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Especialização em Farmacoterapia Aplicada

TRABALHO DE PROJECTO ORIGINAL

ARE PATIENTS READY TO TAKE PART IN PHARMACOVIGILANCE SYSTEM? – A PORTUGUESE PRELIMINARY STUDY CONCERNING ADR REPORTING

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Coimbra, Junho de 2014

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Coimbra, Junho de 2014

"If we keep patients out of the picture,

we will never get the full story about medicines safety."

(Uppsala Report 65, April 2014)

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ABSTRACT

Background: New Pharmacovigilance legislation allows patients to report adverse drug reactions (ADRs) directly to competent authorities in all European Union (EU) member states. Patient reporting is available in Portugal since July 2012. In 2013, the National Pharmacovigilance System (SNF) had received 3461 spontaneous ADR reports, of which only 1.4% (n=50) were reported by patients. Underreporting remains a reality in Portugal, although patient reporting could be one of the measures to reduce the rate of underreporting by healthcare professionals (HCP).

Objectives: The aim of this study was to describe the attitudes and knowledge of the patients regarding spontaneous reporting and the reasons and opinions that can influence patients ADR underreporting.

Methods: A descriptive-correlational study was performed looking for patients' attitudes and knowledge regarding spontaneous reporting. A 6-months survey was conducted from June to November 2013 in general adult patients from a community pharmacy in Coimbra, Portugal, that used prescribed medicines or OTC-drugs. Attitudes and opinions were surveyed in a closed-answer questionnaire using a Likert scale. Incomplete questionnaires and answers from healthcare professionals were excluded from data analysis. The data were analyzed using descriptive statistics, χ^2 tests and Spearman's correlation coefficients.

Results: A total of 1084 questionnaires were collected with a response rate of 81,1% and 948 completed questionnaires were selected for analysis. Of the respondents, 44.1% never heard about SNF. Younger people and those with a higher education were significantly more likely to be aware of SNF. Only 1 patient had previously reported an ADR directly to SNF. Reporting ADRs indirectly through an HCP was preferred by 62.4%. The main reasons for patients reporting spontaneous ADR would be the severity of the reaction (81,1% agreed or strongly agreed) and worries about their own situation (73,4% agreed or strongly agreed). Only weak and moderate correlations were found between studied statements.

Conclusions: Patients are most likely to do a spontaneous report about a severe reaction or if they are worried about the symptoms. Tailored and proactive information on ADR reporting and educational interventions on patients could increase the number of reports from patients in Portugal.

KEYWORDS

Pharmacovigilance; Direct patient reporting; ADR reporting; Attitudes and Knowledge

RESUMO

Background: A nova legislação em Farmacovigilância permite aos pacientes notificarem reacções adversas a medicamentos (RAM) diretamente às autoridades competentes, em todos os estados-membro da União Europeia (EU). Em Portugal, a notificação por pacientes está disponível desde Julho de 2012. Em 2013, o Sistema Nacional de Farmacovigilância (SNF) recebeu 3461 notificações espontâneas de RAM, das quais apenas 1.4% (n=50) foram feitas diretamente por pacientes. Em Portugal, a sub-notificação continua a ser uma realidade, esperando-se que as notificações dos pacientes possam ser uma medida capaz de contribuir para a redução da sub-notificação dos profissionais de saúde.

Objectivo: O objectivo deste estudo foi descrever as atitudes e conhecimento dos pacientes no que diz respeito à notificação espontânea de RAM e as razões e opiniões que podem influenciar a sub-notificação de pacientes.

Métodos: Foi realizado um estudo descritivo-correlacional para descrever as atitudes e conhecimento dos pacientes no que diz respeito à notificação espontânea de RAM. O período de estudo foi de Junho a Novembro de 2013, sendo a amostra composta por consumidores de medicamentos de uma Farmácia Comunitária em Coimbra, Portugal. Foram questionados acerca das atitudes e opiniões com recurso a um questionário de resposta fechada utilizando a escala de Likert. Questionários incompletos ou de profissionais de saúde foram excluídos da análise de dados. Os dados foram analisados com recurso à estatística descritiva, teste χ^2 e coeficientes de correlação de Spearman.

Resultados: Foram recolhidos 1084 questionários, obtendo-se uma taxa de resposta de 81,1%. Foram selecionados 948 questionários para análise. 44.1% dos pacientes nunca ouviram falar do SNF. Os mais jovens e com maior nível educacional estão significativamente mais conscientes da existência do SNF. Apenas um paciente notificou anteriormente uma RAM diretamente ao SNF. 62,4% dos pacientes preferem notificar RAM's através de um profissional de saúde. As razões principais para fazer uma notificação espontânea foram a severidade da reacção (81,1%) e a preocupação pela sua situação (73,4%). Foram encontradas apenas correlações moderadas ou ligeiras entre as razões e opiniões estudadas.

Conclusão: Os pacientes são mais propensos a fazer uma notificação espontânea se a reacção for severa ou se estiverem preocupados com a sua situação. Formação e informação proactivas e personalizadas acerca da notificação de RAM pode aumentar o número de notificações por pacientes, em Portugal.

PALAVRAS-CHAVE

Farmacovigilância, Notificação por pacientes; Notificação de RAM; Conhecimentos e Atitudes

CONTENTS

ACRONYMOUS

ADR – Adverse Drug Reaction

EMA – European Medicines Agency

EU – European Union

GP – General Practitioner

HCP – Healthcare Professional

INFARMED IP – National Authority of Medicines and Health Products

NFC –Pharmacovigilance Unit of Centre region

OTC – Over-the-counter

PAPI – Paper and Pencil Questionnaire

PhT – Pharmacy Technicians

PRAC – Pharmacovigilance and Risk Assessment Committee

RAM – Reacção Adversa a Medicamento (the same as ADR)

RMPs – Risk Management Plans

SNF – National Pharmacovigilance System

SNS – National Health Service

SPSS – IBM® - *Statistical Package for the Social Sciences*

UFLVT – Pharmacovigilance Unit of Lisboa and Vale do Tejo

UFN – North Pharmacovigilance Unit

UFS – South Pharmacovigilance Unit

UK – United Kingdom

UMC – Uppsala Monitoring Centre

URF – Regional Pharmacovigilance Units

USA – United States of America

WHO – World Health Organization

INDEX OF FIGURES

INDEX OF TABLES

INTRODUCTION

This research, "Are patients ready to take part in Pharmacovigilance System? – a Portuguese preliminary study concerning ADR reporting", was submitted to the ESTESC – Coimbra Health School for fulfillment of the requirements for the Master degree in Pharmacy, held under the scientific supervision of Florence P.A.M. van Hunsel, PharmD PhD MEpi (Netherlands Pharmacovigilance Centre - Lareb) and co-orientation of João José Joaquim, MSc (Adjunct Professor of Pharmacy Department - Coimbra Health School).

AIM OF THE STUDY

The aim of the present study is to gain insight into the attitude and behavior of patients in Portugal with respect to the reporting of ADRs. Therefore, our main research questions are: "Which motives for reporting adverse drug reactions are present in a large group of patients in Portugal?" and "What could be the next steps to bring patients to active Pharmacovigilance?".

1. BACKGROUND

This chapter gives a review of the literature concerning Pharmacovigilance, its history, new legislation, and the Portuguese reality and overview on contribution of the patient reporting in Pharmacovigilance.

1.1. INTRODUCTION IN PHARMACOVIGILANCE

Pharmacovigilance can be defined as "the science and activities related to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problems".[1] The main objectives of pharmacovigilance are preventing harm from adverse reactions in humans arising either from the use of authorized medicinal products, within or outside the terms of marketing authorization, or from occupational exposure; and promoting the safe and effective use of medicinal products, through providing timely information about the safety of medicinal products to patients, healthcare professionals (HCPs) and the public.[1]

Lazarou[2] cited the definition of adverse drug reactions (ADRs), based on the World Health Organization (WHO),[3] as "any noxious, unintended, and undesired effect of a drug, which occurs at doses used in humans for prophylaxis, diagnosis, or therapy". This definition excludes therapeutic failures, intentional and accidental poisoning (i.e., overdose), and drug abuse. Also, this does not include adverse events due to errors in drug administration or noncompliance (taking more or less of a drug than the prescribed amount). However, according to the new definition proposed in the *guideline on new good pharmacovigilance practices*, which is a final result of the 2010 pharmacovigilance legislation[4] which will be discussed ahead, "adverse reactions may arise from use of the product within or outside the terms of the marketing authorization or from occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse and medication errors".[1, 5]

Today, its globally accepted that ADRs are a public health problem and have a significant clinical impact related to morbidity and mortality which results in an increased use of

health services in developed countries.[2, 6] ADRs are responsible for about 6,5% of all hospital admissions and many of them were judged preventable[6, 7] and about 2-3% of those patients admitted with an ADR died as a result.[6, 8] Furthermore, ADRs may occur in 6-20% of patients admitted to hospitals, increasing the hospitalization period, thus increasing the costs associated with health care.[9]

ADRs have a direct impact on National Health Services (SNS) costs and even an indirect impact on patients and family in economic, social and psychological way.[10] The average treatment costs of a single ADR were valued up to several thousand euros,[6] that could be even greater when indirect costs are analysed, like patient hospitalization duration – length-of-stay. ADRs can have a significantly impact on hospitals' budget and, consequently, can lead to important charges to healthcare systems.[9]

Because not all adverse drug reactions of a product are known once it's granted marketing authorization, pharmacovigilance is needed to learn more about possible harmful effects of a drug. According to WHO,[1] pharmacovigilance plays a vital role in ensuring that healthcare professionals, such as physicians and pharmacy professionals, together with the patient, have enough information to make an educated decision when it comes to choosing a drug for treatment.[11]

The information gathered during the pre-marketing phase of a medical drug is inevitably limited and incomplete with regard to possible adverse reactions,[12, 13] although its safety profile and efficacy were previously studied. Effectively, the identification of adverse reactions, during the experimental phase, is limited, since the exposed population has particular characteristics, since this is a selected population, contrasting with the population that is exposed to the drug, in a real context, after marketing. During clinical trials, individuals with concomitant diseases and medication, or in specific conditions (pregnant, lactating infants, polymedicated patients, elderly and children) are excluded or underrepresented. In addition, the small number of subjects and the time spent in clinical trials are usually insufficient to detect certain events with lower incidence or which occur over the long term, that are difficult to detect during the phases of clinical trials that precedes the marketing of the product.[14]

Relevant and unidentified ADR can occur after marketing authorization and pharmacovigilance in that phase is of a capital importance since the drug is used in a real-life context and in a large and heterogeneous population, with the majority of unknown ADRs effectively being detected this phase.

For an effective pharmacovigilance, the creation of a pharmacovigilance network between countries to allow exchange of information is necessary.[12] At the time of marketing authorization, the risk-benefit ratio to medicinal products is judged positive for the target population.[13] However, not all actual or potential risks have been identified, becoming essential to introduce risk management plans (RMPs) in order to identify, characterize, prevent or minimize risk relating to medicinal products, including the assessment of the effectiveness of those interventions.[11, 13] The concept of risk management should also consider the combination of information on multiple risks with the aim of ensuring that the benefits exceed the risks by the greatest possible margin for the individual patient.[13]

1.1.1. The start and further organization of pharmacovigilance systems

The most well-known example of an ADR recognized after marketing approval occurred in 1961: the *thalidomide tragedy* has originated the birth of approximately 10,000 children with *phocomelia*. This tragic event led to authorities and healthcare professionals being engaged in the development of different methodologies to detect and study the adverse effects of medicines and the creation of structures suitable for early detection.

In 1968, the first pilot project for the creation of an international system of pharmacovigilance through a "*Programme for International Adverse Event Monitoring*" was started, based on the experience and essential elements collected in the 10 countries who signed the program and who immediately created their National Pharmacovigilance Centres, networking with WHO.

When the program was evaluated in 1970, the World Health Assembly concluded that it should be permanent, being installed, in Uppsala, Sweden, in 1978 - initially under the

designation "*WHO Collaborating Centre for International Drug Monitoring*" and today called as "*Uppsala Monitoring Centre (UMC)*".

The main functions of the WHO Programme for International Drug Monitoring include the "identification and analysis of new adverse reaction signals from the case report information submitted to the National Centres, and sent from them to the WHO database" and "exchange information between WHO, UMC and National Pharmacovigilance Centres".

Since 1978, UMC has managed primary aspects of expanding worldwide pharmacovigilance network of more than 130 countries, nowadays.

