Universidade de Lisboa

Faculdade de Farmácia


# Analysis of the collaboration protocols between the Pharmacovigilance Centres of Porto, Coimbra, and Lisboa, Setúbal e Santarém, with the Central Hospitals of these regions

João Bernardo Lourenço Ribeiro

Dissertation supervised by Professor Carla de Matos Torre and co-supervised by Paula Barão Sousa Ferreira

Master in Regulation and Evaluation of Medicines and Health Products

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## Abstract

### Introduction

In Portugal, since the establishment of the National Pharmacovigilance System (SNF), the reporting rate observed is below the World Health Organization's recommendation for an optimal national centre. Various strategies have been therefore developed, both by the *Autoridade Nacional do Medicamento e Produtos de Saúde, I.P.* (Infarmed), as well as the Pharmacovigilance Centres (PC). Among the various measures implemented to promote ADR notification, the Collaboration Protocols between PC and the Immunoallergology Departments of Central Hospitals of their regions were developed. These were implemented for the first time between the North (now Porto) PC and a Central Hospital in Porto, and were based on the collection of suspected ADR collected by the Immunoallergologists during drug allergy consultations carried out in that Hospital. In a study conducted by the Porto PC, the strategy of Collaboration Protocols proved to be the most cost-effective methodology for the collection of spontaneous ADR reports. This success led to the implementation of two more Collaboration Protocols at this PC. Subsequently, the implementation of similar protocols was also implemented by the Coimbra, and Setúbal e Santarém (now Lisboa, Setúbal e Santarém) PC.

### Objectives and Methods

With this work, we intend to assess the potential impact that the establishment of these Protocols has on the SNF. Thus, we propose to characterise each one of these Protocols, based on interviews conducted with each of the Centres involved, analysing their differences and similarities, both in implementation and operationalisation. Additionally, we also intend to analyse the data of suspected ADR reported through the Protocols, from January 2000 to December 2020. More in depth, a characterisation of these data, identifying their seriousness and previous knowledge; the identification and characterisation of the medicines suspected of causing the ADR; and the evaluation of the impact of data collection on the final assessment of causality imputation.

### Results

There are currently six Collaboration Protocols established between the Porto, Coimbra, and Lisboa, Setúbal e Santarém PC, and the Central Hospitals of their regions. Their main objectives are to collect information on the safety of medicines, but also to increase the

rate of spontaneous reporting in their region. From an operational point of view, all Protocols have been implemented, and operated in similar ways.

In total, 2495 ADR were reported through the Protocols, in the period from 2000 to 2020. Of these, 79.04% were classified as serious. The results showed that 60.56% of patients were female. As for the age group, 19.88% referred to cases with children and adolescents, 42.96% to adults, 8.70% to elderly, and in 28.46% of the cases it was not possible to collect this information. Of the 2495 cases, we were able to identify 2814 suspected medicines. The most frequently reported suspected drugs were, *amoxicillin + clavulanic acid* (17.13%), *ibuprofen* (11.73%), and *amoxicillin* (8.10%). A total of 7577 distinct ADR were identified. These were mostly related to *skin and subcutaneous tissue disorders* (49.48%). In fact, the most frequently reported reactions were *rash* (8.96%), *urticaria* (7.06%), *pruritus* (6.68%). In analysing the causality assessment data, 2307 cases were considered to have a valid assessment. Of these, 91.20% were assessed with a degree of causality of *Certain* or *Probable*. It was possible to analyse that 24.73% of the cases were assessed as unknown at the same time as *Certain* or *Probable*.

**Conclusion**

We conclude that the creation of these Collaboration Protocols has enabled the collection of data which would otherwise be lost to the SNF, on the safety of medicines marketed. These Protocols will feed the SNF of what are mostly serious, known reactions with allergic characteristics. Finally, we consider that an analysis of all ADR data reported to the SNF during the study period (2000 to 2020) is necessary in order to precisely measure the impact that these Collaboration Protocols have had on the Portuguese System.

**Keywords:** Spontaneous report; Underreporting; Immunoallergology; Drug allergy

**Resumo**

**Introdução**

A Farmacovigilância assume cada vez um papel mais importante para a recolha de informação sobre o perfil de segurança dos medicamentos, a partir do primeiro momento em que estes são administrados em humanos. Tendo em conta as limitações na recolha desta informação aquando a fase de estudos clínicos, é necessário monitorizar a segurança dos medicamentos durante o seu uso no mundo real, permitindo uma avaliação contínua da relação benefício-risco dos medicamentos comercializados. Para isto, são implementadas várias metodologias por parte dos Sistemas de Farmacovigilância, sendo que uma das mais utilizadas é a notificação espontânea, através da qual qualquer profissional de saúde ou consumidor pode notificar quaisquer reações adversas que um doente tenha sofrido aquando a toma de um ou mais medicamentos, tanto ao Titular da Autorização de Introdução de Mercado do(s) medicamento(s) suspeito(s), como à Autoridade Competente, e também às Unidades de Farmacovigilância (UF). É estimado que apenas 6% das Reações Adversas a Medicamentos (RAM) sejam notificadas, sendo esta a maior limitação desta metodologia, a subnotificação.

Em Portugal, desde a criação do Sistema Nacional de Farmacovigilância (SNF), em 1992, que a taxa de notificação se encontra abaixo da recomendação da Organização Mundial de Saúde para um centro nacional. Foram assim desenvolvidas várias estratégias, tanto pela Autoridade Nacional do Medicamento e Produtos de Saúde, I.P. (Infarmed), como pelas UF. Estas são parte integrante do SNF, e têm como responsabilidades a recolha, tratamento e avaliação de todas as notificações de RAM na sua região, para além da disseminação e promoção da divulgação de informação relacionada com a segurança dos medicamentos, tanto para profissionais de saúde, como para a população em geral.

Assim, são desenvolvidas diversas medidas para estimular a notificação de RAM, tais como a minstração de ações de formação, o contacto telefónico para sensibilização de profissionais de saúde, e o estabelecimento de Protocolos de Colaboração entre as Unidades de Farmacovigilância e os Departamentos de Imunoalergologia de Hospitais Centrais. Estes foram pela primeira vez implementados entre a UF do Norte (agora UF do Porto) e um Hospital Central do Porto, e tinham como premissa a recolha de suspeitas de RAM recolhidas pelos Imunoalergologistas no decorrer das consultas de alergia a fármacos realizadas naquele Hospital. A implementação deste Protocolo permitiu que a UF atingisse os objetivos quanto à taxa de notificação espontânea na sua região, recolhendo informação que de outra forma não chegaria ao SNF.

Num estudo realizado pela UF do Porto, a estratégia dos Protocolos de Colaboração revelou ser a metodologia mais custo-efetiva para a recolha de notificações espontâneas de RAM. Este sucesso levou à implementação de mais dois Protocolos de Colaboração desta UF. De seguida, a implementação de Protocolos semelhantes foi também posta em prática pelas UF de Coimbra, e UF de Setúbal e Santarém (agora UF de Lisboa, Setúbal e Santarém).

**Objetivos e Métodos**

Com este estudo, pretendemos analisar o potencial impacto que o estabelecimento destes Protocolos tem no SNF. Assim, propomo-nos a caracterizar cada um destes Protocolos, com base em entrevistas realizadas com cada uma das Unidades envolvidas, analisando as suas diferenças e similitudes, quer na implementação, como na operacionalização.

Adicionalmente pretendemos analisar os dados das RAM notificadas ao SNF resultantes destes Protocolos, mais especificamente: uma caracterização destes dados, identificando a sua gravidade e conhecimento prévio; a identificação e caracterização dos medicamentos suspeitos de causar a RAM; e a avaliação do impacto da recolha dos dados na avaliação final de imputação de causalidade.

Para este fim, serão analisados os dados de notificações espontâneas de RAM realizadas por Imunoalergologistas, desde janeiro de 2000 até dezembro de 2020. Apenas serão considerados válidos os casos notificados por via direta, sendo que os casos duplicados, nulos ou inválidos foram retirados da análise. Adicionalmente, foi tida em conta a UF responsável pelo caso, e a data de notificação, para avaliar se o caso foi notificado no âmbito do Protocolo.

**Resultados**

Atualmente, estão em vigor seis Protocolos de Colaboração entre as UF do Porto, Coimbra, e Lisboa, Setúbal e Santarém, e os Hospitais Centrais das suas regiões. Apenas para um dos Protocolos a iniciativa para a sua implementação partiu do Hospital, sendo que nos restantes cinco, partiu das Unidades. Os principais objetivos da implementação dos Protocolos passam pela recolha de informação de segurança dos medicamentos, e também pelo aumento da taxa de notificação espontânea em cada região. De facto, no primeiro ano da sua implementação, o médico Imunoalergologia como notificador representou 10,15% do total de notificações.

De um ponto de vista operacional, todos os Protocolos foram implementados, e operam de forma semelhante. Após a oficialização dos mesmos, foi definido o fluxo de trabalho, e a recolha dos dados é feita com base nos processos clínicos dos doentes, e posteriormente notificada no Portal RAM pelos membros das UF.

