patients are identified by linking dispensing data to specific patients. Physicians will receive a questionnaire for each identified patient. This questionnaire generally contains information the demographics of the patient, the prescribing details, and the details for all events that the patient might have experience during a set period of time. In the UK, questionnaires are sent until a sample of 10,000 patients is reached (Layton et al. 2003; Layton & Shakir 2015).
1.9.2.2 MODIFIED-PEM AND SPECIALIST COHORT EVENT MONITORING

In the UK, PEM has undergone some adaptations over the years. Two subtypes of the method have been developed: Modified PEM (M-PEM) and Specialist Cohort Event Monitoring Studies (SCEM) (Layton et al. 2011; Layton & Shakir 2015). M-PEM uses the same process as conventional PEM, building on its strengths, but tries to overcome its limitations. In the case of M-PEM, the questionnaire is more detailed, enabling to characterize real-life drug use, adherence to prescribing recommendations, and targeted analysis of events. M-PEM is useful for the evaluation of drug safety in special populations or subgroups, or following important changes in the product’s lifecycle such as a formulation change (Layton et al. 2011). SCEM enables a cohort of patients prescribed a medicine in the hospital and secondary care settings to be monitored. The method also permits the inclusion of a comparator cohort of patients receiving standard care, or another counterfactual comparator group, to be monitored concurrently, depending on the study question. The method can provide insight into the adoption of a new product into clinical practice with inclusion of comparator cohorts receiving standard care, if desired (Layton & Shakir 2015).

1.9.2.3 LAREB INTENSIVE MONITORING

In the Netherlands, a PEM scheme has been developed involving patients as the sole providers of information (Puijenbroek & Grootheest 2014). Starting in 2006, this program has been named Lareb Intensive Monitoring (LIM) (Härmark & van Grootheest 2012). It is a prospective observational cohort study that enrolls patients at pharmacies and collects information on adverse events through web-based questionnaires over a period of time (Härmark & van Grootheest 2012). This method has been useful to complement spontaneous reporting. The main idea with web-based questionnaires, using patients as the source of information, is to obtain real-time data not only on ADRs, but as well on other aspects, such as off-label use, adherence, therapeutic effects/response and severity of the reactions (Härmark & van Grootheest 2012). This method has helped in identifying possible new safety signals, such as with amenorrhea, shock-like paraesthesias and micturition problems associated with the use of duloxetine, time of occurrence of the ADR with pregabaline, and confirmation of the safety profile of vaccines (Oosterhuis et al. 2014b; van Balveren-Slingerland et al. 2015). The positive results from the Netherlands show that a PEM scheme like LIM could potentially be set up in other countries and provide a further layer of drug surveillance using patients as a source.

1.9.2.4 INTENSIVE MEDICINES MONITORING PROGRAMME

New Zealand championed a PEM scheme called the Intensive Medicines Monitoring Programme (IMMP) (Clark & Harrison-Woolrych 2006). A cohort of
around 10,000 patients for each monitored medicine was established from dispensing data collected from community and hospital pharmacies throughout New Zealand. Demographic and personal data of patients, as well as details of the prescriber, pharmacy, and the medicine were collected from the dispensing records. The patients in the cohort are then monitored by intensive methods (Zhou et al. 2003). Follow-up questionnaires requesting information on all new clinical events are sent to prescribers. Additional information was obtained from spontaneous reports sent by HCPs, patients and the pharmaceutical industry, as well from linkage to a national mortality dataset (Harrison-Woolrych et al. 2012, 2013). The IMMP allowed for the proactive study of the use of medicines in real-life conditions, investigating exposures and outcomes (Harrison-Woolrych et al. 2010). It has identified several safety signals such as varenicline and memory impairment, and has allowed the study of the exposure of varenicline during pregnancy (Harrison-Woolrych et al. 2010, 2013). This programme was closed in 2014.

1.9.2.5 COHORT EVENT MONITORING

Cohort event monitoring (CEM) is based in PEM, with adaptations. CEM aims to register all adverse events that occur in a defined group of patients after starting treatment with a specific medicine during routine clinical practice, regardless of the cause or severity (Suku et al. 2015). CEM is a prospective, observational cohort study of adverse events associated with one or more medicines (Pal et al. 2013). It differs from PEM in that the cohort is enrolled by HCPs instead of relying on prescription details supplied by the pharmacies (Bassi et al. 2013). The sample size is around 10,000 patients. CEM was developed by the WHO, as a post-marketing surveillance programme for new molecular entities in the market but can be also used for older drugs (Bassi et al. 2013; Suku et al. 2015). CEM captures all medicine-related events, such as ADRs, medication errors, drug interactions and pharmaceutical quality issues (Pal et al. 2013). This method has the advantage of being able to produce incidence rates, rapid results, early detection of signals, fewer missing data and less reporting bias (Pal et al. 2013). However, due to the nature of monitoring a cohort, it is much more resource-intensive than spontaneous reporting, and collection of data personal data from patients can be challenging (Pal et al. 2013). CEM is currently being used for antimalarials such as artemisinin-containing therapies or anti-retroviral therapies for HIV/AIDS in Kenya, Nigeria, Tanzania, Ghana and Zimbabwe (Pal et al. 2013).

1.9.2.6 TARGETED SPONTANEOUS REPORTING

Targeted spontaneous reporting (TSR) is a method that builds on the principles of both spontaneous reporting and cohort event monitoring (Ndagije et al. 2015). In this method, a well-defined group of patients taking the drugs of interest is monitored as part of routine care. In TSR, HCPs managing a well-defined group of patients are sensitized to report specific ADRs related with a
medicine (Pal et al. 2013). This method was developed by the WHO in 2010 (Ndagije et al. 2015). An advantage of TSR is that it can capture measurements over the entire length of the treatment, and because there is a defined denominator it allows for the calculation of incidence rates (Boulle et al. 2007). It can also be adapted to capture all ADRs, only ADRs relevant to the medication of interest, or continual general pharmacovigilance data, with adaptations to the population of interest as well (Karwa et al. 2017). Other advantages of this method are that it is affordable, feasible and suitable in settings with limited financial and human resources (Pal et al. 2013). The use of TSR promotes awareness of pharmacovigilance in the sites it is being used and increases the reporting rate (Ndagije et al. 2015). TSR has been used in some African countries to monitor specific ADRs such as renal toxicity in patients taking antiretroviral therapy (ART), especially tenofovir-based regimens, or anti-tuberculosis medicines (Boulle et al. 2007; Ndagije et al. 2015).

1.9.3 PHARMACOEPIDEMIOLOGY STUDIES

Pharmacoepidemiology is defined as the study in real conditions and on large populations, of use, effectiveness and risk of drugs (Montastruc et al. 2015). These studies allow to characterize conditions of use, misuse, clinical effectiveness, ADRs and risk of drugs (Montastruc et al. 2015). These studies are non-interventional, i.e., the researcher does not intervene, it only measures the outcomes (Song & Chung 2010). Pharmacoepidemiology studies are important when there is limited information regarding the frequency of the harm caused by the medicine, as well about the nature of the harm (Montastruc et al. 2015).

This type of research uses data from patients in real-world conditions (Dreyer 2018). Sources of data include patient registries, electronic health records, administrative claims, and surveys. They assess a medicine’s efficacy outcomes, safety, tolerability, and patient adherence by using relevant long-term outcomes (Sox & Goodman 2012). Increasingly, these studies are also concerned with measuring comparative effectiveness of treatments (Sox & Goodman 2012). Recently, a European initiative piloted direct-to-patient research for pharmacovigilance purposes through the Pharmaepidemiological Research on Outcomes of Therapeutics by a European ConsorTium (PROTECT) (Reynolds et al. 2016). By using direct reporting from patients, researchers hope to address a myriad of questions related to everyday clinical practice (Dreyer 2018). One such example is the information on medication use by pregnant women collected via the internet. Results from direct data collection from patients adds detail, but clinical input may be needed to fully understand patients’ medical histories and capture birth outcomes (Dreyer et al. 2015).

1.9.3.1 CASE-CONTROL STUDIES

Case control studies compare the occurrence of a possible cause in a group of subjects with the outcome variable of interest against a group unaffected by the outcome variable (control group) (DiPietro 2010). These studies start with the
selection of the cases and controls, which should represent all cases in a specified population. The cases are selected based on the outcome variable of interest, not exposure (Etminan & Samii 2004). These studies are longitudinal. They are used for initial evaluations of relative risk factors but are not able to determine the absolute incidence of disease. Case-control studies are especially used to investigate rare outcomes, or when there is a long period between exposure and outcome (Etminan & Samii 2004).

Case-control studies are more cost-efficient to carry out than cohort studies because they use a smaller sample to achieve the same goal as cohort studies (Yang et al. 2010). Once the case and control subjects are established, the distribution of exposure between cases and controls is the explored, enabling the calculation of the odds ratio (OR). The major problems with this type of design are confounding, selection bias and recall bias (Yang et al. 2010).

1.9.3.2 COHORT STUDIES

In cohort studies, an outcome or disease-free population is first identified by the exposure of interest and followed over a period of time to observe if the outcome of interest occurs (Song & Chung 2010). Cohort studies can have a prospective or retrospective design, and are used to study incidence, causes and prognosis (Yang et al. 2010). As the exposure to the outcome of interest is identified before, cohort studies can assess causality (Song & Chung 2010). Cohort studies can thus ascertain the exposure status of the individual, as well as provide person-time information (Klungel et al. 2004). This type of studies is generally preferred over case-control studies because there is the possibility of maximizing the sample size, as new subjects can enter the cohort at any time (Etminan & Samii 2004). The major advantages of this method include: the possibility of measuring directly the relative risk of developing the outcome of interest, compared to those who didn’t develop it; the ability to determine cause-effect relationships, as the characteristics of the individuals is known; absence of bias in determining the presence or non-existence of the risk factor, as this is measured prior the occurrence of disease; ability to identify other diseases related to the same risk factor; and possibility of generalizing the results of the reference population to the general one (Yang et al. 2010).

However, cohort studies suffer from methodological issues such as selection bias of the subjects due to differences between the study groups; they require a long follow-up period, since the outcome of interest can happen a long time after exposure; difficulty in controlling external factors that might be associated with the outcome variable; bias by differential loss to follow-up due to migration, death or drop-outs; and the rare events are difficult to capture because of the large number of subjects (Song & Chung 2010). Furthermore, they are costly in time and personnel (Yang et al. 2010).

1.9.3.3 NESTED-CASE CONTROL STUDIES
Nested case-control studies are a research design showing greater cost-efficiency than cohort studies (Yang et al. 2010). In this epidemiological study design, both cases and controls are chosen from a defined cohort, for which information on exposure and risk factors, as well as other baseline data, were already collected (Etminan & Samii 2004). Cases are usually matched by certain variables such as sex, age, and time of enrolment into the cohort (DiPietro 2010). This design is especially appealing when measuring the exposure is expensive, or the outcome of interest is rare (Yang et al. 2010).

A major advantage of this design is that it allows for the estimation of absolute and relative risk functions (DiPietro 2010). It also allows for better control for confounding, and because baseline and clinical data was already collected from all subjects, recall and selection bias can be minimized (DiPietro 2010). The analysis of the data is also less complex, as confounding is controlled through matching. Nested case control studies show some limitations such as loss to follow-up, and problems with the representativeness of all the controls if the outcome of interest is not rare (DiPietro 2010).

1.9.3.4 CROSS-SECTIONAL STUDIES

Cross-sectional studies are primarily used to measure prevalence of disease. In a cross-sectional study, the measurements of exposure and effect are made simultaneously in the sample population (DiPietro 2010). By taking a representative sample, it is possible to generalize the results obtained in the sample for the population as a whole (Pearce 2012). Cross-sectional studies differ from cohort and case-control studies as some of the research subjects have not been exposed nor have the outcome of interest (Yang et al. 2010). The major advantage of this type of study is that it is quick to set up and conduct and inexpensive, as there is no follow-up (Lu 2009). However, this method cannot differentiate between cause and effect, or the sequence of events when the outcome is rare (Lu 2009).

1.9.3.5 CASE-CROSSOVER

In case-crossover studies, the exposure of each patient is used as its own control. The patients are followed over a period during which an exposure of interest happens and periods without exposure (DiPietro 2010). The controls are the same as the cases, hence the name case-crossover. Case-crossover studies are used when the occurrence of an outcome of interest is rather rare (Pearce 2012).

The strength of this type of study lies in the fact that control selection and confounding by indication are limited as the cases act as their own controls (Donnan & Wang 2001). However, underlying disease states within individuals could still cause confounding between treatment and outcome (Klungel et al. 2004). The main potential of this type of studies in pharmacoepidemiologic research lies in assessing acute transient events following intermittent drug exposure (Donnan & Wang 2001). Hence, this type of design is not suitable to
study chronic conditions that require constant medication (Donnan & Wang 2001).

1.9.4 REGISTRIES

In the context of post-authorisation evaluation of safety outcomes, patient registries are defined as organized systems that use observational methods to collect uniform data on a population defined by a particular disease, condition, or exposure, and that is followed over time (European Medicines Agency 2017). The most common types of registries are:

- Disease registries: focuses on a specific disease or condition of interest;
- Product registries: focuses on the exposure of a population to a therapeutic product;
- Pregnancy registries: focuses on exposure during pregnancy, post-partum and follow-up.

Properly designed and executed, patient registries can play an important role in gathering real world evidence and monitoring the safety of medicines (Martins & Kyosen 2013; Reid 2015). They can be a tool for the monitoring of AEs; evaluate risk and benefit factors; observe the course of disease; understand variations in treatment and outcomes; and to measure quality of care (Willis et al. 2012). Registries have been used as a complementary resource to collect safety information on special populations and periods (such as during pregnancy) or for rare events (Reid 2015).

Studies using registries can be used when clinical trials are not feasible, and registries are able to include a larger study population than trials (Willis et al. 2012). Although patient registries present an opportunity to better explore safety data, various challenges regarding registries still exist, such as a lack of harmonized data structures and harmonized protocols (Travers et al. 2015). The size and variability of the registry is an important limitation. Registries do not routinely include control groups. Furthermore, these databases lack clinical details. These parameters can impact the attainment of critical results (Reid 2015). Electronic health records and data linkage can help offset these limitations (Tubaishat 2017).