1.1.2. Spontaneous reporting of ADRs

According to WHO, spontaneous ADR reporting is defined by "a regional or country-wide system for the reporting of suspected adverse drug reactions". Existing pharmacovigilance systems have proven to be useful in identifying patient safety issues, although there is scope for optimizing and improving their use.[10] Thus, this is the primary method in pharmacovigilance and it is useful to picking up signals of relatively rare, serious and unexpected adverse reactions.[12, 15] Spontaneous reporting is generally used for signal detection purposes and in publications about ADR.[10] This is particularly important for rare or serious reactions to established drugs, or reactions to newly marketed medicines where knowledge about their safety profile is based upon relatively limited exposure information obtained during premarketing clinical trials. A number of important signals of ADRs have been identified through spontaneous reporting.[16]

Voluntary ADR reporting is one of the most versatile pharmacovigilance systems, because, among other advantages, it covers the entire population as well as all drugs throughout their commercial life,[7] being also a method that provides the highest volume of information with relatively lower maintenance cost than other Pharmacovigilance methods.[15]

In fact, spontaneous reporting of ADRs is the most common method used in Pharmacovigilance, and remains one of the most effective methods to detect new,

unusual and serious drug reactions;[17] spontaneous reporting has been the primary post-marketing safety evidences source, that contribute to the early identification and evaluation of the drug safety issues, that could result in different regulatory actions such as product withdrawal, continued monitoring, product labelling changes or new medication guide-related communication, among others.[18] The monitoring of adverse drug reactions through pharmacovigilance is vital to patient safety.[17]

Despite of this, ADRs are estimated as one of the major causes of hospital admissions and death[6] – only around 5 to 6% of all adverse reactions are reported.[19] The success or failure of any spontaneous reporting system depends on the active participation of reporters.[1] Healthcare professionals have been the major providers of case reports of suspected ADRs;[20, 21] although, in recent years, in some countries, such as United Kingdom (UK), Denmark and The Netherlands, systems for direct reporting of suspected adverse reactions by patients have been initiated and the impact of direct patient reporting in these countries has been positive, since it facilitates a better understanding of consumer perspectives.[22, 23] Patient reporting is defined as "users of drugs (or their parents or carers) reporting suspected ADRs directly to a spontaneous reporting system".[24, 25] However, there has been some discussion on the true value of direct reporting by patients. The perceived advantages and possible drawbacks of patient reporting of ADRs are discussed in Chapter 1.3 on the Patients' role in active surveillance.

1.1.3. The introduction of patient reporting in guidelines and legislation

The importance of direct patient reporting has been highlighted by new European legislation on pharmacovigilance. The legislation guides member states to take all appropriate measures to encourage patients to report suspected ADRs to the national authorities. Member states should also facilitate patient reporting through the provision of alternative reporting formats in addition to web-based formats.[4] The aim of the legislation is to improve the participation of patients in the decision-making process and to resolve the lack of a clear legal basis for patient reporting across the European Union (EU).[26]

Allowing patients to report adverse drug reactions directly to the competent authorities is now seen by the European Commission as a way to improve pharmacovigilance and reduce underreporting. Patients' contribution still represents a relatively small percentage of total reports in most countries within the EU.[22, 27, 28] The number of countries who encourage patients to report ADRs has increased and a guideline has been developed for setting up patient reporting systems. Most of EU countries have very recently started with reporting systems for patients, mostly created by imposition of international guidelines, so the amount of reports received from patients is very low and has weak significance in earlier detection of ADR in many countries. However, feedback from countries in which systems have been implemented for a longer period is quite positive.[10] For the pilot countries worldwide we can highlight the United States of America (USA) and Canada, that have started consumer reporting schemes in the 60's and collects a huge number of reports every year. In 2009, USA and Canada had collected, respectively 57% and 32,3% for all reports, directly from patients.[10] More recent pilot studies were launched in Europe in The Netherlands (2003), Denmark (2003) and the UK (2005) and more recently in other countries.[10] In these countries, in 2009, about 15-30% of reports were collected directly from patients. However, the increase in quantity of the number of reports received should be reflected in an increased quality and faster signal detection. The quality of patient reports appears to be similar to that of healthcare professional reports.[29]

However, little formal evaluation has been undertaken of existing patient reporting. The World Health Organization focuses on planning and implementing adverse drug reaction systems for the general public and will probably make an important contribution to pharmacovigilance strategies.[30, 31] The new WHO guidance[30] provides comprehensive advices to implement a well-organized and effective consumer reporting system and it is particularly opportune for European Union countries, which are now required to accept consumer reports by new EU-wide legislation that came into force in July 2012.[4]

The new European legislation about Pharmacovigilance[4] is the biggest change in the human medicines regulation in the EU since 1995. The European Medicines Agency (EMA) is responsible for implementing the new legislation. The new Pharmacovigilance

legislation will allow patients to report ADRs directly in all EU member states. Suspicions of ADR may be reported online by HCPs and patients through a platform that is currently under development in several countries: the introduction of online reporting in Portugal is being progressively implemented.[24] It also entails a revision of the definition of "adverse drug reaction" bringing to "any harmful effects caused by medications".

1.2. PHARMACOVIGILANCE IN PORTUGAL

In contrast to what happened in several European countries, until the early 90s, pharmacovigilance was not implemented in Portugal.[32] The National Pharmacovigilance System (SNF) was created centrally in 1992[a], and has an essential role in the ongoing evaluation of the benefit/risk balance of medicines.[33] The national pharmacovigilance system is a key tool for monitoring and ensuring the safety of patients, with a view to the protection of public health. Since 1999, a reorganization occurred and the SNF has become a decentralized system:[33] regional centres have been created to collect suspected reports of ADRs from healthcare professionals and to encourage reporting, involving universities to promote their scientific and technical expertise and spread the system. Actually, the SNF is coordinated by the INFARMED, IP – (National Authority of Medicines and Health Products), and composed by four Regional Pharmacovigilance Units (URF) that covers the entire region of continental Portugal: North Pharmacovigilance Unit (UFN), the Pharmacovigilance Unit of Centre region (NFC), the Pharmacovigilance Unit of Lisboa and Vale do Tejo (UFLVT) and the South Pharmacovigilance Unit (UFS). Each Unit promotes training activities among reporters and evaluates the ADR reports occurring in their respective geographical areas. The SNF monitors the safety of medicines with marketing authorization in the domestic market, assessing any problems with ADR and implementing security measures whenever necessary.

On 30th August 2006, the Decree-Law No 176/2006 was approved,[34] which unifies the main laws of the medicinal product area and put together all legislation on Pharmacovigilance.[35] This document defines the Portuguese National Pharmacovigilance

[a] The creation of the SNF in 1992 was announced by the Decree -Law No. 72/91 of 08th February and Order No. 107/92 of June 27.

System as we know it today and all of his tasks, of which we can highlight the collection and review of spontaneous reports and detection of previously unknown adverse reactions as well as assessing the impact of already known reactions. All reports are evaluated and analysed in order to generate a signal or warning of the occurrence of a problem related to a drug effect.[34]

Encourage HCPs to report has been one of the major challenges of the SNF. Physicians were represented since the beginning of the SNF. Pharmacists were incorporated into pharmacovigilance in 1995, and reported in collaboration with physicians, who validated their reports until 1997.[7] From 1997, pharmacists were allowed to report directly to health authorities, independently of physicians.[7, 36] Nurses are participating in the SNF since 2000, accounting for the majority of adverse reactions to vaccines.

From 2009, it became possible for other classes of healthcare professionals to report, including pharmacy technicians (PhT) and nutritionists. With the creation of the new form for reporting ADRs for all healthcare professionals, they can submit their reports: until that time the Portuguese system only had forms for physicians, nurses and pharmacists and it was impossible for other professionals to report adverse reactions when they were dealing with them. The involvement of various groups of healthcare professionals has been progressive, which might represent a solution for increasing the rate of spontaneous reporting by health professionals. Although spontaneous reporting is a professional' duty, therefore, HCPs must report ADRs, there is underreporting in the Portuguese system, according to international guidelines.

Since July 2012, with the implementation of the new Directive,[4] it is also possible to patients to report directly to SNF. However, the country' ADR reporting figure of 295 per million population (2012) falls far short of the ideal rates of notification and even below from the WHO target (Fig. 1 and Fig. 2).

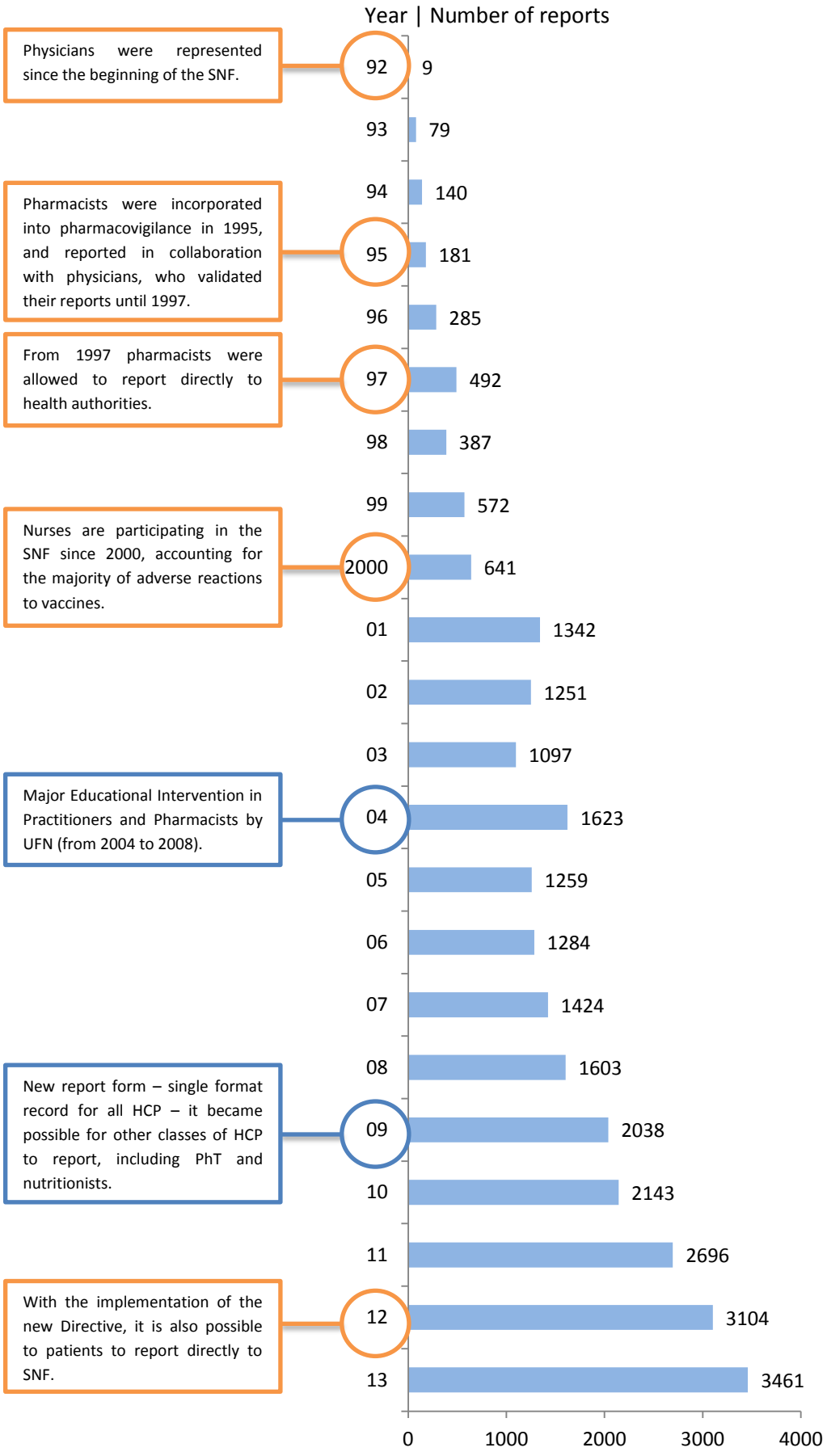

Figure 1 - Spontaneous Reports received by SNF and the actions taken to their growth.