Embora as UF considerem que os Protocolos tenham valor acrescentado, referem também que a celebração destes com outros Centros Hospitalares, ou com outros Serviços para além da Imunoalergologia, poderia trazer um aumento na sua carga de trabalho. Assim, os Protocolos tornar-se-iam, de certa forma, contraproducentes, já que as UF deixariam de ter tanta disponibilidade para a notificação das suspeitas de RAM. Isto torna-se paradoxal, já que um dos principais motivos que levou à implementação dos Protocolos foi a falta de disponibilidade dos profissionais de saúde para notificar as RAM com que se deparam no decorrer do seu dia-a-dia.

Entre as formas de melhoria na recolha de notificações espontâneas de RAM para o SNF, identificadas pelas UF, destaca-se a “exportação” automática” das suspeitas de reação adversa identificadas e registadas no âmbito dos registos clínicos dos doentes e do CPARA (Catálogo Português de Alergias e outras Reações Adversas), para o Portal RAM, com o devido consentimento do notificador.

No total, foram notificadas 2495 RAM através dos Protocolos, no período de 2004 – data de estabelecimento do primeiro Protocolo – até 2020. Destas, 79,04% foram classificadas como graves, o que corresponde a 1972 casos.

Através da análise das características dos doentes, foi possíbel observar que 60,56% dos doentes são do sexo feminino.Quanto à faixa etária, 19,88% são referentes a casos com crianças e adolescentes, 42,96% a adultos, 8,70% a idosos, e em 28,46% dos casos não foi possível recolher esta informação.

Dos 2495 casos, foi possível identificar 2814 medicamentos suspeitos. Os medicamentos suspeitos mais frequentemente notificados foram, por DCI, *amoxicilina + ácido clavulânico* (17,13%), *ibuprofeno* (11,73%), e *amoxicilina* (8,10%). A análise dos Códigos ATC foi também realizada com três grandes grupos a distiguirem-se, foram eles *J01 – Antibacterianos para uso sistémico* (39,13%), *M01 – Produtos anti-inflamatórios e anti-reumáticos* (21,54%), e *N02 – Analgésicos* (11,37%).

Tendo em conta que em cada caso podem ser notificadas várias suspeitas de RAM, identificaram-se 7577 RAM distintas. Estas são maioritariamente relacionadas com *afeções dos tecidos cutâneos e subcutâneos* (49,48%). De facto, as reações mais notificadas foram

*erupção cutânea* (8,96%), *urticária* (7,06%), *prurido* (6,68%), *dispneia* (5,38%), e *eritema* (5,03%).A análise aos dados da imputação de causalidade foi feita com base em cada caso de suspeita de RAM, e foram considerados 2307 casos como tendo uma imputação válida. Destes, 91,20% foram avaliados, com os graus de causalidade de *Definitiva* ou *Provável*, quanto à relação causal entre o medicamento suspeito e a reação adversa. Estes dados foram cruzados com a variável *Descrita*/*Não descrita* em RCM (Resumo das Características do Medicamento), que se refere à existência ou não de conhecimento prévio sobre a reação no perfil de segurança do medicamento, tendo sido possível observar que 24,73% dos casos remetiam para reações adversas não descritas (ditas inesperadas) e avaliadas com os graus de probabildade maois elevados (*Definitiva* e *Provável*).

**Conclusão**

O estabelecimento destes Protocolos de Colaboração permitiu a recolha de informação, que de outra forma seria perdida, para o SNF sobre a segurança dos medicamentos comercializados. Por outro lado, tendo em conta que a informação é recolhida através dos registos clínicos dos doentes, mais dados estão disponíveis, permitindo assim que uma maior quantidade de informação, descrita por um profissional de saúde, seja avaliada pelos peritos de farmacovigilância.

Estes Protocolos contribuem para o SNF principalmente no que diz respeito a reações maioritariamente graves, conhecidas e com características alérgicas. Não obstante, o seu impacto é considerado como positivo pelas UF, sendo que é recomendada a sua implementação no restante país.

Por fim, consideramos que é necessária uma análise a todos os dados de RAM notificadas ao SNF durante o período do estudo, 2000 a 2020, para poder verdadeiramente medir o impacto que estes Protocolos de colaboração tiveram no Sistema Português.

**Palavras-chave:** Notificação Espontânea; Subnotificação; Imunoalergologia; Alergia a fármacos

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**List of Acronyms and Abbreviations**

**ADR** – Adverse Drug Reactions

**ATC** – Anatomical Therapeutic Chemical

**CPARA** – Portuguese Catalogue of Allergies and other Adverse Reactions (*Catálogo Português de Alergias e outras Reações Adversas*)

**DGS** – Directorate-General for Health (*Direção Geral da Saúde*)

**EC** – European Commission

**EMA** – European Medicines Agency

**GVP** – Good Pharmacovigilance Practices

**HCP** – Healthcare Professionals

**Infarmed** – National Authority of Medicines and Health Products, I.P. (*Autoridade Nacional do Medicamento e Produtos de Saúde, I.P.*)

**INN** – International Non-proprietary Names

**KPI** – Key Performance Indicators

**MAH** – Marketing Authorisation Holder

**MedDRA** – Medical Dictionary for Regulatory Activities

**NCA** – National Competent Authority

**PC** – Pharmacovigilance Centres

**PRAC** – Pharmacovigilance Risk Assessment Committee

**PT** – Preferred Term

**RAM** – Adverse Drug Reactions (*Reações Adversas a Medicamentos*)

**SOC** – System Organ Class

**SmPC** – Summary of Product Characteristics

**SNF** – Portuguese National Pharmacovigilance System (*Sistema Nacional de Farmacovigilância*)

**SNS** – National Healthcare Service (*Serviço Nacional de Saúde*)

**WHO** – World Health Organization

## 1. Introduction

### 1.1. Pharmacovigilance

As it is known, no drug is completely safe to use, all have the potential to cause adverse drug reactions (ADR).[1] It was Directive 2010/84/EU of 15 December 2010, that last amended the definition of ADR, now being defined as: "a response to a medicinal product which is noxious and unintended."[2] With this change, aspects relating to abusive and inappropriate use, off-label use, and medication errors are now covered by this definition, besides the reactions that occur during the normal use of the medicine, in accordance to the given marketing authorisation.[3]

ADR are characterised as type A, "augmented", and type B, "bizarre". Type A reactions are associated with the pharmacology of the drug, and are usually dose-dependent, whereas type B reactions are idiosyncratic, non-dose dependent, and not necessarily related to the pharmacology of the drug. However, over the years, there was a necessity to expand on these classifications, thus arising type C, "chronic", type D, "delayed", type E, "end of use", and type F, "failure" reactions.[4,5]

Table 1: Adverse Drug Reactions Classification (adapted from *Kaufman G. Adverse drug reactions: classification, susceptibility and reporting. Nurs Stand. 2016;30(50):53-63. doi:10.7748/ns.2016.e10214* and *Edwards IR, Aronson JK. Adverse drug reactions: Definitions, diagnosis, and management. Lancet. 2000;356(9237):1255-1259. doi:10.1016/S0140-6736(00)02799-9*)

**ADR Classification**

| Type | Key Characteristics | Examples |
|---|---|---|
| **A "augmented"** | Associated with the pharmacology of the drug<br>Predictable | Bleeding with use of anticoagulants |
| **B "bizarre"** | Not associated with the pharmacology of the drug<br>Unpredictable | Anaphylaxis |
| **C "chronic"** | Dose and time related<br>Persist for a long period of time | Osteonecrosis of the jaw with use of bisphosphonates |
| **D "delayed"** | Time related<br>Only manifests after the use of the drug | Carcinogenesis<br>Teratogenesis |
| **E "end of use"** | Associated to the withdrawal of the drug | Opiate withdrawal syndrome |

| | | |
|---|---|---|
| **F "failure"** | Undesirable change in the drug's efficacy<br>Associated with drug interaction | Deficient dosage of oral contraceptives |

Furthermore, we can also classify ADR according to their seriousness. ADR that result in death, are life-threatening, require hospitalisation of the patient, or require that the patient's hospitalisation be prolonged, result in persistent or significant disability or incapacity or congenital anomalies, or require immediate intervention to prevent permanent damage or disability, are considered as serious.[5,6]

Owing to the aforementioned abusive and improper use, off-label use, and medication errors, it is widely regarded that most ADR are preventable. The World Health Organization (WHO) states that costs related to ADR, such as hospitalisations, have a higher economic impact than the cost of medication itself.[7] Furthermore, the figure for hospitalisation rates related to ADR in Europe has been estimated to be approximately 2.5 to 10.6%.[8] This has a major implication, since ADR constitute one of the leading causes of death across the globe.[9]

Therefore, we cannot acknowledge the benefits of each drug without mentioning the risks of its use.[10] This is taken in consideration on the WHO definition of Pharmacovigilance: "The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem".[1]