1.9.5 DRUG UTILISATION STUDIES

Drug utilization studies have become an important research method in drug safety. This research method is defined by the WHO as the marketing, distribution, prescription, and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences (World Health Organization 2004). Drug utilization research provides information on the prevalence, incidence, and duration of drug therapy (Schneeweiss and Avorn 2005). The source of the information derives directly from pharmacy dispensing
databases (Etminan & Samii 2004). This research method allows to describe quantitatively and qualitatively the efficiency of the use of drugs in a certain population, as well as the conditions of their use such as proper use, overuse, or underuse (Williams 2012). This also includes information on the economic value of the medicinal products.

Drug utilization research has become more important due to the increased marketed introduction of new molecular entities, growing consumption of medicines, concerns with costs, and to provide a more effective drug vigilance (Williams 2012).

1.9.6 ELECTRONIC HEALTH RECORDS

Electronic health records (EHR) refer to the systematized, cross-institutional, and longitudinal collection of clinical and administrative data of a patient (Coloma et al. 2013). The collected information reflects not only the patient’s healthcare status but as well information on its general health status and elements of the healthcare providers’ systems (Tomlin et al. 2012).

The use of this type of large databases enables examining a large number of patients for longer periods of time that would be otherwise possible with the use of fewer and smaller clinical trials prior to market approval (Moore and Furberg 2015). They provide an opportunity to explore outcomes associated with chronic exposure to medicines (de Bie et al. 2015). These large databases, comprising populations that can reach tens of millions exposed to a medicine of interest, allow for the quick set-up of studies to detect potential occurring adverse events (Coloma et al. 2013a). Furthermore, they allow to explore aspects of drug safety in special population such as children and adolescents in the post-market phase (de Bie et al. 2015). EHR have become a key element in drug regulation, as they have the potential to give information that would be provided by fewer, smaller clinical trials (Moore & Furberg 2015).

An example of the use of EHR for pharmacoepidemiological research is exemplified with the Sentinel Initiative from the FDA, or the PROTECT studies in Europe (Moore & Furberg 2015; Reynolds et al. 2016). However, the use of EHR has faced some problems such as a limited underlying terminology, few validation studies, and the need for additional statistical standards to deal with complex data (Moore & Furberg 2015).

1.9.7 SYSTEMATIC REVIEWS AND META-ANALYSIS

Systematic reviews are one of the most important methodological advances to summarize aggregate data on interventions (Sox & Goodman 2012). They allow for a comprehensive, transparent and reproducible synthesis of the information on interventions provided by randomised clinical trials (RCTs) or observational studies (O’Neil et al. 2014). RCTs rarely assess harms as their primary outcome; therefore, they typically lack the power to detect differences in harms between groups.
Systematic reviews have a great impact because of its methodological proceedings to avoid bias (Sox & Goodman 2012). They provide qualitative summaries of the body of evidence, alongside with strengths and weaknesses of these studies. If the nature of the included studies allows, meta-analyses (MAs) can aggregate and summarize data on safety outcomes in a quantitative way (Prada-Ramallal et al. 2017). When adequately powered, MAs provide answers to specific drug questions, being valuable tools in clinical and regulatory decision making (Hammad et al. 2013).

Systematic reviews and MAs have raised concerns about drug safety with several classes of medicines. Examples include the detection of cardiovascular risks associated with the use of rosiglitazone, or with inhaled anticholinergics (Kazi 2007; Hammad et al. 2013).

2 PATIENT REPORTING OF ADVERSE DRUG REACTIONS: CHANGING THE PARADIGM

2.1 BRIEF OVERVIEW OF PATIENT REPORTING OF ADVERSE DRUG REACTIONS

As described in previous chapters, the first ADR reporting systems introduced in the 1960s were usually reserved for HCPs. Only in a few countries, including the United States of America (USA), Canada, and New Zealand, were patients provided with the ability to directly submit information on ADRs to their national authorities (van Hunsel et al. 2012). In Europe, this has only changed during the past decade when the Netherlands, Denmark, the UK, and Sweden opened their reporting systems to patients (Aagaard et al. 2009; McLernon et al. 2010; Härmark et al. 2015). In 2012, the EU implemented a sweeping legislative change to pharmacovigilance, which has been described in detail in chapter 1.8. One of the greatest changes brought by this legislation was the requirement that all EU Member States introduce patient reporting of ADRs. With this move, the EU acknowledges patients as key sources of information on medicines safety and paves the way for a faster—and more comprehensive—collection of data on ADRs (Health Action International 2015). As the World Health Organization (WHO) stated “Only a patient knows the actual benefit and harm of a medicine taken. Observations and reports made by a health professional will be an interpretation of a description originally provided by the patient, together with objective measurements” (World Health Organization 2002). The new legislation has been suggested as major step in the right direction, marking the beginning of a new chapter in drug safety, making patients an important part of pharmacovigilance (Vilhelmsson et al. 2012).

2.2 PATIENT INVOLVEMENT IN DRUG SAFETY
One of today’s challenges regulators face is balancing the speedy approval of medicines with high therapeutic value with the need to ensure patient’s safety and trust in the regulatory process. This dilemma has been exacerbated with the high-profile drug withdrawals from the market (such as with rofecoxib and cerivastatin), post-marketing concerns over safety (rosiglitazone and tegaserod), lack of efficacy (like with gefitinib), or integrity of clinical trial data (telithromycin) (Eichler et al. 2008). Regulators have been actively promoting a more patient-centric approach as a hallmark of high-quality care. Patients and the general public have increasing expectations about the safety of medicines (World Health Organization 2002). They are the main beneficiaries of efficient and safe treatments (Sacristán et al. 2016). In the past decades there has been a greater focus on patient-reported outcomes. The patient has turned from being a passive receptor of care to become an active player in the management of its own health status (Smith & Benattia 2016). Patient-centeredness and patient safety have emerged as core elements in today’s interactive and responsive healthcare systems. Regulators and the pharmaceutical industry are compelled to meet increasing patient expectations and engage patients in shared decision making (Banerjee et al. 2013).

There has been concerns that patient-centred medicines might be at odds with evidence-based medicine, which has a focus on the population level. However, it is now accepted that a good outcome must be defined in terms of what is meaningful and valuable to the individual patient (Epstein et al. 2011). Patients are encouraged to take a more active role in their own treatment, having the possibility to discuss and question pharmacotherapy options with different HCPs (Smith & Benattia 2016). Technological developments have also made it easier for patient to be active participants of this process, both in the pre- and the post-approval phases (Sacristán et al. 2016).

Due to the recent changes in legislation both in the EU and the USA, the pharmaceutical industry is required to include patient-reported information in benefit-risk assessment (Banerjee et al. 2013). The collection of this information can be made using of patient-reported outcomes (PROs). These provide insight on patients’ experiences and perspectives on treatment and outcomes. PROs can be defined as measurements of any aspect of a patient’s health status that comes directly from the patient (i.e., without the interpretation of the patient’s responses by a physician or anyone else) (Rothman et al. 2009). The inclusion of PROs has been one of recent advances in assessing outcomes of medical care (Weldring & Smith 2013). In the context of clinical trials, PROs capture a variety of concepts, ranging from symptoms to complex issues such as quality of life. The richness provided by these instruments can provide evidence of a treatment benefit from a patient perspective and are being used to complement safety data (Weldring & Smith 2013). PROs are a development of the need to rethink existing traditional safety reporting methods. There is a need to connect with patients, value their concerns and output, and enrol them continuously in the research process (Berger et al. 2015). The real-world data provided directly by patients has an important role to play in the evaluation of safety outcomes, treatment patterns, compliance, epidemiology and comparative-effectiveness research.
Patient-centeredness has become a hallmark of not only high-quality health but also high-quality drug development and monitoring (Smith & Benattia 2016).

With the technology and information revolution, patients have unprecedented access to tools that provide knowledge on different medicines, treatment options and adverse events. Patients have shown willingness and capacity to be on the forefront of biomedical research (Parsons et al. 2016). It is believed that patient involvement increases the usefulness and sustainability of medicines research and development by promoting innovation and providing more insights into their preferences (Parsons et al. 2016).

Regulators started to recognize and value the importance of patient involvement (Härmark et al. 2016). Patients have been invited to engage in all phases of the lifecycle of medicines, providing input on their needs and perspectives. Both in the FDA and the EMA patients have been involved in different steps of the assessment of medicines (Dal Pan 2014; Smith & Benattia 2016). As an example, both agencies have public hearings on drug safety, helping to engage patients and HCPs in the assessment of medicines, as well as the participation in expert committees (Smith & Benattia 2016).

2.3 CONCERNS EXPRESSED ABOUT PATIENT REPORTING

Despite what was described in the previous chapter, for a long time patient reporting was not valued. As described previously, spontaneous reporting was created with HCPs in mind. Despite the fact that some countries allowed for patient reports, their input was not truly acknowledged (World Health Organization 2002). A key issue raised about officially including patients reports concerned the quality of reports (van Grootheest et al. 2003). However, it was shown that many concerns were interconnected with a paternalistic view of patients’ concerns (Golomb et al. 2007). Physicians were reportedly more likely to deny than affirm the possibility of a connection between a drug and an ADR. Furthermore, in many cases physicians dismissed potential associations reported by patients. For example, in 51% of the cases where patients talked to a physician about neuropathy symptoms, the physician dismissed the potential link to statins (Tuccori et al. 2008).

Secondly, for a long period there was a lack of formal studies on patient reporting (Blenkinsopp et al. 2007). The reluctance of some experts regarding patient reporting was connected to the fear that patients would only report known and already well-documented ADRs, thus swamping pharmacovigilance systems with “noise” and draining much needed resources (Blenkinsopp et al. 2007). As the quality of the spontaneous report is directly connected with its usefulness in signal detection, could lay patients provide clear and objective descriptions of ADRs (van Grootheest et al. 2003).

Yet, there were several motivations for patient reporting to be introduced (Härmark et al. 2016). One of the reasons was under-reporting by HCPs. Tapping
into patients’ experience directly was seen as a means to increase the rate of reporting and to improve signal detection (Härmark et al. 2015). Other reason to open reporting systems to patients included a general tendency in health care to take patients’ experience and reports more seriously, and to value their views (Banerjee et al. 2013; Härmark et al. 2015, 2016; Sacristán et al. 2016). It has also been shown that patient reports have contributed to drug safety signals, leading to regulatory decisions (de Langen et al. 2008).

2.4 THE CONTRIBUTION OF PATIENT REPORTING TO PHARMACOVIGILANCE

2.4.1 OVERVIEW OF FIRST EUROPEAN COUNTRIES INTRODUCING PATIENT REPORTING

As some countries started to introduce patient reporting since the early 2000s, more evidence became available on the quantitative and qualitative input provided by patients (Blenkinsopp et al. 2007). Most of this evidence came from Europe, where a small group of countries started accepting patient reports to competent authorities. Denmark, the Netherlands, United Kingdom and Sweden helped pave the way. Some other European countries, including Italy, Norway or Belgium, started opening their systems to patient reporting before 2012 but the public’s response was negligible (Health Action International 2015). The following sections present a brief overview of the first four countries that introduced patient reporting in Europe.

2.4.2 DENMARK

Denmark was among the first European countries to introduce patient reporting in 2003. Civil society organizations contributed for this development (Health Action International 2015). Reporting can be done online at the Danish Medicines Agency (Laegemiddelstyrelsen), and recent technologic developments have allowed for better possibilities of searching for reported suspected ADRs (Danish Medicines Agency 2016). In 2016, the Agency received 7654 ADR reports, which compares to the 7538 ADR reports received in 2015 (Danish Medicines Agency 2016). Of these, 38% of ADRs has been reported by patients or by the Patient Compensation Association. As of 2016, the share of reports by patients continues to grow (Danish Medicines Agency 2016). Patient reporting also led to a renewed interest from academic research in pharmacovigilance, as demonstrated by the several studies published in Denmark (Aagaard et al. 2009; Aagaard & Hansen 2010).

2.4.3 THE NETHERLANDS

The Netherlands, together with Denmark, pioneered direct patient reporting in 2003. The Netherlands Pharmacovigilance Centre Lareb performs
an evaluation of the reports submitted by HCPs and patients and submits reports on signals to the Dutch regulatory authority (de Langen et al. 2008). Lareb was one of the first pharmacovigilance centres to perform a formal evaluation of the contribution of patient reporting, comparing patient reports to the ones from HCPs (de Langen et al. 2008). This first study showed differences between the categories of seriousness and outcome in the reported ADRs between patients and HCPs, with similarities regarding the most reported ADRs and most frequently reported drugs (de Langen et al. 2008). In the Netherlands, patient reporting has been very successful and the reporting rates have increased steadily (Härmark et al. 2015). As of 2016, 55% of all suspected ADRs were reported by patients (Netherlands Pharmacovigilance Centre Lareb 2017). Lareb is a very active centre for academic pharmacovigilance research, also providing methods development (de Langen et al. 2008; Härmark et al. 2013; Härmark & van Grootheest 2012; Oosterhuis et al. 2017; Rolfes et al. 2017).

### 2.4.4 UNITED KINGDOM

The UK was one of the first countries to introduce spontaneous reporting by HCPs in the world (McLernon et al. 2010). Direct patient reporting was introduced in January 2005 (Fortnum et al. 2012). The first analyses of patient reports showed that patients report a significantly higher number of suspected ADRs per report than healthcare professionals, and the reports contained more than one suspected drug (McLernon et al. 2010). Early results also showed that patient reporting may provide a positive complementary contribution to that of HCPs (Hazell et al. 2013). Patient reports were richer in their descriptions of reactions than those from HCPs, and more often noted the effects of ADRs on patients’ lives (McLernon et al. 2010). A study to evaluate the impact of patient reporting in the UK concluded that patient reporting has the potential to add value to pharmacovigilance by reporting types of drugs and reactions different from those reported by HCPs (Avery et al. 2011).