Spontaneous ADR reporting in Portugal is performed by all stakeholders to SNF, by filling online form or on paper (sent by mail, fax or email) or through phone.[35] The spontaneous reporting by healthcare professionals remains an effective resource for ADR detection; although, underreporting remains a reality, with consequent limitation in the risk evaluation and detection and delay risk signal generation. It is estimated that only 6% of all adverse reactions are reported.[19]

In order to understand the reasons for underreporting in Portugal, it became necessary to identify the attitudes and knowledge of healthcare professionals associated with underreporting of ADR, based on reasons proposed by Inman.[37]

Knowledge and attitudes of healthcare professionals are more related to spontaneous ADR reporting than the personal and professional factors, reinforcing that knowledge and attitudes are potentially modifiable, so that educational interventions designed based on the detected gaps in knowledge and attitudes of health professionals can improve favorably the report rates and quality.[7, 36, 38-40]

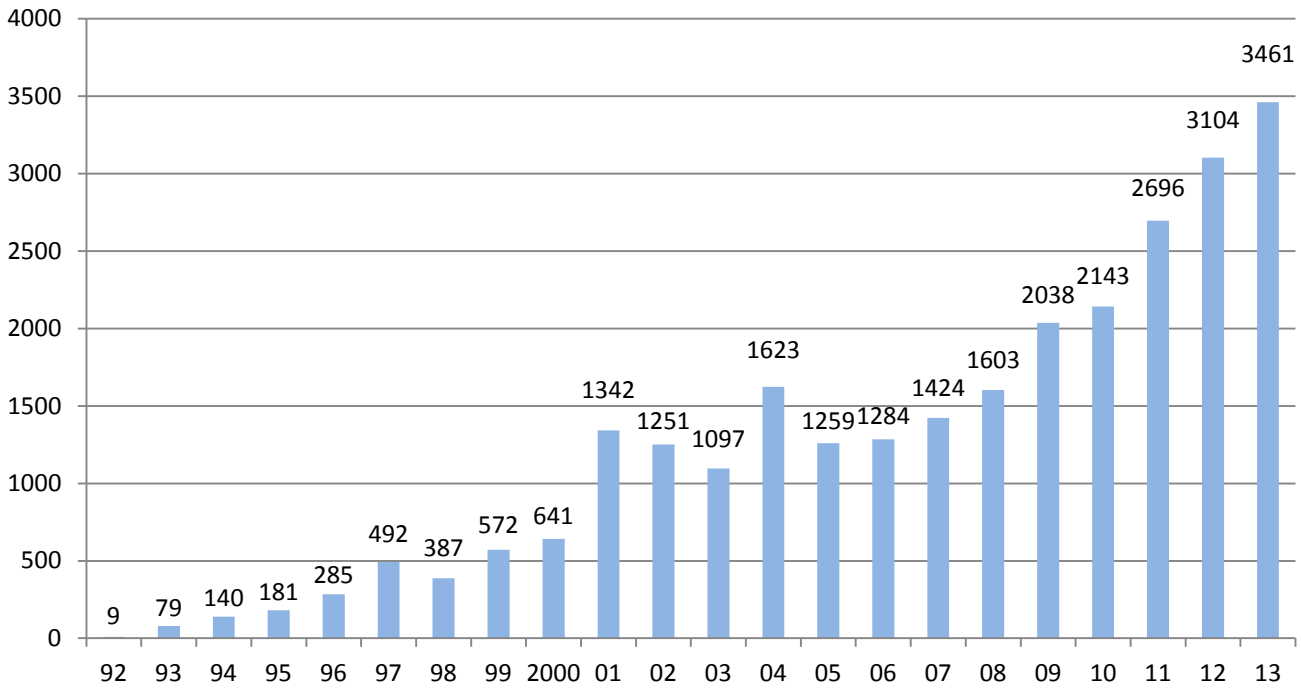

Figure 2 - ADR reports received in SNF from 1992 to 2013 (Adapted from: http://www.infarmed.pt)

In the future, a strengthening of the Pharmacovigilance System is needed, with further motivating healthcare professionals and patients to participate in the pharmacovigilance system and designing new strategies to promote ADR reporting, in order to minimize the risks with medicines and improve patient safety.[33] Regional Pharmacovigilance Units in Portugal should promote training and information in order to achieve the European report targets. The Harmonization of Pharmacovigilance, with the implementation and application of new European directives reveal themselves as tools to increase of patient safety. Also, the creation of European and global networks of pharmacovigilance, like European Medicines Agency Pharmacovigilance Risk Assessment Committee (PRAC) improves the easier and faster access to medicines information, assessing all aspects of the risk management of medicines for human use.[43]

Patient reporting is available in Portugal since July 2012 and after the implementation of EU directive until December 2013, the National Pharmacovigilance System had received 4987 spontaneous ADR reports, of which only 1,28% (n=64) were reported by patients.

Table 1 - Number of patient reporting vs Total Amount of Reports, since new legislation application[41, 42]

	Reports by Patients (relative %)	Total of Reports Received
3rd Trim. 2012	0,8% (n=6)	738
4th Trim. 2012	1,0% (n=8)	788
1st Trim. 2013	1,3% (n=12)	920
2nd Trim. 2013	1,0% (n=8)	789
3rd Trim.2013	1,3% (n=9)	720
4th Trim. 2013	2,0% (n=21)	1032
Total	**1,3% (n=64)**	**4987**

1.3. THE PATIENTS' ROLE IN ACTIVE SURVEILLANCE

Under-reporting of ADRs by healthcare professionals is a well-recognized problem worldwide. The patients' role in actively reporting ADRs is a major factor to improve the global pharmacovigilance system: the pharmacovigilance impact of direct patient reporting could be one of the measures to reduce the rate of under-reporting by HCPs.[19] The importance of direct patient reporting has been highlighted by new European

legislation on pharmacovigilance, in order to strength spontaneous reporting systems in Europe.[24]

The introduction of patient reporting in pharmacovigilance indicates a change in attitude in which patient reporting is valued due to their potential to contribute with useful information on drug safety, which can be used or maximized.[10, 31]

However, there has also been some discussion about the role of patients in pharmacovigilance, mainly about the acceptance of ADRs reported by patients to spontaneous reporting systems: patient reporting could be particularly important to detect serious, unrecognized or unexpected ADR related to a new drug. In the scientific discussion about patient reporting, it could be considered both an opportunity and a threat for spontaneous reporting systems.[29, 44, 45]

The lack of experience with patient reporting has been a contributing factor to this discussion. Over the years, and despite of the attempt to improve the quality and quantity of reports received, Pharmacovigilance has witnessed what some have called a patronising view on the reporting by patients.[46] This view was based on the idea that the suspected unwanted effects were sifted first by prescribers, who could decide whether the alleged problems were worth reporting, in order to reduce the amount of unwanted and useless data that was collected.[46] The under-reporting by healthcare professionals, the potential distortion of patient' descriptions and the reluctance of patients to report to an healthcare professional were key factors to incorporate patients in spontaneous reporting systems. There is some evidence that patients report an ADR when they consider their health professional has not paid attention to their concerns.[29]

Despite of patient spontaneous reporting increase the total amount of reports collected, it is essential to understand if the collected data are useful and that signals of important ADRs can be detected earlier than in the absence of patient reports.[45]

1.3.1. Possible drawbacks of patient reporting

Sceptics of patient reporting have argued that the data collected by patient reporting is usually unsystematic and incomplete.[45] Also, lack of awareness of the possibility to report and patients' limited knowledge about their medications were viewed as main barriers to an effective patient reporting. In the debate surrounding the value of patient reporting, some major drawbacks of patient reporting are also mentioned– first the extra resources involved and secondly the potential for losing support from health professionals who may feel that their report is not needed.[29, 44, 45] Patients' reports may contain incorrect clinical attributions of symptoms to specific medicines and the quality of reports might be lower than those made by healthcare professionals, and might have an higher proportion of non-serious or already known reactions.[29] Most Pharmacovigilance Centers do not seek medical confirmation for each patient report, and in most of the cases, HCPs are only contacted in very serious cases or when the organizations are looking into a potential new signal.[10] Major drawbacks could also include the possible duplication of the same ADR reports, and an increased number of reports, creating additional "noise" that could distract from signal detection, and result in system overload and additional administrative costs.[29]

1.3.2. Possible benefits of patient reporting

The contribution of direct patient reporting to pharmacovigilance has been explored in a number of studies.[27, 28] Since patient reporting has become more common, an increasing number of studies have shown that patient reporting has more potential benefits than drawbacks,[29, 44] indicating that new or different types of ADRs can be identified and described by patients themselves,[10] and contributing to a better knowledge of their impact on daily life.[27, 28, 47, 48]

The information of patients is richer in their descriptions of behaviors and feelings than that from the health professional and often better explains the nature, meaning and consequences of ADRs. Patients reported that they usually initiated the discussion of the possible relationship between the drug and symptoms. Initial results obtained with the

direct reporting by patients demonstrate their ability to report adverse reactions for themselves or their immediate family, and show some differences with health professionals in the assessment of these adverse reactions and also the type of reactions.[26]

Patient reporting experience from different countries seems to be favourable, and patients are well positioned to provide valuable post-marketing information on medicines and to report possible ADRs. Patients reporting has already led to important contributions in valuable information on drug safety.[31] Patients may contribute to the detection of known and unknown ADRs, symptoms or signs earlier than HCPs,[49, 50] and they may identify some different ADRs from those reported by HCPs or those which not feature in existing product information, contributing to a better knowledge of the nature and incidence of ADRs.

Despite of additional noise that could be caused by the increasing of false ADR reports from patients, the experience with patient reporting in other countries, such as the UK, showed that more signals were detected when reports of suspected adverse reactions from both consumers and health professionals were collected.[31]

Patients' descriptions of suspected adverse reactions were more detailed than those of health professionals and were more likely to explain the effect of the reaction on the patients' life.[28] *Avery et al.*[28] have shown the differences between patients and HCPs concerning to the type of drugs and events they report, and how signals of some drug-related reactions might not emerge unless evidence from patients is integrated with that from professionals.

Additionally, patients often supply more detail on how unwanted reactions actually affect their lives.[28, 46] The impact of ADRs on patients' lives is not well understood. Apart from physiological effect of ADRs, patient reporting presents variable experiences of emotional impact: disbelief, anger, fear, frustration and isolation as common among patients that suffered an ADR.[51]

The differences between reports by patients and by HCP indicate different points of view that can enrich spontaneous reporting. Adding patients to the range of potential

reporters of ADRs may increase spontaneous reporting and contribute to faster signal detection[26] and promote the perception of the impact that these ADR can have in people's lives, that leads to better information collection on the adverse effects of drugs and also to give useful details about other problems with treatments, such as inadequate prescriptions or incorrect use of drugs, which would be very difficult to obtain otherwise.[26]

The introduction and active participation of patients in the reporting schemes can make the public aware of possible ADRs and adds value to pharmacovigilance.[44] The access to leaflet information on adverse reactions[49] and HCP' advices helps them to make informed choices about whether or not to use medicines and to recognize ADRs when are experiencing them.[44] The potential benefits of patient report include the promotion of consumer rights and equity, increasing the knowledge of consumers concerning medicines utilization and safety, and the opportunity to have unique perspectives and experiences; healthcare and patients organizations would also benefit from consumer involvement.[28, 44] The involvement of patients directly in Pharmacovigilance was regarded important to provide the patient perspective to manufacturers and regulators, but also because of dismissive attitudes and under-reporting by health professionals.[44]

Patient self-reporting could refer subjective experiences, more sensitive to underlying changes in patients' life,[49] that could be even more complete in behavioural aspects and subjective elements,[49] and show a better understanding of the effect of the ADR on the patient life, instead of healthcare professionals' reports that usually consists of a description of symptoms and is more focused on clinical information.[44] Some studies shown that clinicians systematically downgrade the severity of patients' symptoms, that patients' self-reports frequently capture side effects that clinicians miss, and that clinicians' failure to note these symptoms results in the occurrence of preventable adverse events.[49, 52]

A recent study from The Netherlands has also explored patients' motives and opinions about the reporting of suspected ADRs through qualitative interviews and a questionnaire sent to patient reporters.[47, 53] This study has characterized patient motivation to report an ADR, mainly in two major groups: altruistic and personal reasons. In altruistic motives,

the interests or welfare of others or the public interest was a reason for reporting. Altruistic motives concerned preventing harm to other patients, making the ADR publicly known, increasing medical knowledge, and wanting to improve the patient information leaflet. Personal motives for reporting an ADR included wanting more information about the ADR, indicating that the ADR was too severe not to report, being angry, or wanting confirmation about the ADR, or when they consider that an HCP has not paid attention to their concerns.[47, 53] Patients' reasons to report ADRs include the severity of reaction and their impact on daily life.[48] The opportunity to share their experience in order to prevent harm to other people and contribute to research and knowledge[47] and the curiosity to find out if other people had experienced the same effect or symptom are also major reasons to report. Greater understanding of the reasons for reporting could be beneficial in marketing strategies aiming to increase the number and quality of reports.