One of the main events that lead to the development of Pharmacovigilance as we know it today, was the thalidomide disaster, in 1961. This medicine was used by pregnant women as an antiemetic for morning sickness. The utilisation of this medicine resulted in thousands of birth defects across the world, as children were born with phocomelia. Having observed that, in 1963, at the Sixteenth World Health Assembly, WHO adopted resolution 16.33 that cemented the necessity for a quick dissemination of information relating to a potential ADR. Consequently, in 1968, the WHO Pilot Research Project for International Drug Monitoring was created, whose aim was the creation of an international system, for the detection of previously unknown, or poorly researched, ADR.[1]

Nowadays, Pharmacovigilance has the utmost importance throughout medicines' lifecycle. The safety of a medicine has to be assured as soon as it starts to be administered to humans, namely, in subjects participating in clinical trials.[11] Notwithstanding, clinical trials have many limitations, making it challenging to understand the full safety profile of a drug when it is first introduced on the market. In clinical trials, there is a homogeneous population, usually excluding special populations – such as pregnant women, children and the elderly – and individuals with concomitant diseases and medication. Adding to this, since this population is

comprised of a reduced number of individuals, it is very difficult to detect rare ADR in this phase. Finally, we have to take into consideration that these studies go on for a relatively short period of time, contrary to the real-world use of the medicine, masking delayed type reactions. That being said, we can safely say that there is a real need for real-world data to better understand the safety profile of medicines.[12]

This is where Pharmacovigilance plays an important role, collecting and analysing data, which can originate safety signals. Beyond that, the analysis of the impact that this new information may have in the risk-benefit relation of the medicine has a beneficial influence.[11]

In Europe, the Pharmacovigilance System consists of the regulatory network composed of each Member State's National Competent Authority (NCA), the European Medicines Agency (EMA), and the European Commission (EC). In the centre of this network, there is the EMA's Pharmacovigilance Risk Assessment Committee (PRAC), created in 2012.[13]

Although, before 2012, the European Union existed as a well-established market, where medicinal products were inclusively approved by the Centralised Procedure, several safety signals were identified by Member States, such as the association of cardiovascular disorder with rosiglitazone, and fatal overdose risks with dextropropoxyphene. However, the Member States took different regulatory actions on these safety issues.[14]

Having always the objective of protecting Public Health in the European Union, and reducing the impact of ADR, there was a necessity to revise the legislation, and the European Pharmacovigilance System. That happened in July 2012, when Regulation (EU) No. 1235/2010 and Commission Implementing Regulation (EU) No. 520/2012 came into force, strengthening the European System, and better defining duties and responsibilities to all the stakeholders.[13,15,16]

It is important to highlight one of the changes this legislation brought, by allowing patients and general population to report ADR directly to each Member State's NCA. In this regard, each Member State was responsible for the conception of a website, simplifying the reporting process, for both patients and Healthcare Professionals (HCP).[15] In Portugal, ever since this legislation came to force, and with the creation of Portal RAM in 2012, the Portuguese website for ADR report, we can observe an increase on the number of spontaneous reports to the Portuguese Pharmacovigilance System, as later on described.[17,18]

### 1.2. Spontaneous Reporting as a Methodology

Spontaneous reporting is recognised as one of the most relevant, and often used method to collect and assess real world drug safety data.[12] It is defined by Good Pharmacovigilance Practices (GVP) as: ”an unsolicited communication by a HCP, or consumer to a NCA, Marketing Authorisation Holder (MAH) or other organisations (e.g., regional pharmacovigilance centre, poison control centre) that describes one or more suspected adverse reactions in a patient who was given one or more medicinal products.”[19]

Regardless of whether the notifier is the patient or another person, there are four elements of information that have to be included in order to be considered a valid report. These are an identifiable patient – albeit personal data has to be anonimised –, an identified reporter, at least one suspected medicinal product, and at least one suspected adverse reaction.[19]

This methodology allows to overcome some of the clinical trials’ limitations, by collecting safety data on the real-world use of all drugs in large heterogeneous populations. In addition to these advantages, it also enables to understand the benefit-risk relation of the medicine, throughout its lifecycle, as well as perceive any adverse effects related to its continuing use.[12]

However, spontaneous reporting has some limitations, particularly underreporting. It is estimated that over 94% of all ADR are not reported, and this can lead to some risks not being identified.[20] Many factors contribute to the underreporting of ADR by HCP, most strikingly the lack of interest and time, ignorance on what should be reported, and the perception that a single report will not make a difference.[21] On the other hand, selective reporting can overemphasize to a risk that is not actually real.[20]

As mentioned before, European Legislation encouraged reporting by the general population. At the beginning of legislation implementation, this was a highly discussed topic, as this method was questioned when compared to HCP reporting in regard to the quality of reports, but also claiming that patients will introduce noise to the system, hindering signal generation.[22] However, as time progressed, the opposite effect was observed. In a systematic review published in 2017, it was concluded that not only the patient reporting was valuable, but also contributed to signal generation. This was a result on a different perspective that patients bring, as they tend to report more subjective ADR, with a greater day-to-day relation. Therefore, patient reporting adds to HCP reporting leading to new data and signal generation.[23]

Causality assessment aims to establish a causal relationship between an ADR and a suspected drug. There are three established methods to assess causality: global introspection, probabilistic methods, and algorithms. These three methods have a common characteristic,

they rely on the available data to assess causality.[24] However, the data that reaches Pharmacovigilance Systems is not always good enough to be able to provide a clear assessment. This reaffirms the importance on having an identified notifier, as it opens the possibility for the assessor to contact him/her, as necessary, in order to collect additional data.[25]

### 1.3. The Portuguese Pharmacovigilance System

In Portugal, even though the toxicity of medicines has been studied since the beginnings of the 1950's, it was only in 1992, with the publication of Normative Order No. 107/92, of 1992-06-27, that the Portuguese National Pharmacovigilance System (*Sistema Nacional de Farmacovigilância* – SNF) was established.[10,12,26]

Following several reorganisations after its creation, the Portuguese System operates along EMA and the EC, with the NCA, *Autoridade Nacional do Medicamento e Produtos de Saúde, I.P.* (Infarmed), being the responsible party. As stipulated by the Legislation, all healthcare stakeholders, health systems, HCP, MAH, and patients, also take an active role in this System.[27,28] Lastly, being a decentralized system, it has the participation of ten Regional Pharmacovigilance Centres (PC). Eight of these Centres are distributed in Continental Portugal, with each Autonomous Region having a respective PC.[29]

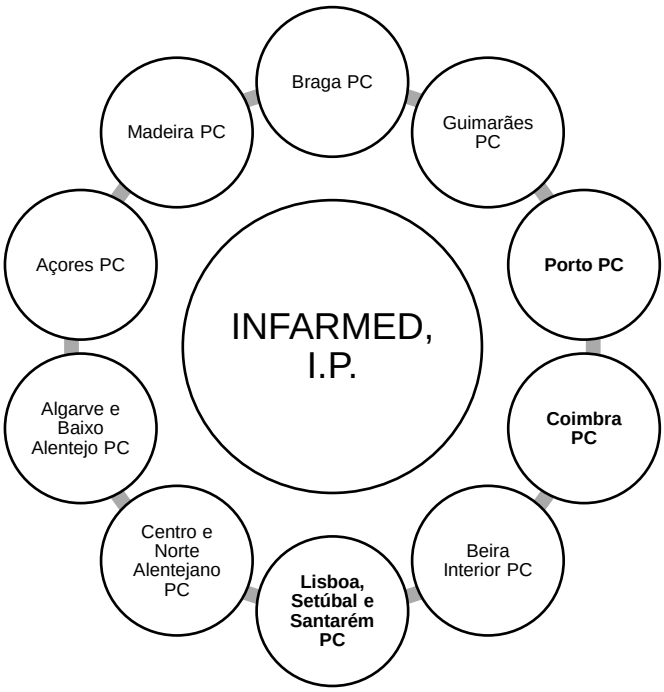


Figure 1: Regional Pharmacovigilance Centres organisation. Adapted from: INFARMED - Autoridade Nacional do Medicamento e Produtos de Saúde I.P. Notificação de Reações Adversas (RAM) FAQ. Available on: https://www.infarmed.pt/web/infarmed/faq

PC have the responsibility to receive, handle and evaluate each report for a suspected ADR, including the causality assessment of their respective regional area. Furthermore, they also have the responsibility to constantly disseminate and promote information regarding the safety of drugs, reaching both HCP and the general population, and conduct pharmacoepidemiologic studies, with collected data.[30]

Portal RAM, Infarmed website for the reporting of ADR, was created to accommodate the legislation changes introduced in Regulation (EU) No. 1235/2010, and became operational in June 2012. Over the years, a large increase in spontaneous reporting to the Portuguese Pharmacovigilance System has been observed. In 2017, Portal RAM was updated, in order to facilitate reporting, which ended up boosting patient reporting, from 304 total reports in 2016, to the peak of 438 in 2018, which represents a 44% increase. In 2020 patients' accounted for 350 spontaneous reports to the SNF.[15,18,31,32]