### 2.4.5 SWEDEN

In Sweden, the national competent authority started patient reporting officially in 2008 after the positive experiences from neighbouring countries Denmark and the Netherlands (Härmark et al. 2015).

Even before that, a non-profit, independent organization named KILEN (the Swedish acronym for Consumer Association for Medicines and Health) collected reports from patients who wished to share their experiences with medicinal products. Patients could report experiences with medicines through an online form that contained free-text section (Vilhelmsson et al. 2011).

Between 2002 and 2009, a total of 665 reports were made (Vilhelmsson et al. 2011). Of these, 442 reports concerned antidepressant medications (Vilhelmsson et al. 2011). The analyses of the free text comments submitted by patients showed that these can be of value in pharmacovigilance and provide
important information on how a drug may affect the person using it and influence his or her personal life (Vilhelmsson et al. 2012, 2013, 2015).

In 2009, during the H1N1 pandemic, awareness of patient reporting was widely disseminated with the help of a media campaign. This helped to capture the association between the influenza H1N1 vaccine and narcolepsy (Verstraeten et al. 2016). As of 2013, patient reports constituted 20% of total ADR reporting to the Swedish Medicines Agency (Härmark et al. 2015).

2.5 QUANTITATIVE AND QUALITATIVE CONTRIBUTION OF PATIENT REPORTS

Patients reporting can be seen as complement to HCP reports and a help in fighting under-reporting of ADRs (Härmark et al. 2016). In countries that have implemented direct patient reporting the share of reports by patients continues to expand, as described in the previous section of the chapter. A considerable proportion of all reports in the Netherlands, Sweden and Denmark come from patients and it is increasing in other countries, as has been confirmed by the most recent World Health Organization Uppsala Monitoring Centre’s (WHO-UMC) repository data (Watson et al. 2018) (Figure 6). However, patient contribution goes beyond just the quantitative aspect.

![Figure 6](image-url)  
*Figure 6* Number of patient reports (defined as reporter type “Consumer/non-health professional” according to the E2B reporting standard, excluding suspected duplicates and reports from patient support programs/studies) in VigiBase (Watson et al. 2018)
The early experience showed that patient reporting has played a substantial role in detecting new signals. Examples include the association between the Pandemrix influenza H1N1 vaccine and narcolepsy (Verstraeten et al. 2016), sexual dysfunction after stopping to take serotonin reuptake inhibitors (Ekhart & van Puijenbroek 2014) or pathological gambling and the use of the dopamine agonist pergolide for treating Parkinson’s disease (de Langen et al. 2008). Several signals were detected solely by patient reports, such as the case of duloxetine and “electric shock feelings” (Härmark et al. 2013, 2015). The latter is also representative of the patient input. HCPs might reject this type of reaction as being strange and difficult to understand leading them to dismiss it (Golomb et al. 2007). As an example, the proportion of signals for which ADR reports from patients contributed increased from 15.6% in 2009 to 23.6% in 2010 in the UK (Hazell et al. 2013).

The detailed descriptions of the daily experience patients have with medicines are a resource that can add a new layer in pharmacovigilance (Rolfes et al. 2016). Patient reports include details include how the medicine is affecting the user in his or her daily life, they also contain valuable information regarding adherence to medicines and how treatment procedures may be optimized (Figure 7) (Härmark et al. 2016). Patient reporting may be one vital way to safeguard public health by collecting as many views and experiences as possible to get a more comprehensive picture of pharmacotherapy (Vilhelmsson 2013, 2015).

<table>
<thead>
<tr>
<th>Contribution of patient reports to pharmacovigilance</th>
<th>Examples</th>
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</thead>
<tbody>
<tr>
<td>Quality and timeliness of information on ADR</td>
<td>Terminology in language which patients and the public use to express harmful effects</td>
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<td></td>
<td>Rich narrative explaining impact of the ADR</td>
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<td></td>
<td>Potentially shorter delay in submitting a report, enabling earlier signal detection</td>
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<tr>
<td>Medication errors</td>
<td>Labelling inadequacies</td>
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<td></td>
<td>Look-alike, sound-alike name confusions</td>
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<td></td>
<td>Generic substitution confusions</td>
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<tr>
<td>Quality failures</td>
<td>Tablets break up in bottles</td>
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<tr>
<td></td>
<td>Tablets too large to swallow</td>
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<tr>
<td>‘Near misses’</td>
<td>Incorrect prescription and dispensing error</td>
</tr>
<tr>
<td></td>
<td>Inappropriate administration (not always a near miss)</td>
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</tbody>
</table>

**Figure 7** Areas in which patient reports in particular contribute to pharmacovigilance (Härmark et al. 2016)
2.6 CHALLENGES AND NEXT STEPS

Despite the positive experience from patients reporting over the years, several challenges still remain. The EU legislation altered pharmacovigilance profoundly (Borg et al. 2011). Among the major changes, the expanded definition of ADR to include medication errors and misuse helped to collect more information on medicine’s use in different instances (European Medicines Agency 2017). Outside of the EU, other countries have started to introduce patient reporting (Margraff & Bertram 2014; Matos et al. 2016).

Current pharmacovigilance systems have been able to identify many major safety issues, even though their functions and methods leave considerable room for improvement (Pal et al. 2013). Patient reporting can help to counter some of the limitations of pharmacovigilance methods and expand the available information of ADRs, such as how these affect their quality of life (Rolfes et al. 2016). Having more information available about ADRs through medicine users can possibly tackle under-reporting and provide a better risk assessment of medicines. Another change brought by the EU legislation was the introduction of measures to increase transparency regarding the communication between on the risk of medicines to patients, strengthening the trust of patients in the regulatory process (Borg et al. 2015).

Is the regulatory landscape ready to make use of the qualitative information provided by patients? Despite all research and efforts that have been made to explore the importance and worth of patient reports in pharmacovigilance, has this been recognized by patients, academia and politicians? There is still a gap in knowledge about the actual importance and usefulness of patient reporting and how this can be improved.
SUMMARY OF KEY FINDINGS

Pharmacovigilance is an integral and important component of public health. It helps to protect and promote public health by reducing the burden of ADRs and optimising the use of medicines. Its scope has grown considerably in the past few decades, encompassing not only ADR reporting but as well medication errors, counterfeit or substandard medicines, lack of efficacy or drug-drug interactions (World Health Organization 2006). Pharmacovigilance play a vital role in regulation of pharmacotherapies. Thalidomide was the greatest man-made drug safety tragedy, and its legacy changed completely the way medicines are regulated. It led to a development of a system to capture suspected ADRs on the post-marketing setting, i.e., the spontaneous reporting system (Pal et al. 2013). Still, despite this tragedy, several drug-related scandals have occurred over the years, such as with rofecoxib, rosiglitazone or benfluorex. These more recent scandals demonstrated the need for changes in the drug safety regulation. Developments have happened since those disasters towards having a more robust pharmacovigilance system to understand and manage risks related to pharmaceutical products and their use in different settings (Santoro et al. 2017).

Patients’ contribution to reporting of ADRs has been possible in some countries since the creation of the spontaneous reporting system; however, it was not overly valued. Societal changes occurring since the 1980s have led to the recognition that patients can play an important role in medicine regulation and safety (Vilhelmsson et al. 2012). In pharmacovigilance, patients started to be seen as important partners in the reporting of ADRs and were gradually incorporated in formal pharmacovigilance processes. Of special importance was the implementation of the EU pharmacovigilance legislation in 2012 (Borg et al. 2015). Patients can provide valuable information about ADRs and how they occur. They provide a more personal, detailed explanation of ADRs and highlight the consequences ADRs have in their lives.

Yet, there are still questions about the usefulness and importance of patient reports. There is great potential and opportunity with the inclusion of the patient view and input in pharmacovigilance. It is important to examine and recognise patient reporting of ADRs in a holistic way.
AIMS OF THE STUDY

The overall objective of this study was to research the value of patient reporting of ADRs to pharmacovigilance systems. Value in this context can be defined as the importance, worth and usefulness of patient reporting.

The specific study objectives were the following (number of the original publication is provided in brackets):

a) To systematically review the evidence of the value of patient reporting to the pharmacovigilance system (I);

b) To explore the views and opinions of different pharmacovigilance experts on the value of patient reporting and its future prospects (II).

c) To analyse the correlation between sociodemographic and economic factors and the direct patient reporting rate in diverse countries (III);

d) To assess discrepancies between ADR reporting and MedDRA codes using healthcare providers as reference (IV).
METHODS AND MATERIALS

STUDY CONTEXT AND DESIGN

This study was a multi-method study in which quantitative and qualitative methods were used to explore the research questions (Table 2). Studies I, II and III had an international scope, while study IV was an application of detailed analysis when ADRs are reported by HCPs who have to interpret patients’ complaints and translate them into a language that is distant from real world communication. The design of the study is schematically represented in Figure 8.

Figure 8 Outline of the studies

Table 2. Methods used in the studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Method</th>
<th>Material/subjects</th>
<th>Analysis of data</th>
</tr>
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<tbody>
<tr>
<td>I</td>
<td>Systematic review</td>
<td>Systematic search for literature from PubMed, CINAHL, Journals@Ovid and the Cochrane Library in January 2015, yielding 34 articles that fulfilled inclusion criteria</td>
<td>Systematic qualitative analysis of studies that fulfilled inclusion criteria (n=34)</td>
</tr>
<tr>
<td>II</td>
<td>Qualitative cross-sectional study with personal semi-structured interviews</td>
<td>Key pharmacovigilance stakeholders Finland, Netherlands, Portugal, United Kingdom, and</td>
<td>Inductive qualitative content analysis</td>
</tr>
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</table>
### METHODS

1 THE IMPORTANCE AND USEFULNESS OF PATIENT REPORTING TO THE PHARMACOVIGILANCE SYSTEM (STUDIES I AND II)

1.1 SYSTEMATIC REVIEW (STUDY I)

A systematic literature search was conducted on the databases PubMed, CINAHL, Journals@Ovid and the Cochrane Library. The following combined text and medical subject headings (MeSH) terms were used: pharmacovigilance, direct patient report, patient adverse drug reaction reporting, consumer reporting and general public reporting. The complete search string used for the search was: ((adverse drug reaction OR adverse drug reactions OR side effect OR side effects OR adverse outcome OR adverse outcomes OR adverse event OR adverse events)) AND (patient OR patients OR consumer OR consumers OR general public)) AND (report OR reports OR spontaneous OR spontaneous report OR monitoring OR intensive monitoring OR direct report OR spontaneous reports)) AND (pharmacovigilance OR pharmacovigilance system). The search was performed in January 2015 and was not limited to any type of study design or publication date. The language for the search was limited to English. The

<table>
<thead>
<tr>
<th>III</th>
<th>Cross-sectional observational study</th>
<th>Sociodemographic and economic factors (n=42) from 44 countries from different continents that had patient reporting system in 2014 (Margraff and Bertram 2014)</th>
<th>Multivariate regression models</th>
</tr>
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<tr>
<td>IV</td>
<td>Retrospective content analysis of spontaneous ADR reports</td>
<td>All spontaneous ADR reports submitted by HCPs to an authorized pharmacovigilance center in Portugal in two distinct years (2004 and 2012) (n=434)</td>
<td>Categorization of report data by exploratory retrospective content analysis and quantitative analysis of categorized data using non-parametric tests (Mann–Whitney U and Kruskal–Wallis $\chi^2$)</td>
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</table>
studies were selected on the basis of their title and abstract. A manual search was also performed; the reference list of key articles identified during the selection process was searched manually to detect further eligible studies not previously found. To complement the information, an internet search was conducted using Google Scholar and the general search engine Google, using the same terms as used in the literature search in the electronic scientific databases. An electronic matrix was developed in Microsoft Excel prior to the full-text review, with predetermined characteristics. The articles were assessed independently by two researchers (PI and MA).

The process of conducting the systematic review followed the steps recommended by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist (Moher et al. 2009). Two researchers read and carefully assessed each retrieved study. The methodological quality of the studies was assessed according to principles of Grading of Recommendations, Assessment, Development and Evaluations (GRADE), and the studies were organized to four categories on the basis of the methodology applied (reviews, observational studies, surveys, other study designs). Due to a lack of homogeneity among the studies, a meta-analysis of the data was not possible, but a qualitative analysis was conducted. This systematic review of published studies did not require ethics approval.

For a more comprehensive description on the steps used in this systematic review please see original publication I.

1.2 KEY PHARMACOVIGILANCE STAKEHOLDERS’ EXPERIENCES OF DIRECT PATIENT REPORTING (STUDY II)

A qualitative cross-sectional design with semi-structured interviews was used. An interview guide with 12 questions was developed (Appendix I). The interview guide questions were constructed based on the study aim and on the results of the systematic review (Study I). The guide explored across the development of pharmacovigilance since the implementation of the EU pharmacovigilance legislation, with a special focus on the value of patient reporting. The interview guide was developed and tested by members of the research team with experience in pharmacovigilance (PI), medication safety (MA), patient involvement in health communication (AC). Main qualitative research principles were checked by the team members AC and MA. All revisions were made according to the all inputs.

After piloting the guide and aiming to capture as most detailed and complete data as possible, the guide was adapted, but kept open to adjustments during data collection, particularly regarding different stakeholders’ roles.

1.2.1 SELECTION OF ORGANIZATIONS AND COUNTRIES
Purposeful sampling was used to select the interviewees. This technique is widely used in qualitative research for the identification and selection of information-rich cases for the most effective use of limited resources (Palinkas et al. 2015). Generalizability was not the primary objective for these interviews, but rather to obtain a rich experiential description and insights from interviewees. The chosen organizations were contacted per e-mail (PI). A date and time for the interview were also agreed per e-mail. There were two pharmaceutical industry organizations from the United Kingdom and the Netherlands that did not provide feedback to the e-mail contacts, despite these being repeated three times.

The research strategy covered four geographically and societal different EU countries. The goal was to capture diversity of countries working within a common framework. For this, Portugal and Finland were initially selected. Given their respective geographies, organizational, political and societally differences, a comparison north-south was aimed. Furthermore, these countries only implemented patient reporting after the 2010 EU legislation, and both present a low patient reporting rate (Banovac et al. 2017). Given their long history and development of patient reporting, the Netherlands and the UK were chosen to report on their experience. The individual differences between countries should allow for a better contextualization of patient reporting. By using multiple dimensions, we aimed to explore the relations and conceptualize relations among them.