Comparisons of patients and healthcare professionals' reports found that patients can provide a valuable contribution for signal detection and in some studies it has been shown that patients and healthcare professionals' reports contribute in equal proportion to generate signals, and the combination of both, generated more potential signals than healthcare professionals' reports alone. A review conducted in 2011 concluded that adverse event reports submitted by consumers can help significantly in early detection of safety signals.[28, 29] Although, healthcare professionals and patients have different views regarding ADR reporting, so, in order to assess the true nature of the ADR, it is important to receive reports from both groups.[48] Patients reported a higher percentage of known and non-serious reactions than HCP. Drugs widely used in the community setting, and over-the-counter (OTC) products, were the drugs most frequently reported by patients. In contrast, few reports involving reactions to antineoplastic agents or contrast media — drugs mostly used in a hospital setting — were sent by patients.[26]

Contrary to earlier concerns, the quality of reports is generally good. Patient reporting of suspected ADRs has the potential to add value to pharmacovigilance by: reporting different types of drugs and reactions than those reported by HCPs; generating new potential signals; and describing suspected ADRs in enough detail to provide useful information on likely causality and impact on patients' lives. These findings suggest that

further promotion of patient reporting schemes are justified, along with improvements to existing reporting systems.[28] If patient reporting is recognized as beneficial for pharmacovigilance and further optimized, methodology and best practice must be internationally shared and promoted.

The awareness that patients can report ADRs is still thought to be low in most countries. However, patients' reporting is not actively promoted in all countries, mainly because the organizations are lacking resources to organize large publicity campaigns and/or to handle a large number of reports in addition to healthcare professional' reports. Also, in some countries, experiences with media attention about safety issues had increased reporting in a positive way, increasing awareness of the reporting scheme to the public.[10, 54] Greater publicity and promotion of the reporting scheme by healthcare professionals, plus wider availability and accessibility of the reporting forms were required.[10, 55]

A better understanding of patient reasons and opinions regarding spontaneous reporting will improve the robustness and ability of pharmacovigilance system relating to the reduction of underreporting, covering blind spots of pharmacovigilance systems like herbal drugs or OTC medication and improve faster signal detection.

High quality of information to patients is crucial, as good information on medicines and adverse drug reactions can empower patients to participate more actively in healthcare-related decisions, together with health professionals.[22, 23, 29]

1.4. JUSTIFICATION OF STUDY AND OBJECTIVE

Although some patients are aware they can report ADRs directly, more insight in patients' attitudes and knowledge regarding ADR reporting should be gained in order to improve the quality and quantity of patient reporting, leading to a better and faster knowledge about drug safety.

The objective of this survey is to describe the attitudes and knowledge of the patients regarding spontaneous reporting and the factors that can influence patients ADR underreporting in Portugal, in order to gain insight in why patients do not report more and how to possibly tackle this problem in Portugal.

2. METHODS

A descriptive-correlational study was conducted looking for patient attitudes and knowledge regarding spontaneous reporting. Patients were asked about the reasons to report and opinions about reporting ADRs. The current study provides an adequate exploration about what motivates patients to report an ADR and the reasons and opinions about reporting.

This chapter will describe the methodology used, which includes the search strategies for a literature review and data collection and the questionnaire design. This is followed by the definition of the study population, administration of the questionnaire by personal face-to-face interviews, statistical methodology and data analysis description.

2.1. THE LITERATURE RESEARCH

For the development of the scientific background that sustains this study, a literature search was conducted using online databases – *PubMed* and *Google Scholar* – of published articles, using queries with specific keywords and MeSH terms combined with the Boolean operators; articles were selected based on a primary analysis of title and abstract. Keywords used included “patient reporting”, “pharmacovigilance”, “ADRs”, and “reporting systems”, including the articles in which “attitudes”, “knowledge”, “motives”, “opinions”, “reasons”, “benefits” and “drawbacks” concerning patient reporting were studied. Additional publications were found manually by identification on reference list of the extracted articles and in citation tracking. Thirty-four studies were selected by the interpretation of their titles and abstracts and the other 25 were added due to their scientific relevance.

2.2. QUESTIONNAIRE DESIGN

Based on information on patient reporting in the literature a survey was created in order to describe the attitudes and knowledge of the patients regarding spontaneous reporting and the factors that can influence patients ADR underreporting in Portugal.

The questionnaire was adapted from previous studies[44, 47, 55, 56] and translated to Portuguese by the author. The Portuguese questionnaire was field-tested by several volunteers, not eligible for the sample, in order to improve the translation and the understanding of the questionnaire. The final questionnaire includes two major sections: Section I asks about respondents' characteristics (gender, age, education and working status) and the Section II relates to reporting attitudes and knowledge of the respondents about reporting. Some questions also asked about the possible suffered ADRs in the past and the attitudes regarding ADR-report knowledge. The whole questionnaire can be found in Appendix 1. Questions relating to reasons and opinions about reporting are shown in Table 2.

Table 2 - Reasons and Opinions about reporting. Adapted from *van Hunsel* et al. (2010)[47]

Reasons
- R1- I wanted extra information
- R2- The adverse drug reaction was severe
- R3- It was difficult to discuss the adverse drug reaction with my medical practitioner or pharmacist
- R4- The possibility for reporting an adverse drug reaction just exists
- R5- I wanted to be heard
- R6- Someone else pointed the possibility for reporting an adverse drug reaction
- R7- I was angry about the situation
- R8- I wanted action to be taken
- R9 -I wanted to share my experiences
- R10- The adverse drug reaction was not mentioned in the patient information leaflet
- R11 -I was worried about my own situation
Opinions
- O1- Reporting an adverse drug reaction can prevent harm to other people
- O2- I felt responsible for reporting an adverse drug reaction
- O3- Reporting an adverse drug reaction that is already mentioned in the patient information leaflet is useless
- O4- I only report an adverse drug reaction if it is serious
- O5- Reporting an adverse drug reaction contributes to research and knowledge
- O6- I report an adverse drug reaction if it is not mentioned in the patient information leaflet
- O7- I benefit from reporting an adverse drug reaction
- O8- Reporting an adverse drug reaction contributes to improvement of drugs
- O9- I report an adverse drug reaction if it is unexpected
- O10- In the future I will report a possible adverse drug reaction once again

The utilization of fixed statements to assess opinions and reasons about reporting, allows for the comparison between results and a greater reliability on response, once the questionnaire has been validated and previously applied.

The reasons and opinions were rated at a five-point Likert scale (strongly agree to strongly disagree), where the middle position was labeled "neutral" to reflect a neutral position, and not an inability to answer the question. The main results were presented below in the Chapter 3.

2.3. The Data Collection

Data were collected during 6 months (from June to November 2013). A large group of medicines' consumers of a community pharmacy were selected as possible respondents and questionnaires were administered by personal interview. A convenience sample was used in order to collect data from medicines users.

2.4. Study Population

The target population included the medicine consumers of a community pharmacy in Coimbra, Portugal. To give an impression of the size of pharmacy, there were 80743 dispensations during the 6 months study period. The main inclusion criteria included people who bought medicines or OTC medicines and that accepted to participate in the study. Another inclusion criteria was age: consumers under 18 years were not included. A record was made to avoid duplicate inclusions. The individual questionnaire was anonymous and the data were intended only for scientific purposes of this study and were stored in agreement with privacy regulations.

2.5. Data analysis

The anonymized data were entered and subsequently analyzed using IBM® - *Statistical Package for the Social Sciences* (SPSS) software version 20.0 for Windows.

Descriptive statistics provided an overview of the patient characteristics, the reasons for reporting ADRs and the opinions of patients on reporting ADRs.

A Pearson's Chi-square (χ^2) test was performed to detect significant differences in motives and opinions between patients of different age groups and levels of education and in differences in answers between men and women. Significance was based on a two-sided χ^2-test and significance was set at $p<0.05$.

The Pearson's Chi-square test (χ^2) assumes a discrete distribution rather than a normal distribution, and Likert scale questions have a discrete range of answers, the results will be statistically valid and can be used as scientific proof. The expected counts were automatically printed in SPSS to check the assumption that the expected frequencies should be greater than 5. If the expected counts are less than 5, the results from the Chi-square test are not statistically valid and Fisher's exact test could be used.

Since age categories and educational level can be seen as ordered categorical variables, we also calculated the χ^2 test for trend (depicted as the linear-by-linear association in the SPSS output). Significance was set at $p<0.05$ in the results we depict this by a Tvalue.

Finally, correlations were carried out and interpreted to measure possible relationships between two or more statements. When data have been measured at only the ordinal level (like a Likert-scale) they are said to be non-parametric and Pearson's correlation is not appropriate. Therefore, Spearman's correlation coefficient was used in this analysis[57] and Bonferroni-adjusted significance level was calculated. A correlation coefficient of 0 indicates no linear relationship, a coefficient of +1 indicates that the two variables are perfectly positively correlated, and a coefficient of -1 indicates a perfect negative relationship.[57] We considered a strong correlation if the correlation coefficient is greater than 0.7, a moderate correlation with a coefficient between 0.4 and 0.7, and a weak correlation if the coefficient is less than 0.4.

3. RESULTS

General results are given by use of descriptive statistics. Answers to general questions and answers on the statements of reasons and opinions to report are shown in this chapter.

3.1. RESPONSE RATE

A total number of 1337 individuals were approached for a face-to-face interview. There were 1084 respondents, leading to a response rate of 81,1%. Of the responses, 2 questionnaires were not completed and were not taken into account. Among the 1082 questionnaires totally completed responses, there were 134 responses (12,38%) by HCPs, that were also excluded for data analysis due to the bias created by these answers. The responses to the questionnaire are shown in Fig. 3 and the characteristics of the respondents are given in Table 3.

The agreements to the statements are given in Table 8 and Table 9. The first gives the distribution of responses on the statements about reasons for reporting ADRs; the second shows the opinions about reporting ADRs.

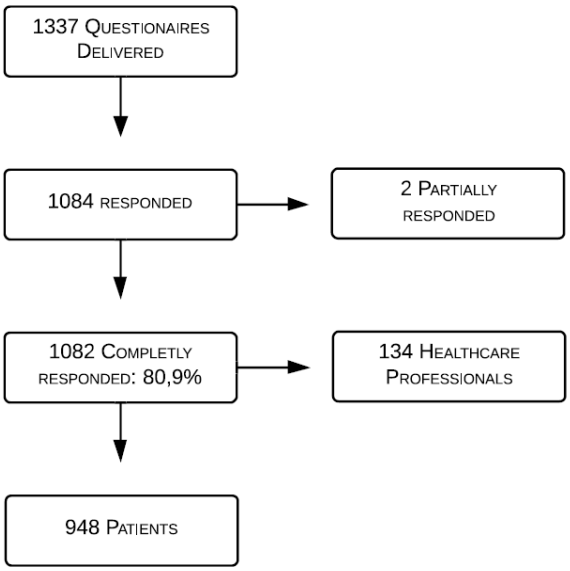

Figure 3- Flowchart of respondents to the questionnaire

Table 3 - Respondent Characteristics

Variable	Percentage (Frequency)
Gender	
Male	40,8% (387)
Female	59,2% (561)
Age	
18-24 Years	8,5% (81)
25-34 Years	18,4% (174)
35-44 Years	11,6% (110)
45-54 Years	23,3% (221)
55-64 Years	27,7% (263)
65 + Years	10,4% (99)
Educational Level	
None	1,1% (17)
Basic Education (1st – 4th)	10,0% (95)
Elementary Education (5th -9th)	33,5% (317)
Secondary Education (10th – 12th)	20,1% (191)
Universitary Formation	34,6% (328)

3.2. GENERAL RESULTS

Table 4 - Knowledge about the SNF and reporting in general

Do you know the National Pharmacovigilance System?	Do you know that is possible to reporting an ADR, either to SNF directly or through an HCP?		
	Yes	**No**	**Total**
Yes	506 (53,4%)	24 (2,5%)	**530 (55,9%)**
No	316 (33,3%)	102 (10,8%)	**418 (44,1%)**
Total	**822 (86,7%)**	**126 (13,3%)**	**948 (100%)**

Regarding attitudes and knowledge, 44,1% of patients never heard about SNF and 13,3% never heard about the possibility of reporting/sharing experiences of an ADR with an HCP or directly to the SNF. 53,4% knew about the SNF and the possibility to report an ADR. Younger people and those with a higher education were significantly more likely to be aware of SNF or the possibility of reporting/sharing an ADR:

- Younger people were significantly more likely to be aware of SNF (χ^2 p= .002 Tvalue: .004). There is also a difference in people from different age categories that know about the possibility of report (χ^2 p = .015), however there was no trend when looking at the categories (Tvalue: .099). The classes 35-44 years and 45-54 years know more about the possibility of report.
- People with higher educational level were significantly more likely to be aware of SNF (χ^2 p = <.001 Tvalue: <.001) and to know about the possibility of report (χ^2 p = <.001; Tvalue: <.001).