Even with a well-established System, a low ADR reporting rate is shown in Portugal, when compared to the WHO recommendation for an Optimal National Centre, of 200 reports/million habitants *per annum*.[33,34] In 2013, the first full year of Portal RAM, the number for direct reports to the National Pharmacovigilance System was around 155 reports/million habitants, however, in 2020, the number of reports has risen to approximately 325 reports/million habitants.[31,32]

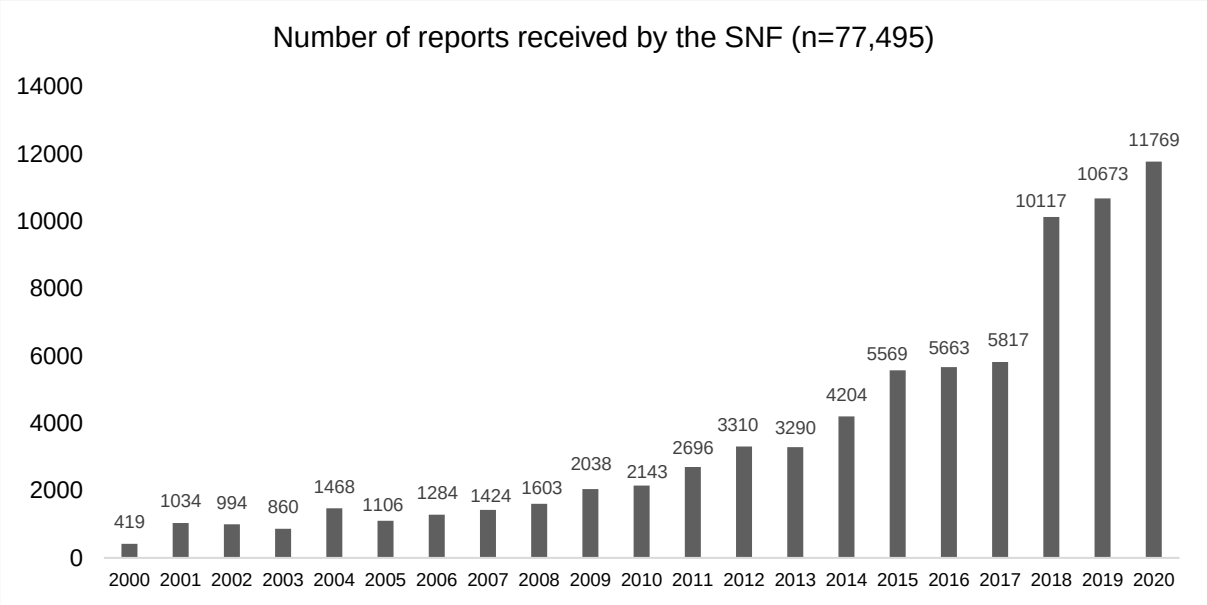


Figure 2: Number of spontaneous reports received by the Portuguese National Pharmacovigilance System, since 2000. Adapted from INFARMED, I.P. https://www.infarmed.pt/web/infarmed/entidades/medicamentos-uso-humano/farmacovigilancia/desempenho-do-snf; https://www.infarmed.pt/documents/15786/2522033/Notificacoes%2bRAM%2b2017/b0cdcfd7-627b-45eb-a0ee-134d8673b37d

In order to promote ADR reporting, for both patients and HCP, different methodologies should be applied by a PC. In a study conducted in Porto PC, four approaches to increase

ADR reporting by HCP were implemented, the hyperlink, the protocols, the educational, and the telephone approach, and their impact was measured. The hyperlink approach was established with 22 Hospitals, where a hyperlink to an online reporting form was included in the patients' electronic health record. The educational approach consisted in workshops, where the PC visited the workplace of physicians and pharmacists, to increase awareness on Pharmacovigilance. Since the PC became aware that the impact of the educational approach to report ADR diminished over time, the telephone approach was established, which focused on contacting HCP, and interviewing them based on a script regarding ADR and spontaneous reporting. The protocol approach was established with the Immunoallergology Department of a Hospital Centre in the PC region, in order to collected suspected ADR flagged by the physicians in the drug allergy consultation. They arrived to the conclusion that the two approaches that best increased reports were the educational approach and the protocol approach.[33]

In the educational approach, 900 HCP received a one-hour training session, with an additional report form and reminder card being presented to them. The results from this approach were more evident in the first four months after each session, however, when compared to HCP that did not take part in the sessions, the ADR report rate was significantly higher for a period of twelve months.[33,35]

The protocol approach, first implemented in 2004, proved to be the most efficient method to increase the number of ADR reports. These were established with three Hospital's Immunoallergology Departments, where doctors flagged cases from drug allergy consultations when a suspected ADR arises. Members of the PC regularly visit these Departments, in order to collect the reports, and fill-in the notification form.[33]

The results from the protocol approach were considered to be satisfying and worthwhile, thus its implementation ought to be recommended across other PC in Portugal.[33] Effectively, both Coimbra and Lisboa, Setúbal e Santarém PC have implemented similar protocols with Immunoallergology Departments of Hospitals in their respective regions.[36,37] These protocols are thoroughly described below.

### 1.4. Immunoallergology Protocols

Type A and Type B ADR are the most common ADR in clinical practice. Type A ADR are related to the pharmacology of the drug, thereby dose-dependent, are predictable and more common. Type B reactions, or "bizarre", while less frequent, are not related to the dose or pharmacology of the drug. In fact, they are almost unpredictable and associated with

hypersensitivity reactions. This presents a particular challenge to public health, as they are linked with higher morbidity and mortality.[4,38,39]

Hypersensitivity reactions are mediated by either immunological or nonimmunologic mechanisms, the former being commonly referred as drug allergy.[39] Drug allergy, as most allergies, is studied in Immunoallergology Departments, across several Hospitals in Portugal.[40]

Moreover, there are cases where it is important to understand the origin of an ADR, as patients may not have an alternative to a drug they have had to discontinue, and there is a very high risk for a similar, or worse, ADR in case the drug is reintroduced. In those cases, one of the standard procedures of *in vivo* confirmation is a drug provocation test, where a patient is administered a drug he/she reacted to, in a controlled environment, in order to assess the causality of the previous reaction.[41,42] This can be considered an example of a rechallenge effect, which helps to understand the existence of a causal relationship between the reaction and the drug, and is a common practice in Portuguese Immunoallergology Departments.[42–44]

In addition to the mandatory ADR report in Portal RAM, physicians need to report all anaphylaxis cases, independent of the origin, drug or not-drug, in a different database, *Catálogo Português de Alergias e outras Reações Adversas* (CPARA). Since CPARA and Portal RAM have different proprietors, and are not linked, physicians need to submit suspected drug-induced anaphylaxis reports twice. From the physician perspective, CPARA has the functionality to access a patient data and query all anaphylactic reactions, which is of added value and allows for the exchange of clinical information of the same patient between physicians. Since both are very important tools in data collection, the possibility to submit drug anaphylaxis cases to both, Portal RAM and CPARA, simultaneously should be evaluated, so that physicians do not have to do it twice, risking losing information.[45]

Immunoallergology Departments, by being in contact with patients with suspected ADR, present a great opportunity to collect real world data on medicines. This was the basis of the first documented protocol, established in 2004 by the Northern PC (now Porto PC) and the Immunoallergology Department of a local Central Hospital. The establishment of the aforementioned protocol proved to be fruitful, as it increased the ADR reporting to the Centre, with efficiency and lower costs when compared to other interventions conducted by the same Centre.[33] Another significant point is the analysis of the ADR clinical data by a physician during the consultations, which presents additional information for the causality assessment, as the preferred method for assessing causality between a suspected medicine and a suspected ADR in Portugal is global introspection by an expert physician working with each PC.[25,33]

While these protocols allow for an increase of ADR reports in the System, there is a need to understand what kind of information they bring. Since all protocols are established with

Immunoallergology Departments, there is a necessity to understand and characterise the information that will be introduced in the System.

## 2. Objectives

Considering the National Pharmacovigilance System and its impact on the generation of new safety signals for marketed medicines, we are confronted with a question when analysing these Protocols: “What is the impact of the Protocols established between Porto, Coimbra, and Lisboa, Setúbal e Santarém PC, and the Immunoallergology Departments of Central Hospitals in these regions on the Portuguese National Pharmacovigilance System?”

Thereby, we intend to characterise each established Protocol, and analyse the differences between them, both in their implementation and their operationalisation. Moreover, we aim to analyse ADR data resulting from the Protocols established between the study PC and their region’s Central Hospital Immunallergology Departments, specifically:

- to characterise the ADR reported to the Portuguese SNF, through the Protocols, their seriousness and their previous knowledge;
- to identify and characterise the medicinal products involved in these ADR;
- to analyse the causality assessment profile of the cases provided by the Protocols.

Knowing that the data generated from the Protocols comes from clinical data from a specific Department, we aim to understand if a pattern is formed in what concerns the patients’ characteristics, and also the suspected ADR that led them to seek medical help.

## 3. Methods

In order to accomplish the objectives proposed, this dissertation will be based on mixed research.