Pharmacovigilance in the EU comprises several stakeholders with a complex network of responsibilities. The organizations screened to be included in this study comprised national competent authorities (NCAs) or pharmacovigilance centres, on top of national pharmaceutical industry trade associations. In addition, supranational organizations were also included. These included the World Health Organization (WHO), the Uppsala Monitoring Centre (WHO-UMC) and the European Federation of Pharmaceutical Industries and Associations (EFPIA). The organizations were chosen due to their involvement in implementing the EU regulations and processing patient reports (national authorities and pharmacovigilance centres); due to their regulatory compliance towards reporting ADRs (pharmaceutical industry trade bodies); and international organizations involved in monitoring health systems and supporting them. Patient or healthcare professionals’ organizations were deliberately not included in this study to focus on opinion of stakeholder involved in the direct regulatory process.

1.2.2 DATA COLLECTION

The male researcher PI conducted all the interviews. He had training in qualitative interviews prior to conducting them. For feasibility reasons, the interview guide was piloted with pharmacovigilance professionals in Portugal and Finland.

Written Informed consent was obtained prior to all interviews. The identities of the participants were anonymized before analysis. No repeat interviews were carried out. Interviews followed the interview guide (Appendix I)
and were audio-recorded. Interviews were conducted with privacy at interviewees' workplaces, in English language. Interviewees were asked to talk about their own views on this issue rather than about their institution’s position. They were also asked to talk about their own experiences and perceptions of patient reporting within their organizations.

1.2.3 ANALYSIS OF THE DATA

Audio records were transcribed verbatim and checked for accuracy. Thematic content analysis was used, a common approach used to analyse qualitative data in health care research (Pope et al. 2000). Two researchers (PI and EA) open coded the same 5 interviews, being the other ones coded by one researcher (PI). The codes were produced in an inductive manner, guided by the constructs present in risk management approach of drug safety (Wise 2015). They were revised iteratively, and during this process similar codes were grouped together into themes. As the process continued, new themes emerged, and groups of related themes (sub-themes) were placed together under larger ones. The process followed the EMA's philosophy of shifting towards a more proactive approach of ensuring patient safety, with efforts to further improve the spontaneous reporting scheme (Lis et al. 2012). A quality check of this study was performed according to the checklist of the consolidated criteria for reporting qualitative research (COREQ) (Tong et al. 2007).

2 THE CORRELATION BETWEEN SEVERAL SOCIODEMOGRAPHIC AND ECONOMIC FACTORS AND DIRECT PATIENT REPORTING RATE IN DIFFERENT COUNTRIES (STUDY III)

The study followed a cross-sectional observational design, with data collection and analysis consisting of three parts: (1) identification of relevant sociodemographic and economic factors, (2) search for and collection of relevant data, and (3) development and application of a statistical model on the dataset.

2.1 IDENTIFICATION OF RELEVANT SOCIODEMOGRAPHIC AND ECONOMIC FACTORS

Fifty countries from different geographical areas that participate in the WHO Programme for International Drug Monitoring in 2014 were included, following previous relevant studies, especially one conducted by Margraff and Bertram (Margraff & Bertram 2014) (Table 3). This study presented an exhaustive comparison between 44 countries that had patient reporting up to 2014 when the study was conducted (Study III), with the aim of identifying differences in the pharmacovigilance systems, as well as presenting data about
the percentage of how much patient reporting contributes to the national pharmacovigilance activities.

Information that can be associated with patient reporting mainly comprised indicators of global public health and economic performance. The selection of relevant factors at this point was based on prior knowledge and theoretical value to address study aims and allowing for further statistical estimations (Walter & Tiemeier 2009). Here, a total of 42 different factors were possible to identify, comprising demographic, socioeconomic and healthcare related information, mainly resulting from the evaluation of the databases mentioned in the next subheading.

Table 3. Sampled countries grouped by continent and marked per patient reporting rate.

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<th>Continents and Countries</th>
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<td>South Africa</td>
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<td><strong>America</strong></td>
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<td>Canada*#, Colombia, Cuba</td>
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<td>USA*#</td>
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<td><strong>Asia &amp; Oceania</strong></td>
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<td><strong>Europe</strong></td>
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<td>Croatia, Cyprus, Czech Republic</td>
</tr>
<tr>
<td>Denmark*#</td>
</tr>
<tr>
<td>Estonia*#</td>
</tr>
<tr>
<td>Finland*#, France</td>
</tr>
<tr>
<td>Germany, Greece</td>
</tr>
<tr>
<td>Hungary</td>
</tr>
<tr>
<td>Ireland, Italy</td>
</tr>
<tr>
<td>Latvia, Lithuania, Luxemburg</td>
</tr>
<tr>
<td>Malta</td>
</tr>
<tr>
<td>Netherlands*#, Norway*#</td>
</tr>
<tr>
<td>Poland, Portugal</td>
</tr>
<tr>
<td>Romania, Russia</td>
</tr>
<tr>
<td>Slovakia, Slovenia, Spain, Sweden*#, Switzerland</td>
</tr>
<tr>
<td>UK*#</td>
</tr>
</tbody>
</table>

§ - Countries that were removed from statistical analysis due to numerical problems
* - Countries included in the statistical analysis
# - Countries that showed patients' reporting of >5% of total report

2.2 DATA COLLECTION
For these 44 countries, data were retrieved from databases maintained by several organizations. These included the United Nations Educational, Scientific and Cultural Organization (UNESCO) Institute of Statistics database, World Health Organization (WHO) Global Health Observatory Data Repository, the Organization for Economic Cooperation and Development (OECD) Health Statistics, complemented by the Central Intelligence Agency (CIA) World Factbook, and the World Bank Databank on missing data. Information on the desired outcome, i.e. the percentage of population reporting ADRs, was only possible to access for 35 different countries (Table 4).

Table 4. Countries with adverse drug reaction reporting systems accepting patient reports and its respective percentage of total reports (adapted from Margraff and Bertram 2014)

<table>
<thead>
<tr>
<th>Continent and country</th>
<th>Patient reporting rate (% of total reports)</th>
<th>Continent and country</th>
<th>Patient reporting rate (% of total reports)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa</td>
<td></td>
<td>Europe</td>
<td></td>
</tr>
<tr>
<td>Morocco</td>
<td>10.4</td>
<td>Austria</td>
<td>5.0</td>
</tr>
<tr>
<td>Nigeria</td>
<td>1.3</td>
<td>Belgium</td>
<td>46.0</td>
</tr>
<tr>
<td>America</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Argentina</td>
<td>2.0</td>
<td>Croatia</td>
<td>2.3</td>
</tr>
<tr>
<td>Brazil</td>
<td>5.0</td>
<td>Czech Republic</td>
<td>3.5</td>
</tr>
<tr>
<td>Canada</td>
<td>30.5</td>
<td>Denmark</td>
<td>34.0</td>
</tr>
<tr>
<td>Mexico</td>
<td>1.0</td>
<td>Estonia</td>
<td>9.0</td>
</tr>
<tr>
<td>United States of America</td>
<td>47.6</td>
<td>Finland</td>
<td>13.9</td>
</tr>
<tr>
<td>Asia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Japan</td>
<td>3.8</td>
<td>Germany</td>
<td>3.6</td>
</tr>
<tr>
<td>Oceania</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Australia</td>
<td>3.0</td>
<td>Ireland</td>
<td>2.0</td>
</tr>
<tr>
<td>New Zealand</td>
<td>1.4</td>
<td>Latvia</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lithuania</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Malta</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Netherlands</td>
<td>35.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Norway</td>
<td>6.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Poland</td>
<td>2.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Portugal</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Slovakia</td>
<td>1.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Slovenia</td>
<td>3.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Spain</td>
<td>1.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sweden</td>
<td>21.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Switzerland</td>
<td>5.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>United Kingdom</td>
<td>13.0</td>
</tr>
</tbody>
</table>
Data from all relevant factors were extracted, providing a comprehensive summary of the circumstances of the economy and general health status of the considered countries. As the data was retrieved from multiple sources, we adapted and used the principles of data quality described by Brown et al (Brown, Stouffer et al. 2007). The data was checked by two researchers (PI and AC) and disagreement was sorted by consensus. Information was collected for the most recent and comparable year that values were available, falling in 2013, where a minimum number of missing information for each individual country existed, diminishing uncertainty. When data were not available for 2013, a range of +/- 2 years was searched for all countries. If again unavailable, information was searched retrospectively until 2005 for specific factors, addressing all countries for the same time interval (e.g. proportion of births attended by skilled health personnel). The factors were disaggregated by sex and age groups, whenever possible.

2.3 DEVELOPMENT AND APPLICATION OF THE STATISTICAL MODEL TO THE DATASET

The raw variables were retrieved to an Excel spreadsheet and the final dataset was checked for consistency prior analysis using the R-CRAN V3.2.0 software (R Development Core Team, 2011). Statistics aimed to evaluate the propensity for a country to have a significant patient reporting level (>5% for all population) based on the existing information associated with each country.

Patient reporting percentage was used as the outcome or dependent variable. Patient reporting can be defined as the reports submitted by patients themselves or consumers in general about suspect ADRs to pharmacovigilance authorities, using means of passive or active surveillance. By screening the database for level of response, it was possible to confirm that most countries presented less than 5% of patient reporting, naturally establishing this value as the cut-off for dichotomisation. Accordingly, a binary variable was defined to allow for studying the propensity for each country to report significantly (i.e. >5%) against those with only a residual report (≤5%).

From the initial 44 countries, data was complete for 35 countries, considering the identified 42 predictors or covariates, all presented in Table 3. Some of these, as marked in the table, had too many missing values, thus raising numerical problems and were removed from further analysis. Univariate logistic regression models (Hosmer and Lemeshow 2005) were computed for all considered covariates, as indicated in Table 5. Association with the outcome variable, even if small, was tested through the Wald test, considering at this phase 0.25 as the maximum value for the probability of type I error (i.e. p-value <2.5%). The most significant covariates were selected both from the numerical point of view, as well as from the point of view of interpretation and representativeness. These covariates were then homogeneously grouped by type of information conveyed: health investment (G1), life expectancy and health of the population (G2), and social literacy and organization (G3) (Table 5). Of the initial 35 countries, two were withdrawn from further analysis: Nigeria, which presented
values associated with the G2 far from the group average; and Morocco, since reported values were less plausible, even regarding the quality of their pharmacovigilance system.

**Table 5. Selected covariables grouped based on the type of information.**

<table>
<thead>
<tr>
<th>Covariables</th>
<th>P-value</th>
<th>Homogenous groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult literacy rate, population 15+ years, both sexes</td>
<td>§</td>
<td></td>
</tr>
<tr>
<td>Average annual growth in public pharmaceuticals expenditure per capita</td>
<td>0.564</td>
<td></td>
</tr>
<tr>
<td>Average of 13 International Health Regulations core capacity scores</td>
<td>0.502</td>
<td></td>
</tr>
<tr>
<td>Adult literacy rate</td>
<td>§</td>
<td></td>
</tr>
<tr>
<td>Antidepressant drugs consumption</td>
<td>0.458</td>
<td></td>
</tr>
<tr>
<td>Antidiabetic drugs consumption</td>
<td>0.526</td>
<td></td>
</tr>
<tr>
<td>Antihypertensive drug consumption</td>
<td>0.777</td>
<td></td>
</tr>
<tr>
<td>Causes of death, communicable diseases</td>
<td>0.348</td>
<td></td>
</tr>
<tr>
<td>Causes of death, non-communicable diseases</td>
<td>0.174*</td>
<td>G2</td>
</tr>
<tr>
<td>Full time employees at pharmacovigilance centre</td>
<td>§</td>
<td></td>
</tr>
<tr>
<td>Gross domestic product</td>
<td>0.204*</td>
<td>G1</td>
</tr>
<tr>
<td>Gross domestic product per capita</td>
<td>0.005*</td>
<td>G1</td>
</tr>
<tr>
<td>Health expenditure, public (% of total health expenditure)</td>
<td>0.03*</td>
<td>G1</td>
</tr>
<tr>
<td>Health expenditure, public (% of government health expenditure)</td>
<td>0.462</td>
<td></td>
</tr>
<tr>
<td>Health expenditure, total (% GDP)</td>
<td>0.049*</td>
<td>G1</td>
</tr>
<tr>
<td>Healthy life expectancy at birth</td>
<td>0.158*</td>
<td>G2</td>
</tr>
<tr>
<td>Hospital bed density</td>
<td>0.081*</td>
<td>G1</td>
</tr>
<tr>
<td>Infants receiving three doses of hepatitis B vaccine</td>
<td>§</td>
<td></td>
</tr>
<tr>
<td>Internet users</td>
<td>0.108*</td>
<td>G3</td>
</tr>
<tr>
<td>Life expectancy at birth, both sexes</td>
<td>0.555</td>
<td></td>
</tr>
<tr>
<td>Life expectancy at birth, female</td>
<td>0.387</td>
<td></td>
</tr>
<tr>
<td>Life expectancy at birth, male</td>
<td>0.035*</td>
<td>G2</td>
</tr>
<tr>
<td>Maternal mortality ratio</td>
<td>0.095*</td>
<td>G2</td>
</tr>
<tr>
<td>Mobile phone users</td>
<td>0.893</td>
<td></td>
</tr>
<tr>
<td>Neonatal mortality rate</td>
<td>0.033*</td>
<td>G2</td>
</tr>
<tr>
<td>Nursery and midwifery density</td>
<td>0.029*</td>
<td>G1</td>
</tr>
<tr>
<td>Out-of-pocket healthcare expenditure (% of private health expenditure)</td>
<td>0.631</td>
<td></td>
</tr>
<tr>
<td>Per capita public health expenditure</td>
<td>0.001*</td>
<td>G1</td>
</tr>
<tr>
<td>Per capita total health expenditure</td>
<td>0.096*</td>
<td>G1</td>
</tr>
<tr>
<td>Pharmacies per 100 000 population</td>
<td>§</td>
<td></td>
</tr>
<tr>
<td>Pharmaceutical density</td>
<td>0.645</td>
<td></td>
</tr>
<tr>
<td>Pharmaceutical sales</td>
<td>0.025*</td>
<td>G1</td>
</tr>
<tr>
<td>Pharmaceutical sales (% of healthcare expenditure)</td>
<td>0.005*</td>
<td>G1</td>
</tr>
<tr>
<td>Physician density</td>
<td>0.885</td>
<td></td>
</tr>
<tr>
<td>Description</td>
<td>Value</td>
<td>Group</td>
</tr>
<tr>
<td>-----------------------------------------------------------------------------</td>
<td>---------</td>
<td>-------</td>
</tr>
<tr>
<td>Proportion of births attended by skilled health personnel</td>
<td>0.725</td>
<td></td>
</tr>
<tr>
<td>Reported number of people requiring interventions against non-transmittable diseases</td>
<td>§</td>
<td></td>
</tr>
<tr>
<td>Skilled health professionals’ density</td>
<td>0.017*</td>
<td>G1</td>
</tr>
<tr>
<td>Total pharmaceutical sales</td>
<td>0.234*</td>
<td>G1</td>
</tr>
<tr>
<td>Total population</td>
<td>0.665</td>
<td></td>
</tr>
<tr>
<td>Under-five mortality rate</td>
<td>0.020*</td>
<td>G2</td>
</tr>
<tr>
<td>Urbanized population</td>
<td>0.171*</td>
<td>G3</td>
</tr>
<tr>
<td>Year of joining WHO Programme for International Drug Monitoring</td>
<td>0.002</td>
<td>G3</td>
</tr>
</tbody>
</table>