Answers to other general questions regarding ADR reporting knowledge, attitudes and perception are shown in table 5:

Table 5 - Participant responses on survey assessing knowledge of consumer ADR reporting systems

Survey question	% (respondents)*
How did you learn about the possibility of reporting possible ADRs from medicines? †	**(n=822)**
From a GP (General Practitioner)	61,2% (n=503)
From a Pharmacy	41,7% (n=343)
INFARMED Website	14,8% (n=122)
From a Hospital	10,7% (n=88)
Internet Research	6,1% (n=50)
Family member or friend	2,2% (n=18)
Magazine or Newspaper	1,5% (n=12)
School/Workshop	0,4% (n=3)

What's for you the best way to do a report?	(n=822)
Indirectly – through an HCP	62,4% (n=513)
Directly - Online / By Computer	31,6% (n=260)
Directly - by telephone	4,4% (n=36)
Directly - by post	1,6% (n=13)
When you have/if will have a suspected ADR what do you do? †	**(n=948)**
Talk to your GP/Doctor	35,9% (n=340)
Talk to your Pharmacy	33,7% (n=319)
Make a spontaneous report	32,2% (n=305)
Stop the medication	17,1%(n=162)
Don't do nothing	5,3% (n=50)
Have you ever had side effects from any medicine?	**(n=948)**
Yes	57,6% (n=546)
No	42,4% (n=402)

*Denominators vary due to missing responses and conditional questions. Cells do not always total 100% due to rounding. † Multiple answers allowed.

Of the respondents, 57,6% had the perception that they had already suffered an ADR; although, only one patient had previously reported an ADR directly to SNF. Another two had reported through an HCP.

All patients that already experienced an ADR but that didn´t report it, were questioned about reasons for non-reporting, see the following table:

Table 6 - Reasons for not reporting the experienced side effect

Reasons for not reporting the experienced side effect	(n=543)
Side effect not serious enough	26,7%(n=145),
Expected/knew side effect	19,5%(n=106)
Didn´t realize side effect due to medicine	17,1% (n=93)
Is unnecessary	12,2% (n=66)
Stopped using medicine	10,9% (n=59)
Other (including embarrassed, abroad, didn´t read instructions)	7,0% (n=38)
Don't know how to report	6,6% (n=36)

On the other hand, patient that never perceived an ADR, received a question about the attitudes for the future: only 49,8% of the respondents that never had side effects from any medicine stated that in the future they would report if they had any side effect, see table 7.

Table 7 - Motivation to reporting in the future, if an ADR occurs

In the future, if you have any side effects will you report?	(n=402)
Yes	49,8% (n=200)
No	24,4% (n=98)
Don't know/ Not Sure	25,9% (n=104)

In order to understand the reasons and opinions about spontaneous reporting, all patients were asked about these. The following tables show the compliance with the statements:

Table 8 - Motives for reporting adverse drug reactions (percentage (frequency))

Reasons	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
I wanted extra information	23,63% (224)	**28,38% (269)**	27,85% (264)	15,30% (145)	4,85% (46)
The adverse drug reaction was severe	**55,06% (522)**	26,05% (247)	12,03% (114)	5,38% (51)	1,48% (14)
It was difficult to discuss the adverse drug reaction with my medical practitioner or pharmacist	**37,45% (355)**	25,42% (241)	22,05% (209)	11,50% (109)	3,59% (34)
The possibility for reporting an adverse drug reaction just exists	24,79% (235)	**32,07% (304)**	29,85% (283)	8,44% (80)	4,85% (46)
I wanted to be heard	**36,60% (347)**	27,00% (256)	22,36% (212)	8,97% (85)	5,06% (48)
Someone else pointed the possibility for reporting an adverse drug reaction	22,57% (214)	16,98% (161)	**29,22% (277)**	22,89% (217)	8,33% (79)
I was angry about the situation	**31,43% (298)**	30,06% (285)	21,52% (204)	12,03% (114)	4,96% (47)
I wanted action to be taken	28,48% (270)	**29,64% (281)**	21,52% (204)	13,29% (126)	7,07% (67)
I wanted to share my experiences	19,51% (185)	**35,13% (333)**	22,36% (212)	18,67% (177)	4,32% (41)
The adverse drug reaction was not mentioned in the patient information leaflet	16,46% (156)	17,09% (162)	28,90% (274)	**29,01% (275)**	8,54% (81)
I was worried about my own situation	**46,73% (443)**	26,69% (253)	16,98% (161)	5,49% (52)	4,11% (39)

Cells do not always total 100% due to rounding

The main reasons for patients to do a spontaneous report would be the severity of the reaction and worries about their own situation. Regarding opinions, patients believe that reporting an ADR can prevent harm to other people and that reporting contributes to research and knowledge or drug improvement. Patients also consider that it was difficult to discuss the ADR with HCPs, such as general practitioners or pharmacists.

Table 9 - Opinions about reporting adverse drug reactions (percentage (frequency))

Opinions	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
Reporting an adverse drug reaction can prevent harm to other people	**53,59% (508)**	34,60% (328)	6,54% (62)	3,90% (37)	1,37% (13)
I felt responsible for reporting an adverse drug reaction	12,87% (122)	14,98% (142)	25,21% (239)	**33,97% (322)**	12,97% (123)
Reporting an ADR that is already mentioned in the patient information leaflet is useless	**38,29% (363)**	21,94% (208)	19,20% (182)	15,30% (145)	5,27% (50)
I only report an adverse drug reaction if it is serious	**44,62% (423)**	22,26% (211)	14,24% (135)	13,71% (130)	5,17% (49)
Reporting an adverse drug reaction contributes to research and knowledge	**52,43% (497)**	27,32% (259)	13,61% (129)	6,12% (58)	0,53% (5)
I report an adverse drug reaction if it is not mentioned in the patient information leaflet	**43,14% (409)**	33,02% (313)	14,24% (135)	6,43% (61)	3,16% (30)
I benefit from reporting an adverse drug reaction	**30,27% (287)**	20,78% (197)	22,36% (212)	20,04% (190)	6,54% (62)
Reporting an adverse drug reaction contributes to improvement of drugs	**49,05% (465)**	33,86% (321)	9,60% (91)	6,86% (65)	0,63% (6)
I report an adverse drug reaction if it is unexpected	19,73% (187)	**35,34% (335)**	23,31% (221)	19,73% (187)	1,90% (18)
In the future I will report a possible ADR	13,19% (125)	25,63% (243)	**33,12% (314)**	21,31% (202)	6,75% (64)

Cells do not always total 100% due to rounding

3.3. DIFFERENCES IN RESPONSES BASED ON PATIENT CHARACTERISTICS

Patients' characteristics, knowledge regarding SNF and the opportunity to report ADR were compared with the other answers. Based on Pearson's chi-square statistics, significant results are given, indicating that the answers were related to patient characteristics.

Based on Gender:

- Women show more agreement with "It was difficult to discuss the adverse drug reaction with my medical practitioner or pharmacist" (reason 3, χ^2 p = .049).
- Women show more agreement with "I was angry about my situation" (reason 7, χ^2 p = .044).

Based on Age:

- Younger people were significantly more likely to be aware of SNF (χ^2 p= .002 Tvalue: .004). There is also a difference in people from different age categories that know about the possibility of report (χ^2 p = .015), however there was no trend when looking at the categories (Tvalue: .099). The classes 35-44 years and 45-54 years know more about the possibility of report.

- Older people show more agreement with "It was difficult to discuss the adverse drug reaction with my medical practitioner or pharmacist" (reason 3, χ^2 p = <.001 Tvalue: <.001).
- Older people show more agreement with "The possibility for reporting an adverse drug reaction just exists" (reason 4, χ^2 p =.026 Tvalue: .019).
- Older people show more agreement with "I wanted to be heard" (reason 5, χ^2 p =.006 Tvalue: <.001).
- Older people show more agreement with "I was angry about my situation" (reason 7, χ^2 p = .044 Tvalue: .003).
- Older people show more agreement with "I wanted action to be taken" (reason 8, χ^2 p = <.001 Tvalue: .007).
- Younger people show more agreement with "The adverse drug reaction was not mentioned in the patient information leaflet" (reason 10, χ^2 p = <.001), however there was no trend when looking at the categories (Tvalue: .752).
- Older people show more agreement with "I was worried about my own situation" (reason 11, χ^2 p = .002 Tvalue: <.001).

- There is a difference between the age categories for agreement with the statement "In the future I will report a possible adverse drug reaction" (opinion 10, χ^2 p = .028), however there was no trend for age (Tvalue: .123).

Based on Educational Level:

- People with higher level of education were significantly more likely to be aware of SNF (χ^2 p = <.001 Tvalue: <.001) and to know about the possibility of report (χ^2 p = <.001 Tvalue: <.001).

- There was a difference based on level of education for agreement with "I was worried about my own situation" (reason 11, χ^2 p = .001). However there was no trend for this statement based on the level of education (Tvalue: .773).

- People with higher level of education show more agreement with "I benefit from reporting an adverse drug reaction" (opinion 7, χ^2 p = .010 Tvalue: <.001).
- People with higher level of education show more agreement with "I report an adverse drug reaction if it is unexpected" (opinion 9, χ^2 p = <.001 Tvalue: <.001).
- People with higher level of education show more agreement with "In the future I will report a possible adverse drug reaction" (opinion 10, χ^2 p = .026 Tvalue*: .045).

3.4. CORRELATIONS

Spearman's correlation coefficients between the statements were displayed in SPSS. All correlations between reasons and opinions, but also separately among the reasons and among the opinions, are presented in Appendix 3.

The highest correlation coefficient found in the present data was 0.54. This means that a strong correlation between all statements was not present, only moderate and weak correlations were found. Therefore, it was difficult to define the meaning of the possible relationships between the statements. Nevertheless, moderate correlations are presented in Table 10 and Table 11 as indication of the results.

Table 10 - Correlations Coefficients – reasons for reporting ADR

Related Reasons	Spearman rho**
"Discuss ADR with HCP" (R3) and "Wanted to be heard" (R5)	0,51
"Discuss ADR with HCP" (R3) and "Angry about situation" (R7)	0,43
"Discuss ADR with HCP" (R3) and "Worried about situation" (R11)	0,39
"Wanted to be heard" (R5) and "Angry about situation" (R7)	0,46
"Angry about situation" (R7) and "Wanted action to be taken" (R8)	0,50
"Wanted action to be taken" (R8) and "Worried about situation" (R11)	0,52

**correlation is significant at the .01 level (2-tailed)

* Marked variables were recoded in order to perceive the trend for age and educational level

The highest correlation was found between reason 8 “I want action to be taken” and reason 11 “I was worried about my own situation”. The correlation coefficient between the two reasons is .52 and the significance value of this coefficient is less than .01.

Table 11 - Correlations Coefficients – opinions about reporting ADR

Related Opinions	Spearman rho**
"Can prevent harm to other people"(O1) / "Contributes to research and knowledge"(O5)	0,40
"Can prevent harm to other people" (O1) / "Contributes to improvement of drugs" (O8)	0,42
"I will report in the future" (O10) and "I felt responsible for reporting" (O2)	0,47
"Report ADR present in leaflet is useless" (O3) and "Only report if it is serious" (O4)	0,54
“Contribute to research and knowledge"(O5) / "Contribute to improvement of drugs"(O8)	0,51

**correlation is significant at the .01 level (2-tailed)

The correlation coefficients between the opinions for reporting ADRs were also only moderate or even weak. No strong correlations were found. The highest correlation was found between opinion 5 “Reporting an ADR contributes to research and knowledge” and opinion 8 “Reporting an ADR contributes to improvement of drugs”. The correlation coefficient between the two opinions is .51 and the significance value of this coefficient is less than .01.

Furthermore, correlations between both sections of the questionnaire, the reasons and opinions, were also carried out. However, this resulted in just one moderate correlation between reason 9 and opinion 2 (correlation coefficient = .42) and furthermore only weak correlations – Appendix 3.

4. DISCUSSION

This section starts with a discussion of the status of Pharmacovigilance in Portugal, and the role of educational interventions in active Pharmacovigilance. The major findings and the relation to other studies with respect to the results are described in the Chapter 4.3 and the Strengths and Weakness of the study are discussed in Chapter 4.4.