Firstly, we conducted a qualitative explanatory research on the Protocols, where we interviewed members of each PC in the study. These interviews were held in a virtual communication platform, based on a script validated by 2 Pharmacists and 1 Immunoallergologist (see Appendix I), in order to extract information from each interview as uniformly as possible.

These interviews focused on what led to the creation of these Protocols, how they are operationalised from the PC's point of view, how and since when they are established and how data are collected. Additionally, the PC members interviewed had the opportunity to speak about what they consider to be the positive and negative aspects of the implementation of the Protocols in their PC and in the SNF as a whole, and their applicability in the rest of the country.

Secondly, observational descriptive research on ADR data was conducted. The data were provided by the Portuguese NCA, Infarmed, and comprised the spontaneous reports received by the Portuguese National Pharmacovigilance System with Immunoallergologists as the notifier, between January 2000 and December 2020.

Data originated from Infarmed was analysed to remove duplicated, null and dismissed reports. Since the data contained all reports with Immunoallergologist identified as the notifier, only reports originating from Portal RAM's back office were considered as stemming from the Protocols, since this feature can only be accessed by Infarmed and the Regional PC.

In this study, we considered direct reports, *i.e.*, ADR that were reported directly to the National Pharmacovigilance System, either to Infarmed, or to each regional PC.

In order to differentiate reports that originated from the Protocols, we identified the PC that received it, taking into account the date of report, so as to establish if it was made before or after the Protocol implementation in that region.

As each report originated a case, several study metrics were analysed in a case basis. These were the patients' characteristics, the seriousness criteria, reaction progression and previous description of the ADR, and the causality assessment. The medicines involved in each case, and the suspected ADR reported, were analysed individually.

ADR data provided by Infarmed was analysed using Microsoft Office Excel 2016.

## 4. Results

### 4.1. Interviews – Qualitative Research

The interviews took place between April and September 2021, lasting on average 35 minutes, and were recorded with the verbal informed consent of both parties. In these interviews, there was the opportunity for the interviewed PC members to openly address the questions presented according to the validated script (Appendix I), with an additional chance to address relevant topics that had not yet been discussed.

The interviewees covered the implementation of the Protocols in their respective PC, revealing expertise over the theme, and a critical approach in their analysis, having thus promoted the discussion of their strengths and weaknesses.

#### 4.1.1. Porto Pharmacovigilance Centre

The interview with the Porto Pharmacovigilance Centre was conducted on the 15th of April 2021, and it had place in a virtual meeting room, via Google Meet.

When asked about the nature of the Protocols, it was stated that in the first Protocol that Porto PC implemented, in 2004, the HCP from the Immunoallergology Department of one of the largest hospitals in Porto made the first approach, by reporting they had several suspected adverse reaction cases, more specifically allergic reactions, that they could not report to the SNF, due to a lack of Human Resources. The PC members agreed to visit the Hospital to collect that information, from the clinical processes of the patients, into an Infarmed template notification sheet, which then followed the normal course of a spontaneous report in the SNF.

Regarding the motive that led to the search for its implementation, the PC referred the low report rate that was observed at the time, and the willingness of the Porto PC to find new ways to collect ADR information to the SNF. This information is scattered all over the National Healthcare Service (*Serviço Nacional de Saúde* – SNS), therefore the team of this Centre is always searching for ways to collect the data to the SNF, and increase the knowledge of the safety profile of medicines, without overburdening the HCP of these institutions.

This was also considered to be one of the main goals of the Protocols, according to the PC. Additionally, the transfer of knowledge between the Porto PC and the HCP participating in the Protocols was highlighted as another goal. “Many times, these professionals contact us to ask for some information, if there are any similar cases to a case that they receive and that is new to them, they ask us if there are more similar reports. They ask a lot of questions about

comparison of excipients […]". This share of knowledge allows both the Centre to gather information that would otherwise be lost, and HCP, who, on a daily basis, deal effectively with these suspected allergies, to better understand drugs and their interactions with other drugs or even other substances.

In 2021, the Centre had three of these protocols. The first, which was also the pioneer in the whole country, was signed in April 2004, with a Central Hospital in Porto. After that, the second protocol was established in July 2007, with a Children's Hospital in Porto, which is no longer active, as a consequence the protocol was transferred to the new Hospital Centre that was created. Finally, the third protocol was established with a Hospital in Vila Nova de Gaia, in August 2009. The Centre also had a fourth protocol, with an Hospital in Guimarães, however, with the creation of the Guimarães PC, the protocol came under its scope.

The initiative for the establishment of the Protocols came both from the Hospitals, in the first Protocol ever established, and from the Porto PC, in all other Protocols. The idea was to find institutions with well-established Immunoallergology Departments and propose the implementation of Protocols, mimicking the first one established, which was accomplished with another Hospital in Porto and a Hospital in Vila Nova de Gaia.

The Protocols were established in a similar way: they all started with a phone call with the head of the Immunoallergology Department of each Hospital. Then, a training meeting was arranged, where the importance of Pharmacovigilance was emphasised, and how relevant the data the Department was collecting is to the SNF. Finally, a document was signed to formalise the Protocol between the two entities, the Hospital Centre and the Porto PC.

Data collection happened in a similar way in all Hospital Centres. To collect the data, the members of the PC visited the Hospitals after receiving the indication, by phone call or by e-mail, from the responsible physician of the Protocol, in each Hospital. The cases were flagged from the drug allergy consultation, then the physicians stored the patient's clinical record with a suspected ADR in a separate location, so that the members of the Porto PC could collect the relevant data. These members collected the information of each case, namely the suspected ADR, the date when it occurred, the details of the suspected medicine, the seriousness of the reaction, and any other clinically relevant information, such as previous reactions and concomitant diseases and medication. The patient's personal data were always anonymous, and the only information that was collected were their initials, date of birth, and gender. Finally, in the Protocols established with Porto PC, each Director of the Immunoallergology Department of their respective Hospital was considered as the notifier, which is one of the four fundamental elements to consider a report as valid.

Regarding the perceived impact the Protocols have had in the Porto PC, it was considered to be highly positive. The PC believes that the Protocols allowed them to raise awareness with HCP to Pharmacovigilance and the importance of reporting ADR to Infarmed. The raise in the spontaneous report in the region of Porto also assumes an important role in the Key Performance Indicators (KPI) of this Centre to Infarmed, besides raising the knowledge of the safety profile of drugs currently marketed. Additionally, it was also considered that the information transfer between the PC and the Immunoallergologists was one of the main drivers for the success of the Protocols, as it allowed a continuous flow of communication between the Centre and some of the main Central Hospitals in the region, ensuring specialised know-how on drug safety during day-to-day clinical practice.

The perceived impact was also positive, when considering the whole SNF, since most of the ADR recorded at the Immunoallergology consultations, and as a consequence originating from the Protocols, were considered as serious. Additionally, it was the understanding of the PC that these ADR would not have been reported if it was not the existence of Protocols. This was mainly attributed to the lack of availability to report such cases by the HCP, and one of the main causes that led to the implementation of the Protocols, which allowed the Centre's members to do the reporting to Portal RAM themselves.

These aspects – the increase in ADR reporting to Infarmed, and a closer collaboration with experts in drug allergy – were also the ones highlighted as the main positives to be drawn from these Protocols. However, there were also negative aspects to be raised, and the bias that these data could introduce in the SNF was the main concern. The Porto PC acknowledged that the ADR resulting from these Protocols were of mainly allergic origin, something that may not correspond to normal clinical practice, recognising that this bias has to be taken into consideration when data are analysed.

Nonetheless, there are opportunities for improvement that have already been identified by the Porto PC team to strengthen these collaboration Protocols. Firstly, the implementation of an automated system to collect information of ADR directly from the patients' health records was seen as added value. This is because, spending part of their days collecting cases *in loco* at the Hospitals creates a serious limitation, and as a consequence, the Porto PC team is beginning to be affected by the lack of Human Resources to collect these data. This revealed itself as an additional problem, when we were confronted with the difficulty in automating this process, since the clinical records are still made on paper, thus there being no computerised medium in which to handle and collect the data. Additionally, another constraint was raised in the reporting of ADR during clinical practice of these doctors, which is the reporting of any allergic reaction in the CPARA portal. The fact that this notification is required by the

Directorate-General for Health (DGS, *Direção Geral da Saúde*) means that physicians and other HCP who encounter an allergic reaction to drugs have to make two distinct records, one for CPARA, and another for Portal RAM. In this sense, the need to implement a cross-reporting function was recognised, *i.e*., whenever an HCP registers an allergic reaction to drugs in the CPARA portal, this notification would also be registered to Portal RAM. This would allow Pharmacovigilance information to reach Infarmed, and to be properly treated as a suspected ADR, without requiring a double notification, facilitating the exchange of information and reducing the burden for the notifier.

On the other hand, regarding the quality of the collected information, it was mentioned that it depends only on the members of the Centre who analysed the clinical cases and collected the information to insert in Portal RAM. This is because the quality of the information in the clinical reports was considered to be excellent, with a detailed description of the suspected drug allergy, as well as the patient's history, concomitant medication and other relevant information for the causality assessment between the ADR and the suspected drug. Frequently, however, a relevant piece of information was not described in the clinical files, which is the brand name of the suspected medicinal product. This could be important as different medicines with the same active substance may have, for example, different excipients, which could hinder causality assessment, as some allergic reactions could be triggered by excipients.