§ - Numerical problems  
* - Significant covariables (p-value <0.25)  
GDP – Gross Domestic Product

2.4 STATISTICAL ANALYSIS FOR MODEL ESTIMATION

Initial non-parametric correlations were calculated to explore possible associations between patient reporting and relevant variables, such as annual growth of pharmaceuticals or total pharmaceutical sales (thus increased population exposure to drugs and possible ADRs) or the year joining the WHO drug monitoring program. Afterwards, and using a multiple logistic regression approach, 3 models were computed using the covariables within each homogenous group and aimed to identify the most relevant ones within G1, G2 and G3. Once investigated the most significant predictors in each homogenous group, these covariables entered a final model, comprising at least one covariable from each group.

Statistical procedures for both multiple regression stages used a stepwise method and the best AIC (Akaike Information Criterium) as decision criteria for model choice. The final solution was selected based on 3 criteria: discriminatory capacity of the model through the area under the ROC curve, pseudo-R², and by comparing the empirical quantiles of the adjusted model with the empirical quantiles of the proportion of significant reports. The pseudo-R², using the Nagelkerke (RN²), were also calculated, and these are indicators of the amount of information explained by the model.

3 VALUATING COMMUNICATION ISSUES AS A MEASURE TO INTRODUCE PATIENT REPORTING (STUDY IV)

3.1 ASSESSING DISCREPANCIES BETWEEN ADR REPORTING AND MEDDRA CODES USING HCPs AS A BENCHMARK
An exploratory retrospective content analysis of spontaneous ADRs reports was conducted. The data retrieved consisted of all ADRs contained in spontaneous reports submitted by HCPs during the years 2004 and 2012 and registered in the Portuguese Southern Pharmacovigilance Unit (UFS) ADR database. This Unit was established in 2004, and it covers the southern administrative districts of Portugal (Batel-Marques et al. 2015; Herdeiro et al. 2012). The database is kept in both electronic and paper formats. In this Unit, two pharmacovigilance officers perform the tasks of receiving the incoming spontaneous reports, analysing and providing the initial codes to be attributed to the ADRs. Causality assessment is performed by an expert (a clinician), which includes validation of reports interpretation and subsequent final validation of the MedDRA codes.

The reports contain the idiomatic description of the ADR, HCP identification (profession and gender), origin of the report and setting of the notification. Patient’s age, gender, concomitant medication and the outcome of the ADR are also available. The study addressed language variation in reports sent in by different HCP, thus data extraction focused on the verbatim of the original reports, plus the corresponding MedDRA codes. Some ADR descriptions corresponded directly to MedDRA codes, while other accounts needed to be interpreted by pharmacovigilance officers.

Each MedDRA code can be composed by one single term, or up to several conjoint terms. Only prosodic words, i.e. those with semantic content, were analyzed. Reflecting the lexical and semantic discrepancies, a dichotomous key to describe the univocal correspondence between each ADR clinical description and the coded MedDRA term was built. This key corresponded to an agreement index, with the value 0 representing an imperfect fit, while 1 represented a perfect fit, the index being a simple mean of all analysed reports. In other words, the outcome evaluated is the exactness of the words describing the ADR compared with the MedDRA code that was awarded: if the spontaneous report wording was exactly the same as the MedDRA code given, then the index equals 1. The study was based on the quantitative fit between ADR wording and the MedDRA codes used; no assessment of other verbatim content was attempted.

### 3.2 DATA EXTRACTION

For the data extraction, a matrix with several parameters was developed. This matrix included information about the type and gender of HCP, detailed origin and report presentation, verbatim of the ADR, agreement between the ADR description and MedDRA code, discrepant words and age and gender of the patient. After the reports were coded, the consistency of the information was checked by the other researcher, and a consensus was reached on the final classification to be attributed to the cases. All personal identification data were already encrypted, guaranteeing the complete anonymity of all participants. Nonetheless, the data was handled with strict confidentiality, within the usual requirements for pharmacovigilance data.
3.3 DATA ANALYSIS

The data were statistically analysed using SPSS v20 (IBM Corporation), through descriptive statistics with a type I error level of $P < 0.05$. To evaluate the influence of variables, (such as the notification geographical origin, i.e., district and HCP working setting and professional background), non-parametric statistics were employed (Mann–Whitney U and Kruskal–Wallis $\chi^2$).
RESULTS

This chapter summarizes the key findings of the original publications I-IV.

1  THE IMPORTANCE AND USEFULNESS OF PATIENT REPORTING TO THE PHARMACOVIGILANCE SYSTEM (STUDIES I AND II)

1.1  SYSTEMATIC REVIEW (STUDY I)

Study I review identified 721 studies, of which 34 full-text studies were included in the qualitative analysis. The identification, screening and evaluation of eligibility of articles for final inclusion are presented in Figure 8. Of the identified 34 studies, 5 were literature reviews, 14 observational studies, 8 surveys, and 6 studies applied mixed methods (Study I). Most of the studies (30 out of 34) came from European countries, particularly from the Netherlands (n= 15), United Kingdom (UK) (n= 10) and Denmark (n= 5). For a full list of the studies included, please refer to Study I.
1.2 SUMMARY OF EVIDENCE

Combining the evidence on the advantages and limitations of direct patient reporting, it was shown that patients report different ADRs when compared with HCPs and identify novel ADRs. Patients provide new insights into ADRs by bringing information on different body systems affected by medicines, such as the central nervous system. Patients can be very important in identifying ADRs in specific populations, or types of medicine. The information provided by patient reports can be significant for ADR signal detection. One important characteristic of patient reports is the subjective description of ADRs. Some of the barriers were also identified. Despite the fact that many countries allow patient reporting to take place, the reporting rate and awareness are still low. It was pointed out that awareness should be raised so that patients can become...
more engaged. The new information provided by patients seemed to be valuable and of high quality (Rolfes et al. 2015). None of the studies provided insight on what is being done to increase participation and awareness.

### 1.2.1 REVIEWS (N=3) AND SYSTEMATIC REVIEWS (N=2)

The search strategy identified five reviews (Blenkinsopp et al. 2007; Herxheimer et al. 2010; Avery et al. 2011; Inch et al. 2012; Härmark et al. 2015), two of which were systematic reviews (Blenkinsopp et al. 2007; Inch et al. 2012). The studies synthesized data to identify the evidence on the potential of direct patient reporting (Blenkinsopp et al. 2007; Herxheimer et al. 2010; Avery et al. 2011), and to compare the differences between patient and HCP reports (Blenkinsopp et al. 2007; Inch et al. 2012). All the reviews concluded that patient reporting was valuable, with the differences between patient and HCP reports adding to the knowledge about ADRs (Blenkinsopp et al. 2007; Avery et al. 2011; Inch et al. 2012; Härmark et al. 2015). Most of the reviews (three out of five) stated the need for further evidence on the benefits and drawbacks of patient reporting (Blenkinsopp et al. 2007; Avery et al. 2011; Inch et al. 2012). As the reviews were published between 2006 and 2015, they included data from different periods and different countries, reflecting the different maturation states of patient involvement in ADR reporting (Blenkinsopp et al. 2007; Herxheimer et al. 2010; Avery et al. 2011; Inch et al. 2012; Härmark et al. 2015).

### 1.2.2 OBSERVATIONAL STUDIES (N=14)

All of the 14 observational studies (de Langen et al. 2008; Aagaard et al. 2009; van Hunsel et al. 2010; McLernon et al. 2010; Aagaard & Hansen 2013, 2013, 2014; Durrieu et al. 2012; Danish Medicines and Health Authority 2013; Hazell et al. 2013; Härmark et al. 2013; Li et al. 2014; Rolfes et al. 2015) were retrospective, and most (8 out of 14 studies) had the aim of comparing patient and HCP ADR reports (de Langen et al. 2008; Aagaard et al. 2009; van Hunsel et al. 2009; McLernon et al. 2010; Danish Medicines and Health Authority 2013; Hazell et al. 2013; Härmark et al. 2013; Rolfes et al. 2015). There were five studies from Denmark (Aagaard et al. 2009, 2010, Aagaard & Hansen 2013; Danish Medicines and Health Authority 2013), five from the Netherlands (de Langen et al. 2008; van Hunsel et al. 2009, 2010; Härmark et al. 2013; Rolfes et al. 2015), two from the UK (McLernon et al. 2010; Hazell et al. 2013), one from France (Durrieu et al. 2012) and one from China (Li et al. 2014). Two of the Danish studies focused on analysing the Danish experience with patient ADR reporting (Aagaard et al. 2009; Danish Medicines and Health Authority 2013), and three studies performed an analysis of the ADRs presented in the European ADR database EudraVigilance (Aagaard & Hansen 2013, 2014). The majority of the studies coming from the Netherlands (Härmark et al. 2013) and the UK (McLernon et al. 2010; Hazell et al. 2013;) compared the differences between ADR reports from patients and HCPs. Two studies were concerned with media exposition of statins (van Hunsel et al. 2009, 2010), and one with the patient...
contribution to ADR signal detection (Hazell et al. 2013). Both UK studies analysed the UK’s national pharmacovigilance database but looked at different outcomes (McLernon et al. 2010; Hazell et al. 2013).

Overall, these studies found that patient reporting is valuable, with no major qualitative differences between patient and HCP reports (Danish Medicines and Health Authority 2013; van Hunsel et al. 2009). Patients provided well-documented, consistent information (Aagaard et al. 2009), reporting different categories of ADRs for different types of medicines when compared with HCPs. Patients provided more consistent information, a greater number of categories of ADRs and a greater range of medicines (de Langen et al. 2008; Aagaard et al. 2009; Durrieu et al. 2012; Aagaard & Hansen 2013; Danish Medicines and Health Authority 2013; Hazell et al. 2013). This contribution can provide a positive, complementary input for safety signal generation (Hazell et al. 2013). Patients were found to report more often than HCPs on the impact of ADRs on daily life, making a more detailed description of reactions (Rolfes et al. 2015). A common feature of almost all of the studies from Denmark was the identification that most of the ADRs reported by patients related to central nervous system medication (Aagaard et al. 2009; Aagaard & Hansen 2013, 2014; Danish Medicines and Health Authority 2013). Four out of the 14 studies referred to the need for further research to clarify the value and characteristics of patient reporting (McLernon et al. 2010; Durrieu et al. 2012; Aagaard & Hansen 2013; Li et al. 2014).

Some of the studies found differences between patient and HCP reporting (van Hunsel et al. 2009, 2010; McLernon et al. 2010). For example, UK patients seemed to report more ADRs with a lesser degree of severity (McLernon et al. 2010). In a study from the Netherlands, differences were found in the level of participation of the population in a web-based intensive monitoring programme, which might have led to an underestimation of ADRs (Härmkö et al. 2013). A study from China investigating ADRs in a paediatric population concluded that patients are more likely to report new ADRs than HCPs, although patient participation was low (Li et al. 2014). Two studies from the Netherlands focused on the impact of media exposition on the reporting of ADRs for a specific class of drugs (statins) (van Hunsel et al. 2009, 2010). In general, media attention led to a peak in patient reports received by the pharmacovigilance authority, without affecting the overall reporting rate by patients.

1.2.3 SURVEYS (N=9)

Nine of the identified studies were surveys, carried out using different methods, such as web-based (Anderson et al. 2011; Margraff & Bertram 2014) or postal (Anderson et al. 2011; Krska et al. 2011) questionnaires, and group (Arnott et al. 2013; Rolfes et al. 2014) or personal (Anderson et al. 2011; Krska et al. 2011; van Hunsel et al. 2012; Rolfes et al. 2014) interviews. Six studies were from either the Netherlands (van Hunsel et al. 2010, 2012; Rolfes et al. 2014) or the UK (Krska et al. 2011; Anderson et al. 2011; Arnott et al. 2013). Most of the studies from the UK (Anderson et al. 2011; Krska et al. 2011; Arnott et al. 2013;) and one
from the Netherlands (van Hunsel et al. 2010) provided an overview of patients’ views and experiences with ADR reporting. These studies showed that patients consider the severity of the ADR and the need to share experiences, such as the impact of ADRs on their daily life, as the main motives to report (van Hunsel et al. 2010; Rolfes et al. 2014). Patients perceived the possibility of reporting ADRs directly as important (Anderson et al. 2011) and were able to identify ADRs in a manner that mirrored HCPs (Krska et al. 2011). Overall, patients’ views were positive (Anderson et al. 2011; Rolfes et al. 2014; Yamamoto et al. 2015). However, studies identified a need to empower people to report, and provide feedback on their reports (Arnott et al. 2013; Yamamoto et al. 2015).