4.1. THE STATUS OF PHARMACOVIGILANCE IN PORTUGAL

In Portugal, the SNF is mostly based on a spontaneous ADR reporting method, being an effective resource for early detection of rare or unexpected ADR. The major limitation regarding the effectiveness of spontaneous ADR reporting system is underreporting of suspected ADRs, with consequent limitations in assessing the risk of drug and delay generation of risk signals, causing serious health repercussions. The identification of attitudes and knowledge of health professionals associated with underreporting in Portugal has become essential to understand the reasons for the underreporting of ADR.[7, 35, 36, 58]

The number of ADR reports received by SNF from different classes of health professionals (pharmacists, physicians and nurses), as well as the pharmaceutical industry, has been increasing considerably (Fig. 1). Although underreporting remains a reality in pharmacovigilance and it's estimated that only 6% of all adverse reactions are reported.[19]

In the last couple of years, pharmacists were the HCPs who reported more than other HCPs to SNF, but whose participation in pharmacovigilance systems is quite variable,[35] depending of area of activity and country: in Portugal it is estimated that about up to 20% of spontaneous reports come from pharmacists, and their participation are variable between hospital and community pharmacists.[7, 33, 36, 41, 42] However, the number of reports received from community pharmacists is growing, and they assumed a fundamental role in the monitoring of ADR events, since they establish the connection with the patient before, during and after treatment.[35] The active and important role

played by pharmacists in promoting reporting by patients and the good patient-pharmacist relationship should be developed in order to promote active pharmacovigilance by patients, acting as facilitators and promoting patient' ADR reporting.[26, 59]

Many factors are associated with ADR underreporting among health professionals and these have been broadly classified. Inman[40, 60] has summarized these factors as the "seven deadly sins". His description of the "sins" include: attitudes relating to professional activities (financial incentives: rewards for reporting; legal aspects: fear of litigation or enquiry into prescribing costs; and ambition to compile or publish a personal case series) and problems associated with ADR-related knowledge and attitudes (complacency: the belief that very serious ADRs are well documented by the time a drug is marketed; diffidence: the belief that reporting an ADR would only be done if there was certainty that it was related to the use of a particular drug; indifference: the belief that the single case an individual doctor might observe could not contribute to medical knowledge; and ignorance: the believe that it is only necessary to report serious or unexpected ADRs), and excuses made by professionals (lethargy: the procrastination and disinterestedness in reporting or lack of time to find a report card and other excuses).[60]

Lopez-Gonzalez et al.[40] have shown that three of the seven "sins" proposed by Inman that are associated with professional activity (financial incentives, fear and ambition to publish) seem to contribute less significantly to underreporting. Insecurity (the belief that it is nearly impossible to determine whether or not a medicine is responsible for a particular ADR) is another factor associated with underreporting[40] but was not proposed by Inman.

Those findings suggests that health professionals need to be informed about ADRs and perhaps to change their practice.[44] In order to improve the reporting rate, it is important to improve the knowledge, attitudes and practices of the HCPs (and patients) regarding ADR reporting and Pharmacovigilance. Two case-control studies were carried out for physicians and pharmacists, whose results allowed, for the design of educational interventions in order to increase the rate of spontaneous reporting.[7, 36, 58, 61] Educational

interventions increased the number of spontaneous reports received in SNF, leading to a peak of spontaneous reports in 2004 by practitioners and pharmacists, reflecting the result of the educational intervention developed at UFN, as shown in Fig. 1.

Subsequently, reinforcing interventions have been conducted in order to improve reporting.[36, 61] The knowledge and attitudes of health professionals are more related to spontaneous ADR reporting than personal and professional factors, reinforcing the premise that knowledge and attitudes are potentially modifiable, so that educational interventions designed based on the detected gaps in knowledge and attitudes of health professionals can favorably improve reporting.[36, 38-40, 61]

4.2. ADVANTAGES AND DISADVANTAGES OF APPLICATION OF EDUCATIONAL INTERVENTIONS FOR PATIENTS

Educational interventions made for HCPs have significantly increased the number and relevance of spontaneous ADR reports in Portugal. This increase declines over time[61] and therefore, regular training should be repeated periodically to keep the participation of HCPs in Pharmacovigilance. These should include discussion of the attitudes of HCPs regarding spontaneous ADR reporting, with attention for the main reasons for underreporting.[38]

Likewise, potential educational interventions targeting patients could be developed, focusing the attitudes associated with underreporting of ADR by patients identified in this study and the dissemination of information by patients. Patients' associations should be a primary target, for being more aware to medicines safety issues. The administrative and financial capacity of the SNF should be taken into account when educational interventions are prepared because structural intervention could be needed to facing the increase of reports received: a spontaneous reporting "boom" may be inappropriate in terms of costs and human resources. According to Hexheimer et al.[62] the pharmacovigilance systems must be restructured to enable direct patient reports to be appropriately handled, that require more pharmacovigilance staff, with new training to learn to analyze qualitative

data and time. The increase in quantity of the number of reports received should also be reflected in an increased quality and faster detection signal.

A wide range of educational interventions, such as the broadcast of television programs on some medicines[54] have also reported an increased patient reporting which demonstrates the vital role that patients can have in Pharmacovigilance systems if they are made aware that they can report.

4.3. Main Findings

The main objective of this survey was studying the attitudes and knowledge of the patients regarding spontaneous reporting and the factors that can influence patients ADR underreporting in Portugal.

The questionnaire resulted in a high response rate of 81,1%, but about 12% of respondents were HCP who were excluded from data analysis due to the possible bias created by their knowledge regarding study issues. The high number of HCP interviewed could be related to the existence of a huge healthcare pole in Coimbra, that is one of the biggest employer of central region of Portugal. Regarding this, the high percentage of respondents that knows about the SNF and the possibility to report an ADR could be related to the proximity to healthcare pole and the existence of patients-HCP proximity that create more knowledge regarding health issues, due to social relation.

55,9% of respondents knows about SNF and 86,7% knows that it is possible to report an ADR, either to SNF directly or through an HCP; these possibilities were learned mainly from practitioners and/or pharmacy. Despite of this good result, for 62,4% of the respondents, the best way to report is indirectly through an HCP, which we could relate to indifference, ignorance of report directly and insecurity to determine causal relationship between the drug and the reaction, already described by Inman as reasons for underreporting.[60]

Despite all efforts to potentiate the online reporting, only 31.6% of respondents prefer this method above other methods. This result is consistent with the SNF results, online reporting is still little used in Portugal.[42]

Asked for what they do when they have or if will have an ADR, patients answered that they talk to their GP (35,9%) or to their pharmacy (33,7%). Although, as discussed above, communication with HCP is a major barrier indicated by patients to do a spontaneous report. Making a spontaneous report was also pointed by 32,2% of respondents as an action to do when they have an ADR, but only 3 of the respondents had already made a spontaneous report. Coimbra, where this study was performed, is located in Central Portugal which is the geographic region that receives less ADR reports.[41, 42] Social desirability bias could be an issue with the question about making a report.

As shown by Inman, there are several reasons related to knowledge and attitudes that could be related to underreporting. The reasons found by HCP could easily be demonstrated as the same by patients. **Complacency** ("side effect not serious enough") **diffidence** ("it's unnecessary"), **ignorance** and **indifference** ("expected/knew side effect") and **insecurity** ("didn't realize that side effect is due to the medicine") are pointed as the main reasons for not reporting the experienced side effects.[60]

It appeared that patients are motivated to report ADR due to several reasons. The most important motives are the severity of the reaction (81,1% agree or strongly agree) and they were worried about their situation (73,4% agree or strongly agree). The need to be heard (63,6% agree or strongly agree) and difficult to discuss the ADR with medical practitioner or pharmacist (62,9% agree or strongly agree) were also main factors to do spontaneous report directly by patients.

The need to be heard and the difficulty to discuss the ADR with HCP suggest that communication between patient and HCP should be improved. It can also reflect the insecurity regarding identification of ADR and the acknowledgement of HCP to handle with ADR proposed by Inman as a motive of underreporting.[60]

Furthermore, patients believe that reporting an ADR can prevent harm to other people (88,2% agree or strongly agree), that reporting contributes for improvement of the drugs

(82,9% agree or strongly agree) and to research and knowledge (79,8% agree or strongly agree).

Portuguese patients also pointed out being angry about their situation as a main motive to report an ADR. It could reflect that ADR knowledge should be improved among patients and the ADR should be clarified to the patients, in order that they understand that is an inherent possibility of the medicines use.

After subdividing the answers on the statements based on the patient characteristics, it appeared that gender, age and level of education had a significant effect on the reasons to report an ADR and/or the opinions about reporting ADRs and also for the knowledge about the possibility of report an ADR and/or about the existence of SNF. More information is needed for patients, especially for older and with lower educational level that demonstrates lowest level of literacy in relation to pharmacovigilance and ADR reporting.

Only moderate and weak correlation coefficients between the statements were found. For the most significantly related reasons and opinions an explanation can be thought of. The difficulty to discuss the ADR with an HCP (reason 3), the need to be heard (reason 5) and being angry about situation (reason 7) are related aspects. The worries about their ADR (reason 11) and wanting action to be taken (reason 8) also show a relation with these reasons.

With concern to opinions on reporting, for respondents, a relation is found between reporting ADR contributes to research and knowledge (opinion 5) and for improvement of the drugs (opinion 8), which seems reasonable. In turn, a better future situation can prevent harm to other people (opinion 1), the feel of responsibility of reporting an ADR (opinion 10) and the intention for reporting in the future (opinion 2) are also related, which indicated that potential modifications in empowering patients with regard to these questions can lead to increased reporting in the future.

On the other side, the strongest correlation of the study is between “reporting an ADR present in the patient information leaflet is useless” (opinion 3) and “ I only report if the ADR is serious” (opinion 4) are also statements with a high agreement. These attitudes

were already described by HCP,[60] and should be priority issues for educational interventions on patients.

4.4. COMPARISON WITH OTHER STUDIES

Several studies have been conducted with the aim of investigating motivations of healthcare professionals for reporting ADRs.[7, 20, 21, 38-40, 58, 63-65] The severity of the reaction was the main factor determining the ADR report or not.[65] Hasford et al.[64] and Ekman et al.[63] indicated that the severity of the reaction, unusual reactions and reactions caused by a new drug were the main reasons motivating HCP to report ADRs. The desire to contribute to medical knowledge, reaction previously unknown to the reporter, reaction to new drug, desire to report all significant reactions, known association between drug and reaction and severity of reaction are also motives that incentive HCP to report an ADR.[66]

Some of the motives found for HCPs are also important reasons for patients to report, such as severity of the reaction and wanting to contribute to medical knowledge. According to a similar study conducted in The Netherlands in patients that already sent a spontaneous reporting to Netherlands Pharmacovigilance Centre- *Lareb* by van Hunsel et al.[47], "the severity of the adverse reaction" and the "need to sharing experiences" were the main reasons to patient reporting.

Among the altruistic motives, preventing harm to other patients, making the ADR publicly known, increasing medical knowledge and wanting to improve the patient information leaflet were indicated as reasons to report. Personal motives to report an ADR included wanting more information about the ADR, indicating that the ADR was too severe not to report, being angry or wanting confirmation of their ADR.[47]

Other studies also expressed altruistic views indicating the need to make the ADR public or making other patients aware of side effects from medicines and also to prevent others from suffering similar problems.[44] The importance of highlighting the patients' perspective on suspected ADRs, particularly their severity and impact, was also described

by Anderson et al.[44]; unexpected reactions to a widely used medicine and worse side effects than the underlying medical problem were also motives among reporters in UK.

Respondents also indicated that the severity of symptoms may be perceived differently by patients and that patient reports might differ from those of HCP.[44]

Despite of our study being conducted similarly to previous studies, the differences in responses between reporters and non-reporters are evident. It can be easily understood thatthese differences in results are based on the fact that our respondents never made a spontaneous reporting before and are due to lower knowledge shown regarding Pharmacovigilance. Respondents did not show so much altruistic motives which concerns to patient attitudes and knowledge on reporting.

Among the altruistic motives present in the motives and opinions of report, all of them show less agreement than in the similar study performed in The Netherlands.[47] The greatest differences are present in the "wanting to share experiences" - only 54,6% of the respondents shows agreement with this statement, instead of 89,0% in the compared study;[47] likewise, patients didn't "feel responsible for reporting an adverse drug reaction" - only 27,9% of the respondents shows agreement with this statement, instead of 90,7% in The Netherlands;[47] "reporting an adverse drug reaction can prevent harm to other people", "Reporting contributes to research and knowledge" and " Reporting can help the improvement of drugs" shown similar results.

Comparing the knowledge about the ADR reporting, our results are consistent to earlier studies[44, 55] regarding to how respondents learned about the possibility of reporting possible ADRs, which shows that most of patients learned it from their pharmacy or GP.