When questioned "Would it make sense to implement these Protocols with other [Hospital] Departments? Which ones?", two Departments were highlighted, Oncology and Nephrology. It was the understanding of the Porto PC that oncological patients receiving treatment have an almost 100% rate of developing some sort of ADR to said treatment. However, since this is viewed as normal, it is not common for physicians or other HCP to report these suspicions to the SNF, since the benefit of the treatment clearly outweighs its risks. In addition, it was mentioned that Oncology is a relevant Department to establish a collaboration Protocol, as the possibility of observing undocumented ADR is significant, and it would be important to acknowledge that they exist so as to try to minimise their frequency and severity, and improve the quality of life of these patients. As for Nephrology, the reasoning of the Porto PC was that numerous drugs are eliminated through the kidneys, with a high incidence of ADR in these organs. Thus, it would be important to promote the awareness of HCP in this field to report the suspected ADR they come across in the course of normal clinical practice.

Concerning the applicability of the Protocols throughout the country, the Porto PC considered that it was a measure that ought to be implemented, and urged other Centres to do so. Not only because it is one of the objectives of the Centres to promote spontaneous

reporting among their target population, but also because it is the most cost-effective method to collect reports for the SNF, and thus feed it with data that otherwise would not be known, even if more suspected ADR of allergic nature are being introduced in the SNF than would be expected through spontaneous report.

It was to be expected that the information resulting from these Protocols, taking into account their origin, had some particularities. The main one highlighted by the Porto PC was the results of the provocation tests made to patients, to confirm their allergic condition. Although this information was not essential for the suspected reaction to be considered as an ADR, it was collected whenever available to Portal RAM. It is important to note that the Porto PC did not consider this information as a rechallenge, at the time of assessing causality. As this is a topic on which there is no consensus, this position was explained by stating that the provocation tests were performed in a controlled environment, often with medicines of different brands from the one in which the suspected ADR was observed, and not in the real-world context, where the patient took the medicine and had the reaction that triggered them to go to the drug allergy consultation at the Hospital.

When assessing causality, besides the information from the provocation tests, all clinical information taken from the patient's clinical file, and considered as relevant, was considered, with emphasis on the history of the reaction, concomitant medication, and underlying medical conditions, such as liver or kidney diseases.

As a final remark, it was added that the only difference these cases had in the spontaneous report circuit was the moment of the report itself, since usually each report is completed by an individual – HCP or not – and in the cases from the Protocols, the Centre's own elements made this report to the SNF.

#### 4.1.2. Lisboa, Setúbal e Santarém Pharmacovigilance Centre

The interview with the Lisboa, Setúbal e Santarém Pharmacovigilance Centre was conducted on the 17th of June 2021, and it had place in a virtual meeting room, via Google Meet.

When questioned about the essence of the Protocol, we were told that it all stemmed from a restructuration of the SNF. The team from the now Lisboa, Setúbal e Santarém Pharmacovigilance Centre was once responsible for the regions of Algarve and Alentejo, and when faced with a new region, then Setúbal and Santarém, they were confronted with a report rate lower than the one defined by Infarmed as the ideal. Inevitably, this led to the Centre having to find new ways to increase the reporting rate, which could also be considered one of

the fundamental principles of the existence of said Centres throughout the country. Having identified the problem, they were then challenged to find solutions.

Firstly, they identified the Health Institutions where it would be possible to establish these Protocols, having selected a Hospital Centre in Setúbal as the main target, as it was the only one with a dedicated Immunoallergology Department. The first approach was to provide a training session to raise awareness among the HCP of that Hospital about Pharmacovigilance, and to propose a closer partnership between the Immunoallergology Department and the Pharmacovigilance Centre. This partnership aimed to allow the PC to collect and report ADR information from the drug allergy appointment that took place in the Hospital, information that would otherwise not be able to reach the SNF, both because of its volume, and also the lack of availability of the HCP for reporting it. This information, similarly to what happened with the Protocols in the Porto PC, would then be transposed to a Infarmed template Notification Sheet, that then followed the normal course of a spontaneous report to the SNF.

Additionally, this allowed for a share of knowledge, as the collected information was then analysed, and reports were made every six months – sometimes annually – so that the people in charge of the Immunoallergology Department could access the compilated information, with some basic statistical analysis. The information shared does not stop there, however, as the Centre also prepared support material for Interns who entered the Department, within the scope of Pharmacovigilance. This measure helped new HCP become aware of this often-overlooked topic.

The Lisboa, Setúbal e Santarém PC, when questioned about the motive that led to the search for the Protocol implementation, also told us about the raise of the reporting rate in the district of Setúbal, and the fact that the HCP had the insight that all the information they collected during the allergy consultations was not lost in their Department but ended up reaching the SNF.

In this respect, one of the main objectives of the Protocol establishment was to promote a culture of reporting ADR, not only among Immunoallergologists, but also among HCP in general, even if only on the more serious or less common ADR. But, until then, the main goal was to not lose information to the SNF, that otherwise could not help collect more data on the safety of medicines.

At the moment, the Centre established only one Protocol, with a Central Hospital in Setúbal. This protocol began in 2017, the year in which the Centre was established in the Setúbal and Santarém regions. Since the establishment of the Lisboa, Setubal e Santarém

PC, in 2021, contact has also been established with one of the largest Hospital Centres in Lisbon, even though the spontaneous reporting rate is robust in this region.

It was from the Setúbal e Santarém PC – now the Lisboa, Setúbal e Santarém PC – that the initiative to implement the Protocol arose, after observing the success of such Protocols in the other regions. In addition, the decision to seek these protocols was also based on a study previously mentioned, conducted by the Porto PC, in which the collaboration protocols proved to be the most cost-effective strategy for collecting suspected cases of ADR.

As a result, contact was then made with the Hospital to establish a Protocol with the respective Immunoallergology Department. A first training session was held, where the importance of Pharmacovigilance for Public Health and spontaneous reporting was discussed, as well as the importance for the SNF of the data on suspected ADR that are collected, but not reported, daily in drug allergy consultations. After this session, the members of the Hospital recognised the importance of establishing this Protocol, which was then formalised by a contract between this Hospital Centre and the Lisboa, Setúbal e Santarém PC.

For data collection, it was agreed that approximately every month, the physician in charge of the drug allergy consultation would contact the members of the Centre to visit the Hospital and collect data on suspected ADR, from the clinical records that had been identified, with the necessary information for the report to be considered as valid. The information was then collected onto an Infarmed template notification sheet, with the patient's personal data anonymised, the identification of the suspected medicine – where in most cases only the INN (International Non-proprietary Names) information was available –, and the suspected ADR. It was also emphasised that some patients had several ADR documented, with different suspected medicines, and those were considered as separate cases, therefore the same patient's clinical record may originate multiple reports. The notifier was identified as the physician in charge of the drug allergy consultation at the Department of Immunoallergology. Additionally, relevant clinical information was collected, such as concomitant medication, the history of the reaction, and the results of provocation tests performed with the suspected drug. This information was then introduced in Portal RAM, for the report to advance to the necessary steps for its assessment.

The impact that this Protocol had on the Lisboa, Setúbal e Santarém PC was perceived as very positive by this PC, as the Setúbal region had a lower reporting rate than the one defined by Infarmed, and this measure was fundamental for the Centre to increase the reporting rate, and thus achieve its targets.

On the other hand, and regarding the impact on the SNF, the message was that it is necessary to view the data resulting from the Protocols with a critical approach. First of all,

these Protocols brought the Immunoallergologist to the top of the notifiers in the SNF. Additionally, and because data were collected from drug allergy consultations, there was the perception of the expected reporting profile changing. By way of explanation, it is now expected that innovative drugs are more closely monitored, however, the drugs that tend to lead patients to seek these consultations had better known safety profiles, such as anti-inflammatory drugs, antibacterials and angiotensin-converting enzyme inhibitors.

The key positive aspects highlighted were similar to those previously pointed out, in particular the increase in spontaneous reporting, even if mainly allergic ADR, and the closer collaboration with Immunoallergologists, which also allowed for an increase in awareness for Pharmacovigilance to these HCP. Additionally, these Protocols enabled a better understanding of the medicines that are more likely to cause allergies, and the profile of the patient most commonly associated with them. However, we could also find in these points the main negative aspects. This is because, generally, the suspected drugs that made patients seek drug allergy consultations had a well-defined safety profile, and the suspected ADR were already well documented. So, although the amount of data received was large, this information was unlikely to generate new safety signals.

The Lisboa, Setúbal e Santarém PC considered that this Protocol brought an increased workload for this Centre, since the members had to physically go to the Hospital, and insert the data to Portal RAM. Thus, in order to improve it, it would be desirable not to require the members of these Centres to collect the data *in loco*. For this, the increased participation of the Immunoallergologists in spontaneous reporting would be necessary, selecting the most relevant cases, either by seriousness or by their particularity, so as not to overburden these HCP. Since the registration of severe ADR has to be done in the CPARA Portal by the HCP, it was considered of general interest that this information migrated to Portal RAM, thus allowing HCP to make only one record, saving time, and feeding the two equally important platforms simultaneously.