Two studies, one from the Netherlands (van Hunsel et al. 2012) and the other from France (Margraff & Bertram 2014), aimed to study the countries in which patient reporting was available. It was found to be available in 44 countries worldwide in 2012 (Margraff & Bertram 2014). Although there were some differences in the way that different countries dealt with these reports, patient reporting was recognized as valuable (van Hunsel et al. 2012; Margraff & Bertram 2014). The availability of the reporting form online seemed to increase the reporting rate (Margraff & Bertram 2014). However, the content of the form was different for different countries and should be harmonized (Margraff & Bertram 2014).

1.2.4 MIXED METHODS (N=6)

Almost all (5/6) of the studies (Avery et al. 2011; van Hunsel et al. 2011; Härmark et al. 2011, 2013; Oosterhuis et al. 2014; van Balveren-Slingerland et al. 2015) were from the Netherlands. They explored the value of a web-based intensive monitoring system using patients as an information source. These studies focused on specific drugs, such as pregabalin (Härmark et al. 2011) and duloxetine (Härmark et al. 2013). The studies concluded that this type of intensive monitoring can gain insights onto daily use of medicines and its safety profile (Härmark et al. 2011, 2013; Oosterhuis et al. 2014). It can generate other types of information when compared with SR, and provide more information about reactions, including the quantification of latency (Härmark et al. 2011, 2013; Oosterhuis et al. 2014).

One of the Dutch studies focused on the contribution that patient reports provide to ADR signal generation (van Hunsel et al. 2011). It concluded that patients provide a valuable and considerable contribution to the detection of safety signals, in addition to that of HCPs (van Hunsel et al. 2011). This has also been corroborated in another study (Härmark et al. 2013). A UK study aimed to provide a general evaluation of the impact of patient reporting on the UK pharmacovigilance system. It concluded that patient reporting has the potential to add value to the pharmacovigilance system by providing reports with novel information about different types of drug and ADRs, thus complementing HCP reports and generating new safety signals. Reports by patients were found to describe ADRs in sufficient detail (Avery et al. 2011).
2 KEY PHARMACOVIGILANCE STAKEHOLDERS’ EXPERIENCES OF DIRECT PATIENT REPORTING (STUDY II)

Four themes (attitudes and beliefs, system maturation factors, regulatory improvements, and cultural shifts) emerged from data, and were found to be conceptually interconnected (Figure 9). Participants from countries that introduced patient reporting recently expressed a more negative attitude, if compared with ones that have had it for longer. All participants stated system maturation issues, such as the time to process this type of reports or other methodology factors, as pivotal on how effective the information provided by patients is used for safety purposes. All participants also highlighted the need for additional resources, both human and financial, to honestly address patient reporting and address its advantages.

Figure 9 Conceptual model of the themes emerging from Study II.

2.1 THEME 1: ATTITUDES AND BELIEFS

Apart from national regulators in Portugal and Finland, most interviewees expressed a moderate to very positive attitude towards patient reporting. This attitude derived from an opinion on the role of the patient in drug safety, to the experience gained with this type of reporting. Both in Portugal and Finland, interviewees from NCAs expressed a more negative attitude. On contrary, NCAs and pharmacovigilance centres from the UK and the Netherlands have a very positive attitude towards it. In Portugal, the collection and analysis of ADR reports is made by regional pharmacovigilance centres before being processed by the NCA. The interviewees from these centres also had a very positive opinion, as
did interviewees from international public health organizations. All pharmaceutical industry trade body interviewees have a moderately positive attitude towards patient reporting, stating that patients can only bring a limited amount of information.

Interviewees with positive opinions detailed that patient reports add other drugs and information that HCPs miss, also an opportunity to hear about patients’ views, namely the severity of the reactions and the impact in the quality of life.

Interviewees with positive opinions pointed to patient reporting contributing to signal detection. It was suggested that patients could add even more to this if patient reporting were more widespread. On the other side, more sceptical interviewees stated that patient reports provide weak clinical information on ADRs, with subjectivity from patients being a problem. One of the most stated concerns from NCAs in Portugal and Finland, as well as some industry interviewees, was that patients would add “noise” to the system, not contributing to detect safety signals. It was also stated that patients use the spontaneous reporting system to air complaints about other issues rather than reporting ADRs. Interviewees from NCAs in Portugal and Finland expressed some resignation about having to implement patient reporting. Despite their concerns, these interviewees recognized that patients could eventually add more information on ADRs and medicine use, thus helping to mitigate underreporting. Hence, efforts should be made in education, which should focus on HCPs as well. It was acknowledged by all interviewees that the quality of HCP reports is not ideal, and awareness for reporting among health professionals is low. The need for further education and training was a topic mentioned by all interviewees, regardless of their opinion on patient reporting.

2.2 THEME 2: SYSTEM MATURATION FACTORS

All the interviewees stated concerns with time needed to process patient reports. Interviewees from pharmacovigilance centres in Portugal, the Netherlands, UK, as well as from WHO-UMC, which are working directly with the reports, accepted that it is more work-intensive, taking more time to process, but provide an opportunity to have more, differentiated information on ADRs. On the other hand, interviewees from regulatory agencies in Portugal and Finland, stated that patient reports add a workload that is not cost-effective, i.e., the quality of the information provided does not justify the amount of time and resources involved. Pharmaceutical industry interviewees stated some apprehension about the burden of processing these reports, as the legislation already imposes other liabilities. A common complaint by both the industry and Portuguese and Finnish NCAs is the way ADRs are described by patients. Patients do not use clinical terminology and that makes it more difficult to retrieve information.

For different reasons, the awareness of the pharmacovigilance system and the importance of ADR reporting were acknowledged by all participants. All participants referred ongoing EU-wide projects, highlighting measures taken
locally to increase awareness. Interviewees from Portuguese and Dutch pharmacovigilance centres, UK’s NCA, WHO and WHO-UMC suggested that the low awareness and reporting rates by patients are a product of under promotion, not lack of interest from patients. Interviewees from Portuguese and Finnish NCAs admitted that patient reporting had not been very actively promoted. The reasons linked to the need for more resources, the uncertainty about what would the patients start reporting, and how to process the technical aspects of the reports.

2.3 THEME 3: REGULATORY IMPROVEMENTS AND IMPACT

Both industry, NCA and pharmacovigilance centres interviewees stated the EU pharmacovigilance legislation created an extensive impact. This impact has been felt in the operational side, in the requirements that both regulators and industry are subjected, as well on how to account and integrate patients in drug development and safety processes. It was noted by most interviewees that the legislation is still being implemented and improved. One perceived aspect that the legislation introduced was greater transparency in the pharmacovigilance processes. All interviewees, bar the Portuguese and Finnish NCA interviewees, considered this to be a positive step, as a way of participation in society in a democratic way. The interviewees that considered the increase of transparency not to be a helpful step questioned how the publication of technical, complex information can be understood by patients.

There was a general agreement among all interviewees about the need for adaptations to the way the regulatory system incorporates the new information coming from patients. Interviewees from the organizations working directly with patient reports, such as the Dutch, Portuguese and UK pharmacovigilance centres, as well as the WHO-UMC, mentioned that patient-reported information is not being fully used in the current regulatory process. One such example is the use of case-report narratives, which can be a prodigious source of extra information especially about quality of life impacts, although challenging to code. The same group of interviewees highlighted that the definition of a safety signal should be broadened. The interviewees from Portuguese and Finnish NCA stated some doubt about the input provided by patients, agreeing that in some cases signals could be picked up earlier but there was the need to tread slowly.

2.4 THEME 4: CULTURAL SHIFT IN PHARMACOVIGILANCE

All interviewees acknowledged that patient reporting is a major change in the way pharmacovigilance is developing. Interviewees from the WHO and UMC, pharmacovigilance centres in Portugal and Netherlands, as well from the UK, considered patient reporting the future of pharmacovigilance. However, remarks by interviewees in pharmacovigilance centres in Portugal and the Netherlands stressed the need to continue to continuously engage with HCPs. For all interviewees from the industry the involvement of patients in all phases of the product development and safety surveillance resulted in a more patient-focused
3 EXPLORING DEMOGRAPHIC AND ECONOMIC FACTORS THAT PROMOTE PATIENT REPORTING (STUDY III)

The analysis performed for study III resulted in a total of 35 countries being included. These came from the Americas, Asia and Oceania, and the overwhelming majority came from Europe. No country came from Africa. Apart from Argentina, Brazil and Mexico all other were high income countries. Of these 35 countries entering the data analysis, only 10 of them presented a significant level of direct patient reporting (Table 3 and 4). Apart from Canada and the US, the remaining were European countries. Belgium, Estonia, and Finland introduced the possibility of patient reporting in 2012. The other countries have had this possibility for longer, especially Canada and the US, which have it since the 1960s. All these countries present a big variability in terms of population, from a small, homogeneous one (e.g. Estonia) to a large and diverse one (e.g. US or UK).

There are negative correlations between highly consumed drugs and ADRs reporting, but positive with the overall market value. Stronger health systems e.g. having a better professional coverage present also higher patient reporting, this also happening with more Internet usage (Table 6).

Table 6 Selected significant nonparametric correlations between the outcome and covariables used as a potential predictor.

<table>
<thead>
<tr>
<th>Covariable</th>
<th>Rho</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidiabetic drugs consumption</td>
<td>-0.423 *</td>
</tr>
<tr>
<td>Antihypertension drugs consumption</td>
<td>-0.368 *</td>
</tr>
<tr>
<td>GDP per capita</td>
<td>0.628**</td>
</tr>
<tr>
<td>Internet users</td>
<td>0.561**</td>
</tr>
<tr>
<td>Life expectancy at birth, both sexes</td>
<td>0.444**</td>
</tr>
<tr>
<td>Nursery and midwife density</td>
<td>0.530**</td>
</tr>
<tr>
<td>Skilled healthcare professionals density</td>
<td>0.551**</td>
</tr>
<tr>
<td>Total pharmaceutical sales</td>
<td>0.447**</td>
</tr>
<tr>
<td>Year of joining WHO Programme for International Drug Monitoring</td>
<td>-0.541**</td>
</tr>
</tbody>
</table>

*p<0.05
**p<0.01
GDP – Gross Domestic Product
There are negative correlations between highly consumed drugs and ADRs reporting, but positive with the overall market value. Stronger health systems e.g. having a better professional coverage present also higher patient reporting, this also happening with more Internet usage (Table 6). A negative correlation was obtained with the establishment of the formal pharmacovigilance system reporting to WHO i.e. recent national systems present a poorer patient participation.

Looking to find causal relationships between patient reporting and covariables, univariate regressions were calculated and presented previously (Table 3). After selecting the relevant variables and clustering them, regression calculations within the homogenous groups of covariables selected the following variables (Table 5).

After selecting the relevant variables and clustering them, regression calculations within the homogenous groups of covariables selected the following variables:

- **G1**: Per capita public health expenditure and hospital bed density, \( R^2 N = 41\% \)
- **G2**: Under five mortality rate, \( R^2 N = 40\% \)
- **G3**: Year of joining WHO Programme for International Drug Monitoring, \( R^2 N = 56\% \)

These covariables entered a final model estimation, with a non-relevant predictor abandoning the model (Year of joining WHO Programme for International Drug Monitoring). The final model parameters are presented in Table 7. As explained in the methods section, the best AIC criterion was used, justifying one covariable presenting a high p-value, which from a parsimonious theoretical point of view was left in the final solution since countries with low child mortality rate present a good propensity to have a significant patient report. The final model revealed a very good discriminatory capacity with an area under ROC curve (AUC) of 0.89, allowing to say it is capable of separating countries without significant report from those with more than 5% patient reporting. Additionally, the percentage of explained pseudo-variance equalled 56%, which is a good value regarding the present social and economic areas study field.

### Table 7 Covariables in the final statistical model

<table>
<thead>
<tr>
<th>Covariable</th>
<th>OR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per capita public health expenditure (PPP int. $US)</td>
<td>1.001</td>
<td>0.054</td>
</tr>
<tr>
<td>Hospital bed density</td>
<td>0.578</td>
<td>0.087</td>
</tr>
<tr>
<td>Under five mortality rate</td>
<td>0.465</td>
<td>0.181</td>
</tr>
</tbody>
</table>
4 VALUATING COMUNICATION ISSUES AS A MEASURE TO INTRODUCE PATIENT REPORTING (STUDY IV)

Study IV made a comparison between ADR reports submitted by HCPs in two different years, 2004 and 2012. There are clear differences between the two years: 2004 was the first year that the pharmacovigilance unit collected ADR reports, while in 2012 the system already had greater maturity. A total of 403 reports were included in the study, 53 (13%) from 2004 and 350 (87%) from 2012. This corresponded to 130 and 766 reported ADRs, respectively, i.e. 14.5% of ADRs in 2004 and 85.5% in 2012. Community pharmacists had the highest relative ADR reporting activity in both 2004 and 2012, although hospital pharmacists had become almost as common source of reports in 2012 (relative reporting activity 16.9% vs. 13.4% in 2012, respectively). GPs contributed less to the system in 2012 than in 2004. The reports sent by nurses were more numerous in 2012.

For the two years in analysis, a total of 896 words describing ADRs were collected (please refer to study IV for further details). The agreement between the language used in spontaneous reports and the corresponding MedDRA codes varied by professional background. No statistically significant associations were found in 2004, while in 2012 there were significant influences on the agreement index from professionals’ setting, background and geographical location. It was possible to confirm that working within the community pharmacy and the hospital setting presented an agreement index significantly higher than other work settings and locations.