Comparing the attitudes concerning the type of reactions to be reported there are also some interesting findings. Patients states that "reporting an ADR present in the patient information leaflet is useless" (60,2%) and "I only report if the ADR is serious" (66,9%): this ignorance about the types of reactions that should be reported should be addressed by providing useful information to patients; on the other side, "the ADR was not mentioned in the leaflet"(33,6%) and "reporting an ADR if it is unexpected"(50,1%) doesn't pointed as major reasons to report, that could represent insecurity from patients

to establish causal relation, or even complacency that medicines are safe and ADR are well documented by the time the drug is marketed.

The HCP-patient communication barrier has also been discussed in other studies: the issue of dismissive attitudes among HCPs and their failure to report ADRs was already discussed[44] and some patients were concerned that GP reports may not always be accurate and that doctors may not even consider suspected ADRs, expressing a lack of awareness among health professionals about patient reporting and the need for reporting mechanism independent of health professionals and for patients' voices to be heard.[44]

A final statement intended to understand the action of patients if they experience a possible ADR in the future, shows an evident difference with the previously performed study in The Netherlands. Only 38,8% of Portuguese patients appear to be motivated to do a report of ADR in future. About one third are not sure about what to do and 28,1% even say that would not report. This could be explained by the fact of our respondents never reported an ADR before, contrary to the patients of The Netherlands study.

4.5. Strengths and Weaknesses of the Study

4.5.1. Strengths

- The questionnaire has been partly validated previously in another study. The utilization of a developed instrument for gaining insight in patient-motives for reporting ADRs it's a measure to improve the robustness of data collected.
- High response rate: the high response rate could be considered one of the strengths of the study. We attempted to explain high response rate achieved below in the chapter 5.3 – Bias.
- As far as we know, this is the first national study regarding patients reporting. Further opportunity for a purposive sample of reporters to describe their opinions should be taken. However, patients that had reported to the SNF constitute a minority of the population.

4.5.2. Weaknesses

- Proper randomization was not possible in selecting patients, mainly due to the selection method of sampling (convenience sample).
- Comparison of data collected with other studies carried on patients that already report ADR, could reflect inconclusive and non-comparable results.
- There are some differences between our study population (Table 12) and the general Portuguese population, which suggests that our results cannot be extrapolated fully to the Portuguese population.

5. VALIDITY

This Chapter discusses validity aspects of the study, like the study population and respondent characteristics.

5.1. SELECTED POPULATION STUDY

The sample of patients was limited to one Portuguese region, from an urban area, which could create a bias in final results. For this preliminary study in a Portuguese population face-to-face interviews were chosen in order to do not discard the older or lower-literacy population so that they would be represented in the study. Despite of this, bias could also be related to the population of the study that lives in Coimbra. The city is better known for its university, the great quantity of students and when it was created a reference pole of health services in Portugal (with the University Hospitals that are a huge health pole of Portugal), which could create positive bias concerning educational level and more knowledge regarding health issues, which are both higher than expected for Portuguese population. It is estimated that the high response rate and the huge amount of respondents knowing about SNF could be related with it.

5.2. RESPONDENTS' CHARACTERISTICS

In the comparison of patient characteristics of study population to the Portuguese population we could find similarities and differences in characteristics. The comparison between study sample and Portuguese population is represented in the table 12.

Analysing the variables under study, it appears that gender does not appear to have differences that may have interference in the results. However, regarding to age, the comparison with the general Portuguese population shows us that there is a greater representation of [45-64] classes, which results in an underrepresentation of the elderly class of 65+ years.

Table 12 - Respondent Characteristics vs. Characteristics of Portuguese Population

Variable	Sample Percentage	Portuguese Characteristics
Gender		
Male	40,8%	46,9%
Female	59,2%	53,1%
Age		
18-24 Years	8,5%	9,2%
25-34 Years	18,4%	15,4%
35-44 Years	11,6%	18,7%
45-54 Years	23,3%	17,6%
55-64 Years	27,7%	15,4%
65 + Years	10,4%	23,6%
Educational Level*		
Pre-primary, primary and lower secondary education (levels 0-2)	45,3%	63,4%
Upper secondary and post-secondary non-tertiary education (levels 3 and 4)	20,1%	20,3%
First and second stage of tertiary education (levels 5 and 6)	34,6%	16,3%

Source: EUROSTAT
*Educational level was reclassified according to ISCED and levels are grouped to easier comparison.

With concern to education, the discrepancies are even more evident. There is an underrepresentation of classes with lower-literacy, resulting in an overrepresentation of tertiary education classes. Although, we thought that the results reflect the trend of the general population concerning to attitudes and knowledge regarding ADR report, however, caution is needed before extrapolating these data to the general population, because older[67] or lower-literacy populations cannot be represented correctly, and even worst results are expected in rural areas, with lower-literacy and older populations.

5.3. TYPES OF BIAS

5.3.1. Questionnaire wording and translation – Translational Bias

Translation procedures play a central and important role in multilingual survey projects. Although good translation products do not assure the success of a survey, badly translated questionnaires can ensure that an otherwise sound project fails because the poor quality of translation prevents researchers from collecting comparable data.[68] Some study limitations were due to the questionnaire itself. The Portuguese questionnaire version was translated and adapted by the authors, following pre-test that was performed in volunteers in order to understand major drawbacks of the translation and possible corrections. Pre-test respondents mentioned that a few statements were confusing, these were rewritten to provide an easy understanding of Portuguese version and the comparability of the data collected with other studies.

This questionnaire was adapted from a similar study conducted by The Netherlands Pharmacovigilance Centre in patients that have already report an ADR.[47] Comparison becomes important to understand the trend that the introduction of the patients in the pharmacovigilance system in Portugal, and how these trends can be modified to achieve positive results.

5.3.2. Questionnaire administration Bias

The mode of questionnaire administration is likely to affect the quality and quantity of data collected. The data collection process involves an interaction between the questionnaire, the respondent and, in case of face-to-face interviews, the interviewer.[69] There are many potential influences on responses that can have effect on quality of data obtained. Personal face-to-face interview using traditional paper and pencil questionnaires (PAPI) were conducted.

Face-to-face interviews can have potential benefits, like a higher preference for this administration mode by respondents, more complete population coverage for sampling, high survey response rate, the high completion and item response of the questionnaires and finally the amount of information collected.[69]

In contrast, the influence of the social setting could cause desirability bias, acquiescence bias and interviewer bias that which be considered as major potential negative biases in our questionnaire administration mode. Social interaction between the interviewer and respondent can lead to respondents taking social norms into account when responding, resulting in social desirability bias. Additionally, an interviewer can also cause biases due to the reluctance caused in people to reveal beliefs unlikely to be endorsed by the interviewer.[69] Question order effects and response-choice order effects does not appear to have great influence in face-to-face questionnaires, so they are not considered as major biases of our study.[69]

Specifically in this study, sample selection bias could also be present. Non-randomized method of selection of the sample could cause a biased sample, which commonly does not have significant value in the extrapolation of the results to the population. Selection method might contribute to the exclusion of some drug users' classes, such as some of the oldest patients as suggested by Frisk et al.[67]

Communication barrier was also a potential bias due to literacy barriers. Interviewer efforts to motivate respondents, clarifying questions can lead to interviewer and social desirability bias. The burden of patient-HCP relation between interviewer and respondents could also affect the data collection, contributing to a high response rate and high completion of the questionnaires.

6. FINAL REMARKS

In this chapter, meaning of the study and unanswered questions and future research are discussed. The last paragraph gives the conclusions based on this research.

6.1. MEANING OF THE STUDY

The aim of the present study was to gain insight into the attitude and behaviour of patients in Portugal, with respect to the reporting of ADRs. Our main and additional research questions will be answered one by one below.

Which motives for reporting adverse drug reactions are present in a large group of patients in Portugal?

As described in the first paragraph of this chapter, several motives are present:

- Severity of the reaction
- Worried about situation
- Contribution to research and knowledge
- Contribution to improvement of drugs
- ADR not mentioned in patient information leaflet
- Prevent harm to other people
- The reaction is serious

These motives can be classified in reporting for oneself (severity, worried, problems), reporting for others (share experiences, preventing harm, feeling responsible) or reporting for improvement (research and knowledge, patient information leaflet). It appeared that various patient characteristics (gender, age and level of education) had an effect on the motives of patients to report their ADR.

What could be the next steps to bring patients to active Pharmacovigilance?

The development of online form for all countries, and its disclosure by patients will cause an increasing in reports. Educational interventions with information disclosure to patients, regarding forms and general pharmacovigilance could be one of the measures to improve patients' knowledge and attitudes regarding pharmacovigilance. Regular training sessions to promote pharmacovigilance for patients and to address the various perceived obstacles to spontaneous reporting are very necessary for a long term improvement of ADR reporting and for the active involvement of patients in active Pharmacovigilance. The patient-HCP relationship should be encouraged because HCP could play an important role in spontaneous reporting system by acting as facilitator and promoting patient' ADR reporting.

6.2. UNANSWERED QUESTIONS AND FURTHER RESEARCH

The main question which remains unanswered after this study is why patients do not report their experienced ADRs. Further work is needed to study a random sample of the Portuguese population as a reference-group, to make a comparison with the results found. Other Portuguese regions should be taken into account and the possibility of educational interventions, starting to patients' associations that could be a measure to spread information among patients.

Finally, further investigation is needed to gain information on the importance of patient reports in signal detection activities, which should be evaluated at a national level, with great number of reports. A new strategy to promote spontaneous ADR reporting also involves the use of technology as a facilitator of the act of report, including the implementation of online reporting, which has the advantage of being quicker to send and simpler to complete.

6.3. CONCLUSIONS

Few studies are available about the reasons or motives why patients actually report suspected ADRs. Patients had potential to contribute with useful information on drug safety, which should be maximized. Because HCPs and patients have different views regarding ADR reporting, in daily practice it is important to receive reports from both groups to assess the true nature of the ADR. Consumer reporting had already shown important and valuable information on drug safety. Despite of this, this contribution can be maximized. From these results we hypothesize that the management of ADR monitoring is not perfect and need serious rethinking. Lack of knowledge would automatically affect reporting, therefore, awareness programs; through educational intervention are needed to improve ADR reporting. There is a great need to create awareness and to promote the reporting of ADR.

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APPENDIX I – QUESTIONNAIRE (ENGLISH)

Patient Reporting – Are Patients ready to take part in Pharmacovigilance System? – Questionnaire Final Version

According to WHO, spontaneous adverse drug reactions (ADR) reporting is defined by "a regional or country-wide system for the reporting of suspected adverse drug reactions". Thus, this is the primary method in pharmacovigilance and it is useful to picking up signals of relatively rare, serious and unexpected adverse reactions. Voluntary ADR reporting is one of the most versatile pharmacovigilance systems, because, among other advantages, it covers the entire population as well as all medicals drugs throughout their commercial life, being also a free method.

Section I – Personal Information

Gender

- ☐ Male
- ☐ Female

Age Group

- ☐ 18-24 Years
- ☐ 25-34 Years
- ☐ 35-44 Years
- ☐ 45-54Years
- ☐ 55-64Years
- ☐ 65 + Years

Highest education Level

- ☐ None
- ☐ Primary
- ☐ Few Years Secundary
- ☐ Secundary Completed
- ☐ High School
- ☐ Bachelor
- ☐ Master
- ☐ Doctorate

Working Status

- ☐ Full time
- ☐ Part time
- ☐ Not working
- ☐ Retired
- ☐ Studying

I am an healthcare professional:

- ☐ Yes
- ☐ No

Section II– Reporting Knowledge

1) Do you know the Portuguese NPS (National Pharmacovigilance System)?

- ☐ Yes
- ☐ No

2) Did you know that is possible for patients to do a spontaneous reporting of a possible ADR?

- ☐ Yes
- ☐ No

Answer **YES** in the question 2

2.1 - How did you learn about the possibility of doing a reporting of possible ADR from medicines?

- ☐ From a GP
- ☐ From a hospital
- ☐ From a pharmacy
- ☐ From a family member or friend
- ☐ From a magazine or newspaper
- ☐ From internet research
- ☐ From INFARMED website
- ☐ I've learned at School (Formation)
- ☐ Other_____

2.2 – What's for you the best way to do a report?

- ☐ Directly - Online / By Computer
- ☐ Directly - by post
- ☐ Directly - by telephone
- ☐ Indirectly - throw an HCP

2.3 - Would you recommend to someone to do a spontaneous report about an adverse drug reaction?