However, and taking into account the perceived added value of this Protocol, and the burden it takes away from HCP, this PC believed that it made sense to implement similar approaches in other Hospitals Departments. The Oncology Department was thus referred, given the quantity and severity of the ADR observed during the treatments of these patients. Additionally, the Department of Infectiology was also suggested, as many of the drugs used in the treatment of these patients are also innovative, making it more important to monitor them closely.

The stance was the same when asked about the national panorama, that the Protocols should be implemented throughout the country. Firstly, and as previously mentioned, they

allowed a closer relationship between Pharmacovigilance professionals, and the HCP who deal with potential ADR every day. And on the other hand, this proximity also allowed a closer and more effective monitoring of the use of medicines in a real-world context, thus strengthening the SNF.

When asked if the originating data from the Protocol had any peculiarity, we were told that both the most reported medicines in this Protocol – which were medicines with well-known safety profiles – and the most commonly encountered suspected ADR – which were related to an allergic condition, such as anaphylaxis, angioedema and urticaria – could be considered as interesting particularities. Additionally, what may be considered as the most particular data resulting from this Protocol, was the reintroduction of the suspected drug during Immunoallergology consultations, through provocation tests. In this Protocol established between the Central Hospital in Setúbal and the Lisboa, Setúbal e Santarém PC, it was considered that we are in the presence of a “rechallenge effect-like”, and that this information would then be of further relevance when the clinical expert is assessing causality.

We could appreciate that the patient’s clinical information was used when assessing causality. This is done by a clinical expert with experience in Pharmacovigilance who, in the Lisboa, Setúbal e Santarém PC, uses the Bradford-Hill criteria to help determine the degree of causality between the suspected drug and the ADR. In this assessment the patient’s clinical history, concomitant medication and possible dechallenge and rechallenge effects, if available, are then considered, consequently contributing to the fact that suspicions of ADR arising from this Protocol may reach the grade of “Definitive” causality more often than in the regular spontaneous reporting.

To conclude, it was also emphasised that underreporting could be attributed to the lack of Human Resources in the Healthcare Facilities of the country, thus leading to an overwork of HCP, which made it impossible for them to notify the ADR they encounter. It is therefore incumbent upon the members of the SNF to find ways to combat underreporting, and improve the System, which still has a lot of scope to develop.

#### 4.1.3. Coimbra Pharmacovigilance Centre

The interview with the Coimbra Pharmacovigilance Centre was conducted on the 21st of September 2021, and it had place in a virtual meeting room, via Google Meet.

The essence of these Protocols, as defined by the Coimbra PC, was to identify the hypersensitivity reactions to drugs that HCP encountered during their clinical practice, so that the PC could collect and process these data, resulting in its introduction in the SNF.

It was also from this perspective that the major motivations for the implementation of these Protocols arose. It was necessary to identify cases of hypersensitivity to drugs in order to subsequently characterise them, identifying the most frequently involved medicinal products and the profile of the patients most likely to suffer these ADR. Contrary to the previous, it was understood that the process of ADR reporting by HCP could be time-consuming and too complicated, which caused them to not report the suspected ADR they may encounter, making the SNF lose valuable information. As such, the implementation of the Collaboration Protocols was also sought in order to collect all possible information for the SNF, improving the capture of information, and contributing to a better monitoring of drugs, minimising the loss of information.

On that account, two main objectives were defined with their implementation. Firstly, there was the monitoring of the safety of medicines associated with hypersensitivity ADR, and the collection of data to characterise them, and the population that suffers most from this type of ADR. The other major objective was defined as the implementation of a methodology to allow for an alternative form of spontaneous reporting, which enabled the identification and collection of these cases in a more simplified way for HCP, tackling underreporting, which is one of the main limitations of this method.

At the moment, the Coimbra PC has two active Protocols, one with the Immunoallergology Department of a Hospital Centre in Coimbra, established in November 2017, and the other one with the Immunoallergology Department of a Hospital Centre in Aveiro, that started in January 2020.

The initiative for the implementation of these Protocols came from the Coimbra PC, which proposed them to the two Hospital Centres. This proposition arose not only due to the aforementioned interests for the Centre, but also due to the benefits that the Immunoallergology Departments could have in collaborating with the PC. This is because they had at their disposal a database with already processed data on hypersensitivity to medicinal products – the number of cases reported, the types of reaction, and the suspected drugs – which may be useful for the medical teams at these Hospitals, for research and publication purposes.

For the Protocols to be established with the Hospital Centres, training sessions on Pharmacovigilance and the spontaneous reporting method were given to the HCP involved. In order to determine a work and information flow for these Protocols, a written agreement was defined, describing the scope of the Protocol, what its objectives were, and how data were to be collected and processed. Two documents have been made so far, one for the Hospital

Centre in Coimbra, and one for the Hospital Centre in Aveiro, which were subsequently signed by both parties, each Hospital Centre and the Coimbra PC, for the Protocols to be made official.

Data were collected differently depending on the Hospital Centre. In Coimbra, the physician responsible for each patient's consultation identified and collected the clinical reports with the suspected hypersensitivity ADR, anonymising the patients' personal data. After that, the reports were kept in a separate location, so that the members of the Coimbra PC visited the Hospital and collected the cases, approximately on a monthly basis, to then insert the data in Portal RAM. The physician responsible for each patient, who is identified as the notifier, would then receive a copy of the reporting form. By contrast, in Aveiro, the process is different, given the distance to the Centre. In this case, there was only one physician responsible for the consultation of drug hypersensitivity, who similarly collected all the relevant clinical reports, with the patients' data anonymised. However, the clinical reports were then sent by e-mail, approximately monthly, although there is no well-defined periodicity. After the Coimbra PC received the cases, the data were inserted in Portal RAM, and the proof of the report was sent to the physician, who was also identified as the notifier.

As for the impact that the Protocols have had on the Coimbra PC, it was considered to be positive. Firstly, the Protocols made the increase in the reporting rate possible, meeting the objectives set by Infarmed. Additionally, they also allowed a better characterisation of hypersensitivity ADR, fostering research work in this area, as it led to the publication of several scientific articles by the PC.

Regarding the SNF, it was also considered to have a positive impact, as it allowed the gathering of information that would otherwise be lost. However, the Coimbra PC considered important to note that the Protocols could introduce a bias in the System, by having what could be treated as selective reporting, as more cases of hypersensitivity are being collected when compared to other types of ADR, and also placing the Immunoallergologist at the top of the notifiers, in detriment of other HCP. The balance remained positive, in the PC opinion, if we considered the existence of these Protocols in the analysis of SNF data, and discussed it with a critical approach.

This bias was also considered as the least positive point of the Protocols, according to the PC, although it could be countered by recognising that this limitation existed, analysing the data accordingly. As for the positive points, the increased reporting rate, and the dissemination of the SNF among HCP, were highlighted. The information that was collected, even if it may bring biases to the System, was considered as very important, because it was information that otherwise would not be collected and analysed. It also comprised mainly of serious ADR, so is of added value. In addition, the importance that these alternative methods had for the collection

of information on Pharmacovigilance was mentioned, and that the PC should always look for new ways to collect information on the safety of medicines. In the Coimbra PC viewpoint, these Protocols brought another perspective of what the alternatives to be developed in the future may be. These new forms of data collection could be crucial for the SNF, and for regulators to make decisions about the safety profiles and risk-benefit relations of medicinal products on the market.

In this respect, the Coimbra PC considered that the improvements to be implemented ought to encompass the SNF as a whole, not focusing particularly on the Protocols with Immunoallergology Departments. One of the improvements that would make sense to be implemented at national level was the automated collection of information from the Clinical Risk Management Systems of the various Health Institutions in Portugal directly to Portal RAM. This would involve including the option to register ADR that are reported by patients to HCP in the Hospitalar IT Systems. Ideally, there would then be an automated communication to Portal RAM, avoiding a new record on another platform to report a suspected ADR. This method was already used in an Oncology Hospital in Coimbra, where HCP registered the ADR that they come across in the Hospital's IT System, which in turn communicated directly to Portal RAM, creating an automatic report. This facilitated their work, and the work of the PC members, as they did not need to travel to the Hospital to collect ADR data, to insert it manually in Portal RAM, as in the case of Collaboration Protocols with Immunoallergology Departments. Additionally, the need for double registration of ADR of hypersensitivity to drugs in Portal RAM and CPARA was mentioned, and it was considered of added value that this information should automatically migrate between the two platforms, since HCP tended to prioritise the notification in CPARA, and the information on drug hypersensitivity would otherwise never reach the SNF.