The key findings will be discussed in the following sections.
DISCUSSION OF THE KEY FINDINGS OF THIS STUDY

1 THE IMPORTANCE AND USEFULNESS OF PATIENT REPORTING TO THE PHARMACOVIGILANCE SYSTEM (STUDIES I AND II)

1.1 THE VALUE OF PATIENT REPORTING OF ADVERSE DRUG REACTIONS

The evidence gathered in Study I confirmed that patient reporting makes a positive contribution to the general knowledge about ADRs (Blenkisopp et al. 2007; de Langen et al. 2008; Aagaard et al. 2009; Inch et al. 2012; van Hunsel et al. 2012; Härmärk et al. 2015). This study summarized current evidence on patient reporting to pharmacovigilance systems systematically, pulling together evidence from different countries and settings. The majority of the evidence comes from countries in Europe with well-established patient reporting systems. Patients report mainly on ADRs and drugs affecting the central nervous system, general disorders and administration site conditions, and this has helped to strengthen ADR signal detection. They also play an important role in providing a perspective on the experience and impact of ADRs on daily life. However, there was a lack of evidence on any of the possible drawbacks of patient reporting, such as identification and accuracy of reported symptoms, the seriousness of the reactions and costs to the system. Granting that patients report clinical information at a similar level as HCPs, recent studies have provided evidence that up to date patients report mostly non-serious ADRs comprising of general disorders, nervous system disorders and gastrointestinal disorders (Banovac et al. 2017; Oosterhuis et al. 2017; Kheloufi et al. 2017). The study also identified that there is a general trend in the evidence towards the positive impact of patient reporting. Further research is needed to improve our understanding of the value and problems in patient reporting to pharmacovigilance authorities.

Present evidence is not representative of world picture regarding patient reporting. A recent study provided supporting evidence about the limited origin of studies (Al Dweik et al. 2017). Currently, at least 102 countries in the world have functioning spontaneous reporting system that accepts both patient and HCP report (Matos et al. 2016). Further research is needed from other countries. As an example, in low and middle and income countries ADR reporting is still residual, and the classes of products and age groups differ from the rest of the world (Ampadu et al. 2016). This limitations could be reduced by increasing patient reporting (Jha, Rathore et al. 2014). Recent research from Ghana showed that patients have a positive attitude towards reporting and emphasized the need to engage HCPs in helping patients to report (Sabblah, Darko et al. 2017).

Study I focused on patient reporting of ADRs through national competent authorities’ official channels. It was found that the intensive monitoring scheme
developed in The Netherlands can be used to obtain a deeper understanding of ADR experiences in patients (Härmark et al. 2011c; Härmark & van Grootheest 2012). This method could be replicated. Due to the Study I inclusion and exclusion criteria, other channels to report ADRs such as through patient or consumer associations were not evaluated. Further research should be focused on this.

Pharmacovigilance is made of the contribution of different stakeholders, including patients, HCPs, academia and national competent authorities (NCAs). Shedding some light on the attitudes towards the value of patient reporting was being explored with Study II. A minority of interviewees had a negative attitude towards patient reporting. These were NCAs from countries that implemented patient reporting after the EU legislative changes. This contrasts with the positive attitude of pharmacovigilance centres in Portugal, the Netherlands, UK’s NCA, and international organizations like the WHO and the Uppsala Monitoring Centre (UMC). The pharmaceutical industry is also supportive of patient reporting. The negative attitude seems to be directly associated with a more conservative approach to patient reporting, regardless of an already robust share of patient reports, such as in Finland (Margraff and Bertram 2014; Kaeding, Schmälter, and Klika 2017). This indicates that other European countries introducing patient reporting in 2012 might have the same attitude, thus keeping patient reporting as a regulatory mandate, but having a far more restrictive policy of promoting it.

The pharmaceutical industry showed a positive attitude towards patient reporting and to the legislative changes in general, which is surprising considering the additional regulatory burden that the legislation entailed. Patient reporting could be seen as a good opportunity for getting in touch with those using their products, the (increasingly) empowered final consumer and payer. One explanation for this may be that recent developments focusing on the role of the patient have brought the industry on board accepting the patient’s role in research and safety surveillance, as a well in the development of new medicines through initiatives as the European Patients’ Academy (EUPATI) (Parsons et al. 2016; Smith et al. 2016; Smith & Benattia 2016).

Patient reports are not meant to replace the reports coming from HCPs, but to provide an additional source of clinical and real-world information. However, HCP reports are often incomplete, and the quality of the language can be a barrier in the description of the ADR (Durrieu et al. 2016). Despite their important contribution in detecting new and serious ADRs, some other aspects might not get to be reported. Patient reports provide different input on ADRs and medicines when compared with HCPs (de Langen et al. 2008; McLernon et al. 2010; Rolfes et al. 2015, 2017). An example is the difference of SOCs reported by HCPs and patients present in EudraVigilance (Banovac, Candore et al. 2017). At present, few individual intra-country comparisons exist (Rolfes, van Hunsel et al. 2017). Further research in this area should be targeted. They have also allowed for the identification of new ADRs and led to the strengthening of safety signals. Although methodologies using patient reports in signal detection are still lacking, recent studies have reaffirmed the important contribution that patients have in

As ascertained by study I, an important aspect of patient reports is that they describe the ADRs with more detail and subjective factors than HCPs. Patients can provide first-hand information about medicine use and experiences, such as the way an ADR affects their daily lives (Rolfes et al. 2016). However, the studies did not provide data about the number of patient reports that need to be followed up, in order to be confirmed medically. Although all such reports are treated in the same way in the EU, there is scant information about how the rest of the world treats patient reports. With the number of countries accepting patient reporting worldwide, there is a need to access if the standards are the same (Matos, Härmark et al. 2016).

Both Study I and II identified low awareness to reporting ADRs as an issue to address. Despite the possibility of patient reporting increasing worldwide, awareness is still low (Al Dweik et al. 2017). The UK has had patient involvement in SR since 2005, but only 8.5% of patients are aware of the possibility of reporting (Avery et al. 2011). The length of time since the introduction of direct patient reporting seems to play a part in this – e.g. the countries that introduced patient reporting earlier, such as the Netherlands, Denmark and the UK, have a higher reporting rate (McLernon et al. 2010; Danish Medicines Agency 2016; Netherlands Pharmacovigilance Centre Lareb 2017). By contrast, countries such as Portugal, Malta and Hungary, which introduced this facility more recently, show low levels of patient reporting (Margraff & Bertram 2014). This could be perhaps explained using Rogers’ Theory of Diffusion of Innovations, with some countries being the innovators and/or early adopters, others the early majority and finally some the late majority, and laggards (Valente & Rogers 1995). Patients who report have different characteristics to those who do not; further research should focus on identifying the characteristics of patient who report, in particular the socio-psychological aspects that help explain desire to participate.

Existing pharmacovigilance systems have proven to be useful in identifying patient safety issues, although there is scope for optimizing and improving. SR has known limitations on data collection and reporting (Pal et al. 2013). The inclusion of an active form of vigilance seems to play an important role (Härmark et al. 2011; van Balveren-Slingerland et al. 2015). Web-based sources are becoming increasingly important, and this method can collect more information about certain drugs (de Jong et al. 2016). The fact that this form of stimulated reporting targets specific drugs or patient populations can play a role in providing more safety data in a shorter period of time (Härmark & van Grootheest 2012). However, only the Netherlands has experience of this type of reporting. This example could be extended to other countries. The majority of studies have shown that patients provide mostly confirmatory information on the safety profile of drugs (Härmark et al. 2011, 2013; Oosterhuis et al. 2014; van Balveren-Slingerland et al. 2015). Further research on this topic is needed.

**1.2 PATIENT REPORTING THROUGH KEY STAKEHOLDERS LENS’**
European pharmacovigilance has undergone significant changes in recent years (Arlett & Kurz 2011). These changes have had a big impact in the way that regulators and market authorization holders work.

Raising the awareness of patients to the possibility of reporting was mentioned by most interviewees as a goal to achieve, regardless of the general patients’ attitude. Educational campaigns to raise awareness should be continuously targeted. Raising awareness, both to HCP and patients, could harness more and better-quality information. In late 2016, a common European media campaign was launched to explain and promote patient reporting. This campaign has increased the reporting rate by 13% during the week it aired. It seems that both HCP and patients are willing to report if the opportunity is better known (SCOPE Work Package 4 2016). Maintaining this growth will require the dedication of resources, both financial and human.

The successful engagement of both HCPs and patients regarding reporting can help in detecting and preventing serious ADRs. A recent systematic review identified the factors that affect patient reporting. It was found that poor awareness, confusion about who should report the ADR, difficulties with the procedures, lack of feedback on reports, mailing costs and poor negative experiences were to blame (Al Dweik et al. 2017). Similarly, even with good knowledge of pharmacovigilance, many HCPs don’t get to report ADRs (Alsaleh et al. 2017). Evidence from various international study suggested that lethargy, diffidence, insecurity and overwork hinder ADR reporting from HCPs (Tegegn et al. 2017). Therefore, awareness raising campaigns should be attempted with a higher periodicity for both patients and HCPs. Social media tools should also be more explored, as they help raise the awareness. As part of the Strengthening Collaboration for Operating Pharmacovigilance in Europe (SCOPE) research package, it was discovered that 60% of NCA in the EU haven’t had any public campaign since 2003 (SCOPE Work Package 4 2016).

Most interviewees recognized the positive aspects of patient reporting and believe it to be the key to the future of pharmacovigilance. However, both interviewees who felt positively and negatively about patient reporting raised several challenges. These include the quality of patient reports, the use of patient-reported information, contribution to safety signals, the public’s knowledge about suspected ADRs, as well as the economic burden of processing these reports. Patient reporting is well established in some EU countries (Danish Medicines Agency 2016; Netherlands Pharmacovigilance Centre Lareb 2017). However, there’s a potential for further qualitative increases in the future. Other EU countries should aim to both quantitative and qualitative increases. However, and as discussed previously, there is the need to have more research in countries other than European ones, especially on the quantification of signal detection (van Hunsel et al. 2017; Watson et al. 2018).

The growing body of evidence that patient reporting adds an important contribution to pharmacovigilance should allow for less concern and be embraced as a positive step. Nevertheless, there should be further dissemination of these results to change public perceptions and to tackle the belief that patients
are often ill-informed. It is important to note that many interviewees, especially the industry ones, mentioned the increasing role of patients in the life-cycle regulation of medicinal products. This participation is becoming significant not only in the post-market phase, but as well earlier in the drug development process (Parsons et al. 2016). New approaches to medicines development have started to be implemented in Europe, with the aim of facilitating access to medicines that address patients’ unmet needs (Eichler et al. 2015). These approaches have shorter timelines, which increases the level of uncertainty (Baird et al. 2014). However, there is still resistance to admitting that patients can take responsibility and have the proper knowledge to report the effects of their own medical treatment. According to the predominant culture, research is performed on patients, not with patients (Sacristán et al. 2016). The results of this study highlight the need to disseminate more actively the value of patient reporting to relevant stakeholders, so that campaigns and engagement of patients is taken full-heartedly.

Underreporting by HCPs was mentioned by all interviewees, and some suggested how patient reporting could help counter it. However, there is uncertainty about how to proceed. Considering the current reporting rates, it is essential to keep stimulating both HCP and patients to report. The quality of the spontaneous report is very important for the proper evaluation of drug safety signals. Sanchez-Sanchez et al studied the completeness of spontaneous reports from the pharmaceutical industry and HCPs, and concluded that most were incomplete (Sánchez-Sánchez et al. 2012). HCPs suffer from a number of attitudes such as complacency, ignorance, or indifference towards reporting ADRs (Lopez-Gonzalez et al. 2009). Considering that patients can complement HCP reports, stimulating their reporting, both quantitatively and qualitatively, is important.

2 EXPLORING SOCIODEMOGRAPHIC FACTORS THAT PROMOTE REPORTING FROM PATIENTS (STUDY III)

Study III aimed to explore characteristics of healthcare systems that could explain and predict an increased patient report of ADRs, or at least could help to separate higher from lower reporting. The initial goal was to move from already identified barriers and facilitators of patients’ reporting, many times placed on individuals’ features, i.e. beyond HCPs and patients’ education or motivation (Arnott et al. 2013). The study wanted to explore associations between organizational and population aspects that should not be neglected if aiming to improve patient reporting and pharmacovigilance effectiveness, thus helping authorities to better allocate resources. In other words, not only thinking at the micro/individual level but also at the macro/societal level.

It was found a divide between developed countries and developing ones concerning patients’ reporting. Low reporting was confirmed for all developing countries, but it was interesting to find countries such as New Zealand, Japan and
Germany not following the high-level group. Nevertheless, these countries perform much better in terms of population health status than other high-level output SRs e.g. the USA. This suggests also that the present study might have limitations on countries data completeness, accuracy and/or detail. Anyway, the variables found to be related with an increased patient participation in pharmacovigilance were, by nature, quite ample in scope.

The initial correlations showed a high coherency within the database, with expectedly greater reporting for richer and well healthcare-serviced countries, particularly concerning medicines consumption and consequent exposure to drugs side-effects. A higher usage of therapies for non-communicable diseases was associated with less patient reporting, which possibly means a lower level of medication safety attention for patients under prolonged condition control. General indicators such as public health expenditure and hospital care were significantly predicting a higher patient reporting. These two variables are characteristic of developed countries, which allows speculating that better organized and probably overall efficient systems are already taking pharmacovigilance seriously from the medicines users’ end, beyond a professional or expert responsibility. These variables were related to the expenditure on health (Legido-Quigley et al. 2016).

Although this study included a large set of quantitative variables, qualitative ones also play a role. Factors such as the regulatory views on patient reporting, attitude of pharmacovigilance centres, citizen activism, or pharmacovigilance awareness among HCPs and patients can potentially help explain why countries with similar society and economic characteristics perform differently. Pharmacovigilance is at the heart of public health programmes, as it intends to prevent the harm caused by medicines, improve clinical practice, and promote the rational use of drug (World Health Organization 2002). Recently, the world economy suffered an acute recession, causing turmoil in labour, housing, and financial markets (Quaglio et al. 2013; Toffolutti & Suhrcke 2014). It also impacted health care in a negative way, especially in countries that had to take measures to cut aggressively budget deficits (Toffolutti & Suhrcke 2014). Recession, followed by austerity measures, are accompanied by a worsening access to health care (Quaglio et al. 2013). In a context of financial crisis or budget cuts, lesser funding of pharmacovigilance activities might lead to a decrease in the patient reporting rate, following the causal relationship found in this study. Although the identified variables that can predict patient ADR reporting are quite ample, future research should not forget the health budgetary matrix, while determining which of the components of health expenditure can make a bigger impact on the reporting levels.