- ☐ Yes
- ☐ No

Answer **NO** in the question 2

Follow to question 3

3) When you a have/if will have a suspected ADR what do you do? (Tick all that apply)

- ☐ Talk with your GP/doctor
- ☐ Talk to your pharmacy
- ☐ Make a spontaneous reporting
- ☐ Stop the medication
- ☐ Don't do nothing

4) Have you ever had side effects from any medicine?

- ☐ Yes
- ☐ No

Answer **YES** in the question 4

4.1 - If yes, did you report it?

- ☐ Yes
- ☐ No

Answer NO in the question 4

4.2 - In the future, if you have any side effects will you report?

- ☐ Yes
- ☐ No
- ☐ Not Sure/Don't know

Answer YES in the question 4.1

4.1.1.1 - Do you think it's a easy method?

- ☐ Yes
- ☐ No

4.1.1.2 - Did you expect to get any feedback (confirmation/scientific explanation) from NPS (National Pharmacovigilance System) about your report?

- ☐ Yes
- ☐ No

Answer NO in the question 4.1

4.1.2.1 - If not, why not?

- ☐ Side effect not serious enough
- ☐ Didn´t realize side effect due to medicine
- ☐ Expected/knew side effect
- ☐ Stopped using medicine
- ☐ Is unnecessary
- ☐ Other (including embarrassed, abroad, didn´t read instructions)
- ☐ Don't know how to report

4.1.2.2 - Do you know the spontaneous report patients form?

- ☐ Yes
- ☐ No

Answer YES in the question 4.1.2.2

4.1.2.2.1 - Do you know how to obtain it?

- ☐ Yes
- ☐ No

5 - Rate each of the following items, at a five-point Likert scale (strongly agree to strongly disagree), where the middle position was labeled 'neutral' to reflect a neutral position.

Reasons to report:

	SA	A	N	D	SD
I wanted extra information					
The adverse drug reaction was severe					
It was difficult to discuss the adverse drug reaction with my medical practitioner or pharmacist					
The possibility for reporting an adverse drug reaction just exists					
I wanted to be heard					
Someone else pointed the possibility for reporting an adverse drug reaction					
I was angry about the situation					
I wanted action to be taken					
I wanted to share my experiences					
The adverse drug reaction was not mentioned in the patient information leaflet					
I was worried about my own situation					

Opinions to report:

	SA	A	N	D	SD
Reporting an adverse drug reaction can prevent harm to other people					
I felt responsible for reporting an adverse drug reaction					
Reporting an adverse drug reaction that is already mentioned in the patient information leaflet is useless					
I only report an adverse drug reaction if it is serious					
Reporting an adverse drug reaction contributes to research and knowledge					
I report an adverse drug reaction if it is not mentioned in the patient information leaflet					
I benefit from reporting an adverse drug reaction					
Reporting an adverse drug reaction contributes to improvement of drugs					
I report an adverse drug reaction if it is unexpected					
In the future, I will report a possible adverse drug reaction					

Adapted from:

- Anderson C, Krska J, Murphy E, Avery A. The importance of direct patient reporting of suspected adverse drug reactions: a patient perspective. British journal of clinical pharmacology. 2011;72(5):806-22.
- van Hunsel F, van der Welle C, Passier A, van Puijenbroek E, van Grootheest K. Motives for reporting adverse drug reactions by patient-reporters in the Netherlands. European journal of clinical pharmacology. 2010;66(11):1143-50.

APPENDIX II – QUESTIONÁRIO (PORTUGUÊS)

Patient Reporting – Are Patients ready to take part in Pharmacovigilance System? – Versão final do questionário

Segundo a OMS, a notificação espontânea de reacções adversas a medicamentos (RAM) é definida como "um sistema regional ou nacional para a notificação de suspeitas de reações adversas a medicamentos". Assim, este é o principal método de farmacovigilância e é útil para captar sinais relativamente a reacções adversas graves, raras e inesperadas. A notificação voluntária é um dos sistemas de farmacovigilância mais versáteis, porque, entre outras vantagens, abrange toda a população, bem como todos os medicamentos durante toda a sua vida comercial, sendo também um método praticamente grátis. A informação recolhida neste questionário é anónima e confidencial e destina-se a fins meramente académicos, para o estudo em que se insere ou outros estudos futuros dos mesmos autores.

Secção I – Informação Pessoal

Género:

- ☐ Masculino
- ☐ Feminino

Faixa etária:

- ☐ 18-24 Anos
- ☐ 25-34 Anos
- ☐ 35-44 Anos
- ☐ 45-54 Anos
- ☐ 55-64 Anos
- ☐ 65 + Anos

Nível Educacional:

- ☐ Nenhum
- ☐ Escola Primária
- ☐ 2º ou 3º Ciclo
- ☐ Secundário não Completo
- ☐ Ensino Secundário
- ☐ Licenciatura
- ☐ Mestrado
- ☐ Doutoramento

Emprego:

- ☐ Tempo Inteiro
- ☐ Part time
- ☐ Desempregado
- ☐ Reformado
- ☐ Estudante

Profissional de Saúde

- ☐ Sim
- ☐ Não

Secção II– Conhecimento em Farmacovigilância

1) Conhece o Sistema Nacional de Farmacovigilância (SNF)?

- ☐ Sim
- ☐ Não

2) Tem conhecimento da possibilidade de notificar uma reacção adversa a medicamentos (RAM) ?

- ☐ Sim
- ☐ Não

Resposta SIM à questão 2

2.1 –Como teve conhecimento acerca da possibilidade de notificar uma RAM?

- ☐ Através do meu médico
- ☐ No hospital
- ☐ Na farmácia
- ☐ Através de um familiar ou amigo
- ☐ Num jornal/revista
- ☐ Na internet
- ☐ No website do INFARMED
- ☐ Na escolar (em disciplinas)
- ☐ Outra_____

2.2 – Na sua opinião, qual é a melhor maneira para notificar?

- ☐ Diretamente ao SNF - Online (através do computador)
- ☐ Diretamente ao SNF - Por carta/correio
- ☐ Diretamente ao SNF - Por telefone
- ☐ Indiretamente através de um Profissional de Saúde

2.3 – Recomendaria a alguém fazer uma notificação espontânea de uma possível reacção adversa?

- ☐ Sim
- ☐ Não

Resposta NÃO à questão 2

Seguir para a questão 3

3) O que faz quando tem/se tiver uma possível RAM? (Pode assinalar várias opções)

- ☐ Falo com o meu médico de família/especialista
- ☐ Falo com a minha farmácia
- ☐ Faço uma notificação espontânea
- ☐ Paro a medicação
- ☐ Não faço nada

4) Alguma vez sentiu alguma reacção adversa a um medicamento?

- ☐ Sim
- ☐ Não

Resposta SIM à questão 4

4.1 – Se sim, notificou?

- ☐ Sim
- ☐ Não

Resposta NÃO à questão 4

No futuro, se tiver uma reação adversa a um medicamento, irá notificar esse acontecimento?

- ☐ Sim
- ☐ Não

Resposta SIM à questão 4.1

4.1.1.1 – Achou que é um método fácil?

- ☐ Sim
- ☐ Não

4.1.1.2 – Espera obter algum feedback (confirmação/explicação científica) do SNF sobre a sua notificação?

- ☐ Sim
- ☐ Não

Resposta NÃO à questão 4.1

4.1.2.1 – Caso não tenha notificado, porque não o fez?

- ☐ A RAM não era séria
- ☐ Não tenho certeza que a RAM tenha sido provocada pelo medicamento.
- ☐ A RAM era esperada/conhecida para aquele medicamento
- ☐ Parei de utilizar o medicamento
- ☐ Não é necessário notificar
- ☐ Outro (incluindo vergonha, má utilização do medicamento/não li as instruções)
- ☐ Não sei como notificar

4.1.2.2 – Conhece o formulário de notificação de RAM para pacientes?

- ☐ Sim
- ☐ Não

Resposta SIM à questão 4.1.2.2

4.1.2.2.1 – Sabe como obter esse formulário?

- ☐ Sim
- ☐ Não

5 – Classifique cada um dos seguintes pontos segundo a escala de corcordância apresentada (concordo plenamente, corcordo, neutro, discordo, discordo plenamente). O ponto intermédio serve para tomar uma posição neutra e não uma incapacidade de responder.

Razões para notificar (no caso de sofrer uma reacção adversa):

	CP	C	N	D	DP
Quero informação extra acerca da reacção					
A reação adversa é grave					
É difícil discutir a reação adversa com o meu médico ou farmacêutico					
Tenho vontade de notificar a reação adversa que aconteceu					
Quero ser ouvido					
Alguém me alertou para a possibilidade de notificar uma RAM					
Sinto-me irritado/frustrado com a situação provocada pela RAM					
Quero que sejam tomadas medidas					
Quero compartilhar a minha experiência					
A reacção adversa não está mencionada no folheto informativo					
Estou preocupado com a minha própria situação					

Opiniões acerca da notificação:

	SA	A	N	D	SD
Notificar uma reacção adversa ao medicamento pode evitar danos a outras pessoas					
Sinto-me responsável por notificar uma reacção adversa ao medicamento					
Notificar uma RAM, quando esta está descrita no folheto informativo, é inútil					
Apenas notifico uma reação adversa a medicamentos, se for grave					
Notificar uma RAM contribui para a pesquisa e conhecimento					
Notifico uma RAM, se esta não estiver descrita no folheto informativo					
Eu beneficio se notificar uma reação adversa a medicamento					
Notificar uma reacção adversa a medicamentos contribui para melhorar os medicamentos					
Notifico uma reação adversa a medicamentos, se for inesperada					
No futuro, vou notificar uma possível reação adversa a medicamentos					

Adaptado de:

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APPENDIX III - CORRELATIONS

	R1	R2	R3	R4	R5	R6	R7	R8	R9	R10	R11	O1	O2	O3	O4	O5	O6	O7	O8	O9	O10
R1	--	0,027	0,029	0,01	0,004	0,029	0,039	0,041	0,017	-0,023	0,031	-0,117	0,092**	-0,033	-0,006	0,103	-0,032	0,007	-0,034	-0,019	0,034
R2		--	0,245**	-0,097**	0,291**	0,039	0,329**	0,247**	0,064	-0,005	0,156**	0,003	0,078*	0,06	0,069*	0,025	-0,034	0,017	0,042	0,043	0,011
R3			--	0,006	**0,512****	-0,015	**0,427****	**0,382****	0,016	-0,023	**0,394****	0,025	0,074*	-0,001	-0,031	0,054	0,01	0,025	0,076*	-0,012	0,05
R4				--	-0,053	0,05	-0,011	0,004	-0,011	-0,009	-0,028	0,051	0,008	0,075*	0,075*	-0,017	-0,006	0,000	-0,033	-0,043	-0,005
R5					--	0,019	**0,459****	0,311**	0,005	-0,017	0,286**	-0,004	0,075*	0,028	0,042	0,04	-0,008	0,076*	0,058	-0,017	0,046
R6						--	-0,068*	-0,038	0,036	-0,005	-0,026	0,009	0,083*	0,052	0,062	0,061	-0,007	0,005	0,055	-0,023	0,029
R7							--	**0,503****	-0,008	-0,032	**0,381****	0,016	0,038	0,009	0,079*	0,043	0,02	0,05	0,059	-0,025	-0,017
R8								--	0,007	-0,039	**0,517****	-0,007	0,075*	0,037	0,071*	0,028	0,052	0,08*	0,034	0,049	0,007
R9									--	-0,067*	0,058	0,074*	**0,424****	-0,023	-0,084*	0,064	0,073*	0,068*	0,092**	0,045	0,126**
R10										--	0,004	-0,041	-0,084**	0,016	0,019	0,008	-0,042	-0,023	0,062	0,000	-0,097**
R11											--	0,031	0,059	0,003	0,007	-0,005	0,034	0,031	-0,007	0,015	0,054
O1												--	0,145**	0,039	0,024	**0,397****	-0,021	-0,053	**0,421****	-0,006	0,054
O2													--	0,019	-0,041	0,302**	0,049	0,006	0,255**	0,069*	**0,470****
O3														--	**0,538****	0,087**	-0,167**	-0,045	0,047	-0,076*	-0,042
O4															--	0,042	0,012	-0,008	0,02	-0,013	-0,076*
O5																--	-0,077*	-0,044	**0,508****	0,001	0,166**
O6																	--	0,011	-0,025	0,166**	0,081*
O7																		--	-0,008	-0,051	-0,017
O8																			--	-0,037	0,187**
O9																				--	0,102**
O10																					--

** - Correlation is significant at 0.01 level

* - Correlation is significant at 0.05 level

R1 = reason 1

R2 = reason 2

...

O1 = opinion 1

O2 = opinion 2