By contrary, several other variables, more specific and theoretically associated with the outcome variable, that could be considered as natural predictors according to linear correlation results, did not prove so. For example, pharmaceutical sales, which can be considered as an indirect indicator of medicines circulating in the market, thus available to most patients and prone to reveal ADR profiles, was not relevant according to study results. Similarly, IT variables such as internet access facilitating communications, as well as the
maturity of the pharmacovigilance system, knowing to high level of external relations from long existing centres (e.g. The Netherlands), did not prove to be influential for patient reporting with other simultaneous factors. Physician or pharmacist density also did not prove to be significant to predict patient reporting. Research has shown that one of the motives that lead patients to directly report ADRs is the dismissive attitudes of HCPs (Lopez-Gonzalez et al. 2009; dos Santos Pernas et al. 2012). This could explain why a higher density of physicians or pharmacists doesn’t impact the propensity of patients to report. Healthcare policies need therefore to be oriented to raise awareness of HCPs to the patient reporting. Pharmacists should be especially targeted, as the scope of their practice is centred in medicines use and converging more into patient-focused clinical services (van Grootheest et al. 2004; Rutter et al. 2014; Liu et al. 2015).

3 THE NEED FOR DATA QUALITY (STUDY IV)

Pharmacovigilance relies on the information gathered in case reports and other pharmacoepidemiological data (Durrieu et al. 2016). The value of individual case ADR reports is directly proportional to the amount of clinically relevant information they include. A detailed description of ADRs and its context bring valuable support to causality assessment (Norén 2017).

To investigate the variation of language used by HCPs when describing ADRs, a retrospective analysis of spontaneous reports at a Portuguese regional pharmacovigilance centre was conducted. HCPs are a large and diverse group. Lexical accuracy and semantic variations exist between different HCP groups. When describing an ADR, these differences may interfere with the strength of a generated safety signal. Ideally, HCPs would use more clinical terminology with less resource to common jargon. Sometimes bizarre or complex ADRs descriptions do not fit into a simple single description. Due to the nature of the MedDRA dictionary, a clearer use of words by HCPs could help pharmacovigilance coders to choose the right term for coding an ADR, therefore increasing the strength of a safety signal.

The results of study IV showed that the linguistic congruity to describe ADRs decreased from 2004 to 2012, taking as an example an EU peripheral PV team, while it seemed to improve if the ADR reporter was located in a city near to that regional pharmacovigilance headquarters. Other factors might also explain this result, especially in 2012, such as a larger population of HPCs and more health-related infrastructures, i.e. district hospitals, health care centres and pharmacies. More production and input are expected to also decrease the agreement between MedDRA terms and verbatim accounts, due to probable lexical variety, thus less chances of linguistic accuracy.

It was found that public health care institutions, in particular health care centres, performed worse than community pharmacies. Community pharmacists showed a slight increase in the accuracy of language used from 2004 to 2012. This confirms Portuguese pharmacists’ concerns with medicines outcomes and safety
issues, which is not necessarily the practice in other EU countries (e.g. Denmark). Sometimes regarded as an “incomplete” or somehow limited profession, having to deal with non-patient and non-health care-oriented issues (e.g. management and stock activities) (Rutter et al. 2014; Alsaleh et al. 2017), pharmacists confirm their good position to gather information about ADRs (Yu et al. 2015). Results show that pharmacists lexical variety in describing ADRs was high. However, as pharmacists deal with less serious types of ADRs, which are supposedly easier to describe, a higher agreement index was expected.

Physicians working in health care centres or hospitals have a high probability to come in contact with ADRs. This is true especially for hospitals, as patients can be hospitalized due to an ADR. A good agreement between spontaneous written language used to describe ADRs and MedDRA codes coming from physicians was expected, as they are expected to be the HCPs who make the most use of clinical jargon. Physicians and nurses were the HCPs that showed a greater agreement index between years. This variation might be not only from the different ADRs that these HCPs encounter but may result from a more complex description of the reactions. Potential lack of awareness of how to complete a spontaneous report, and other factors such as lack of time or diffidence, might as well be to blame. Both HCP groups only slightly increased their general participation from 2004 to 2012, despite the growth in the number of working staff and a higher pharmacovigilance visibility. There are reasons to believe that the curriculum of physicians might not have sufficient emphasis in the detection and mitigation of ADRs as a health-related hazard. Education in pharmacovigilance is the cornerstone for good quality reporting. Active reporting both in quantity and quality is crucial and must become part of continuing medical education and clinical governance. Study IV also identified the need for more educational activities targeting both patients and HCPs.

In order to raise the quality of reported data by HCPs, more education is needed. Several studies have indicated that continuous educational activities can raise the qualitative and quantitative contributions from HCPs (Figueiras et al. 2006; Herdeiro et al. 2008; Ribeiro-Vaz et al. 2016). A recent study showed that pharmacovigilance undergraduate education is increasing worldwide (Hartman et al. 2017). More training during undergraduate studies could change attitudes and behaviour related to ADR reporting. Clinical and MedDRA terminology training should be targeted to increase not only the frequency, but also the quality of spontaneous reports. HCPs also need to be better trained in using the specific fields of the spontaneous reporting forms. A possible tool to be more explored is the WHO-International Society of Pharmacovigilance (ISoP) joint curriculum (Beckmann et al. 2014). One of the major limitations of spontaneous reports is the incomplete data, which restricts drawing conclusions on causality. A recent study from France showed that only around 13% of spontaneous reports by physicians were classified as well-documented (Durrieu et al. 2016). A Mexican study pointed to the lack of completeness of reports coming from HCPs and the pharmaceutical industry (Sánchez-Sánchez et al. 2012). Regional pharmacovigilance centres, such as the one that provide the data for study II, are a feature of many pharmacovigilance systems worldwide. They play an important
role in collecting and analysing individual reports of ADRs, follow-up of cases, and are in close contact with HCPs and patients regarding early safety alerts (World Health Organization 2002). These centres can have a proactive role in liaising with both HCPs and patients to further enhance completeness of ADRs reports (Kheloufi et al. 2017). Moreover, they can act as a source of training and awareness-raising (Durrieu et al. 2016; Kheloufi et al. 2017). Signal detection and causality assessment both benefit from case reports with a high completeness (Norén 2017).

Patients’ added value may result from their different points of view and experiences (Watson et al. 2018). The narratives provided by patients are a valuable source of further information. This was pointed by interviewees in study II. To take full advantage of narratives from both patient and HCPs, signal detection should consider engaging with natural language processing methods or develop new methods to explore this relatively untapped source of information (Bousquet et al. 2017; Segura-Bedmar & Martínez 2015). Regional pharmacovigilance centres should be at the front of such a task, engaging with both HCPs and patients. This collaboration is perhaps more valuable than investing in web-based screening of potential new ADRs (Ghosh & Lewis 2015). Pharmacovigilance should maintain a strong focus on patients’ actual experiences, concerns, and outcomes, and this approach can be expected to uncover hidden adverse event signals earlier and to help us understand adverse events in a patient-centred way (Matsuda et al. 2017).

4 FURTHER RESEARCH

Further research is needed in order to better understand the full potential of patient reporting. As stated in previous Chapters, Study I analysed only published studies concerning patient reports to pharmacovigilance authorities. Although there is extensive literature on patients reporting in hospital settings or to consumer organizations, the use of this information remains limited (Vilhelmsson 2015). This should be addressed in future research.

The development of new methods related to patient reporting also needs to be considered. As was shown in Study I, intensive monitoring methods provide the opportunity to follow drugs more closely than the current spontaneous reporting system (Oosterhuis et al. 2014). This method gives a clear insight of the use of these drugs in daily practice. A web-based intensive monitoring system could be implemented elsewhere, providing a valuable and supplementary system to the spontaneous reporting system (Härmark & van Grootheest 2012). However, this is only available in the Netherlands. Further research should be placed in developing and analysing methods like this in other parts of the world.

Most of the information on patient reporting came from Europe (de Lange et al. 2008; Aagaard et al. 2009; Avery et al. 2011; van Hunsel et al. 2012) Generalization should be done with caution, as there are cultural factors that have not been covered. In order to confirm the value of patient reporting, further research should be placed in other geographies (Al Dweik et al. 2017).
The involvement of patients, use of information, and dissemination of patient reporting are also far from optimal. Several challenges to patient reporting were identified such as the awareness of both patients and HCPs, the quality and use of patient-reported information on ADRs, their concrete contribution for safety signals, and the costs of processing patient reports. Identifying the causes of perceived challenges and best practices should allow to formulate recommendations for the robust and effective dissemination of patient reporting.

It was identified that in order to strengthen patient reporting, awareness needs to be raised for both HCPs and patients. Over the years, research has been made on targeting awareness in HCPs (Figueiras et al. 2006; Herdeiro et al. 2008). It remains to be seen if the same methods can be used with patients. For that, a more thorough evaluation of which methods can help in raising awareness for patients is needed. This should be targeted in future research.

Study III provided a novel approach to the patient reporting. Notwithstanding, health expenditure is an ample indicator that contains several detailed items. Further research is needed to evaluate which of the health economic and financial items can better explain patient reporting. Running a deeper investigation is advisable to confirm factors that were deemed non-significant but are closely related to pharmacovigilance activities. Qualitative variables were not assessed in this study. These can possibly impact the propensity to report. By further exploring this study results it should be possible providing policy makers with tools to better allocate resources to promote patients’ participation.

Further studies are also required to assess the impact of language variation and corresponding MedDRA codes, as safety signals generated might be weaker. These could help health authorities when evaluating the safety profile of drugs and the regulatory action. The research done with Study IV targeted HCPs-only, showcasing them as bench-markers. Future research should explore the semantic diversity and language variation of patient reports in order to identify ways to facilitate reporting (Bousquet et al. 2017). Initiatives to improve reporting such as online reporting tool need to be linked with continuing education and training.
CONCLUSIONS

Patient reporting adds new information and perspective about ADRs in a way otherwise unavailable. This new information can lead to the strengthening of safety signals and increase the knowledge about ADRs. There are differences between patient and HCP reports. This is seen as positive, as the information provided by patients complements the one coming from HCPs. The subjective information that patients bring to the system can be used to strengthen the current pharmacovigilance system with more evidence about the impact of ADRs on patients’ daily lives. However, identified gaps should be addressed in future research in order to understand better the full potential of patient reporting. The involvement of patients, use of information, and dissemination of patient reporting are far from optimal.

It is important to understand what the opinions and experiences of different actors regarding patient reporting are. Several challenges were identified. Among the most important, awareness of both patients and HCPs, the quality and use of patient-reported information on ADRs, their concrete contribution for safety signals and the costs of processing patient reports emerged from this research. Identifying the causes of perceived challenges and best practices should allow to formulate recommendations for the robust and effective dissemination of patient reporting.

Analysing the correlation between several sociodemographic and economic factors and the direct patient reporting rate in diverse countries showed that health investment-related factors help explain the propensity of patients to report suspected ADRs to the pharmacovigilance system. A healthcare system able to provide secondary care coverage, usually including maternity and childhood proper care, seems to have also developed strategies to improve population awareness of their contribution to medicines safe use. Notwithstanding, health expenditure is an ample indicator that contains several detailed items. By further exploring these results it should be possible to provide policy makers with tools to better allocate resources to promote patients’ participation.

The quality of language in spontaneous reports is a factor to consider in order to have strong drug safety signals. Improvements in the MedDRA dictionary should be devised, adjusting the term organization to facilitate the HCP and patient truthful and thorough participation. Further studies are required to assess the impact of language variation and corresponding MedDRA codes, as safety signals generated might be weaker. These could help health authorities when evaluating the safety profile of drugs and the regulatory action. Initiatives to improve reporting such as online reporting and increase HCP participation need to be linked with continuing education and training.
APPENDICES

Appendix I: Interview Guide (study II)

1. The new Pharmacovigilance Directive 84/2010 was enacted in 2012 in all EU countries. Can you tell me how has this new legislation influenced your organization? What have been the biggest changes?

2. What is your view on the evolution of pharmacovigilance in your organization and in your country in the past few years?

3. Can you describe how do you see the role that your organization plays in drug safety from a medicine users’ perspective?

4. How do you see the reporting of medication errors to the pharmacovigilance system?

5. The Directive introduced the possibility of direct patient reporting. How do you see this type of reporting? Do you think patient reports bring value in drug safety?

6. What aspects, positive or negative, would you highlight from patient reporting?

7. Do you think patient reports can help in the detection of adverse drug reactions?

8. How do you think the subjective information provided by patients can help in the regulation of the medicinal product?

9. During my research, I’ve identified that one of the most referred barriers to increase patient reporting is the awareness that the general public has about the pharmacovigilance system. Can you tell me what has been done to promote patient involvement in the drug safety surveillance? And what could be done in the future to further increase this awareness?

10. How do you see the use of social media in adverse drug reaction detection and reporting?

11. How do you see the evolution of pharmacovigilance system, particularly patient reporting? Is there anything you could recommend or suggest?

12. What do you think are the challenges pharmacovigilance has in the near future, both in terms of patient reporting and the pharmacovigilance system in general.
REFERENCES


Affairs, 34(2), 319–327.

Danish Medicines and Health Authority. (2013). Report: Adverse Drug Reactions Reported by Consumers in Denmark – compared with reports from healthcare professionals 2013. Available at: https://laegemiddelstyrelsen.dk/~media/B71CB7AF2879471ABE9DCF23BF853B18.ashx [Assessed 10 May 2018].


Hammad, T. A., Neyarapally, G. A., Pinheiro, S. P., Iyasu, S.,


Lane, S., Lynn, E., & Shakir, S. (2018). Investigation assessing the
publicly available evidence supporting postmarketing withdrawals, revocations and suspensions of marketing authorisations in the EU since 2012. *BMJ Open*, 8(1), e019759.


Safety, 16(3), 271–275.


Boxed Warnings and Safety Withdrawals. Drug Safety, 40(6), 497–503.