Nonetheless, the opinion was that it made sense to establish Protocols with other Departments, as it would standardise the information collected, so that not only allergic reactions would enter the System by this method. Although we should be able to have data from all specialties, Dermatology was highlighted, as we can observe several serious, potentially fatal reactions, such as DRESS Syndrome, Stevens-Johnson Syndrome and Lyell Syndrome, even if these are associated to hypersensitivity reactions. Additionally, Neurology, which has gained a new relevance with COVID-19 vaccines, with their association with Guillain-Barré Syndrome, was also mentioned. Finally, Cardiology was also discussed, as several drugs were associated with abnormalities in the QT interval, having even been withdrawn from the market due to safety issues, and Nephrology, as it is related to the organ system closely associated with drug elimination.

The sentiment was the same when discussing its implementation throughout the country. It made sense to establish the Protocols, for uniformity reasons since we were talking about a National System. Also for data analysis purposes, in order to understand the similarities and differences between the various regions of Portugal.

It was also expected that the information obtained through the Protocols had its particularities, and the Coimbra PC confirmed it. Since the information was extracted from the patients' clinical records, and these were described in more detail, it was possible to collect more complete data. It was therefore common for the Coimbra PC to have information available on the patient's medical history, concomitant medication and possible other suspected ADR associated with other medicines. The PC members could also find information regarding the provocation tests performed during the consultation, which were carried out with the various suspected drugs, or similar drugs, which may allow a better characterisation of the ADR observed. These tests were of great relevance for the assessment of causality.

While all relevant clinical information was taken into consideration when assessing causality, it was important to reinforce that provocation tests were not considered as a rechallenge, for the Coimbra PC. However, it was their understanding that the results of provocations teste were of great importance and can be considered confirmatory when the patient reverts to the ADR that motivated them to seek medical help in the first place.

### 4.2. ADR spontaneous report data from Immunoallergology Protocols – Quantitative Research

Overall, data from Infarmed were received on the 3rd of November 2021. Regarding these data, in total, in the period between January 2000 and December 2020, the SNF received 3324 reports stemming from Immunoallergologists. From these, 2495 (75.06%) were concerned to the Protocols involving the Porto PC, Coimbra PC, and Lisboa, Setúbal e Santarém PC.

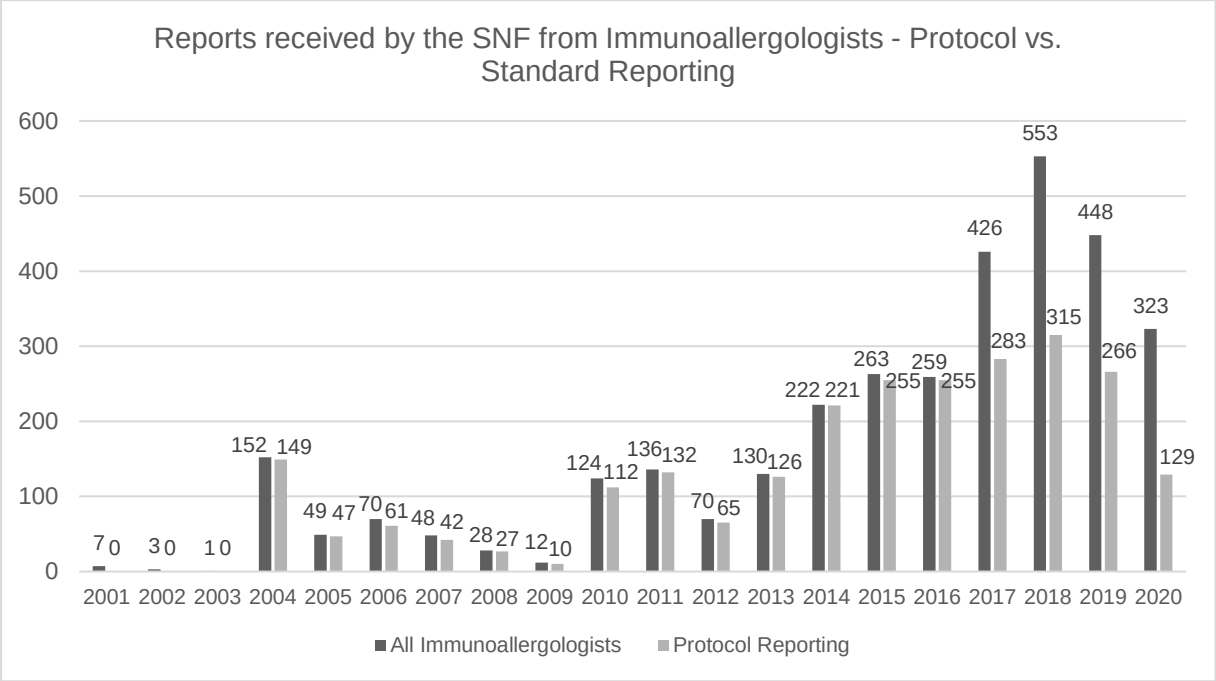


Figure 3: Reports received by the Portuguese National Pharmacovigilance System from Immunoallergologists – Protocol vs. Standard Reporting (n=3324)

It is important to note that each case may concern to more than one reaction, and to more than one suspected medicine. Thus, out of the 2495 cases, 2814 suspected medicines and 7577 suspected ADR were identified. We could also analyse that, from the 2495 cases, 1972 (79.04%) were classified as serious.

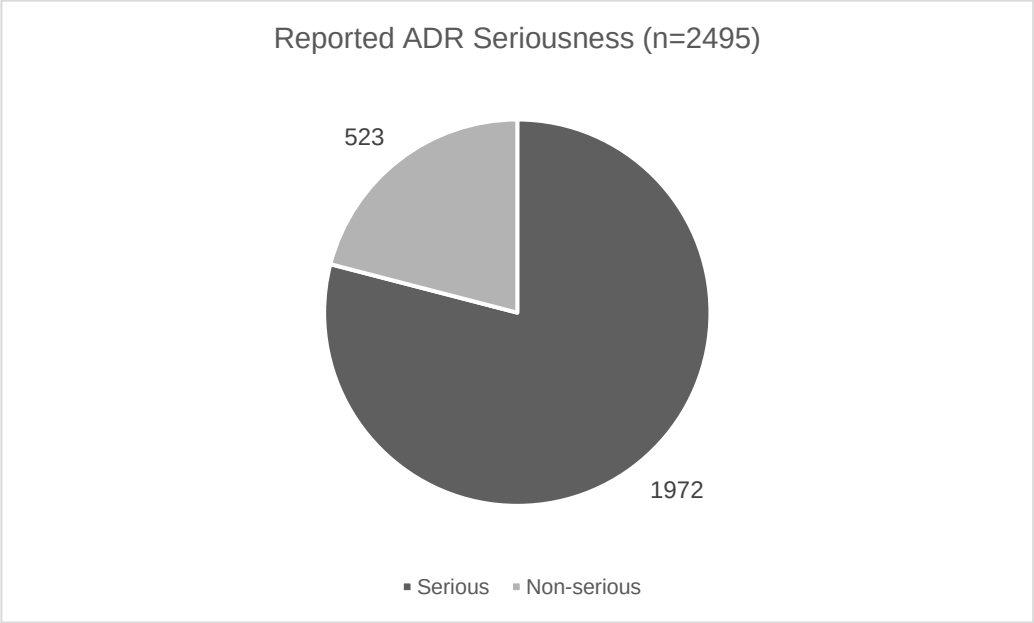


Figure 4: Reported Adverse Drug Reactions by seriousness

Concerning data from the Protocols, the 2495 cases were distributed as shown in Table 2. It is of note that only valid cases, as defined in the Methods section, were considered.

Table 2: Total reports received through the Protocols, organised by Pharmacovigilance Centre

| **Reports by PC (n=2495)** | | |
|---|---|---|
| | *Frequency* | *Percentage* |
| Coimbra PC | 86 | 3.45% |
| Serious | 83 | |
| Non-serious | 3 | |
| Lisboa, Setúbal e Santarém PC | 358 | 14.35% |
| Serious | 207 | |
| Non-serious | 151 | |
| Porto PC | 2051 | 82.20% |
| Serious | 1682 | |
| Non-serious | 369 | |

#### 4.2.1. Patients' characteristics

The patients' affected by the ADR profile (n=2495) could be described as mainly female (60.56%), aged between 35-54 years old (23.16%). It is also relevant to mention that 19.88% of the total sample (496 cases) were children and adolescents under 18 years of age. However, it was not possible to analyse patient age data in 710 cases (28.46%). A summary of the characteristics of the population can be consulted in Table 3.

Table 3: Patients' characteristics, and Adverse Drug Reactions seriousness summary

| **Gender (n=2495)** | | |
|---|---|---|
| | *Frequency* | *Percentage* |
| **Female** | **1511** | **60.56%** |
| Serious | 1214 | 80.34% |
| Non-Serious | 297 | 19.66% |
| **Male** | **957** | **38.36%** |
| Serious | 740 | 77.32% |
| Non-Serious | 217 | 22.68% |
| **Data Not Available** | **27** | **1.08%** |
| Serious | 18 | 66.67% |
| Non-Serious | 9 | 33.33% |
| **Age Group [years] (n=2495)** | | |
| | *Frequency* | *Percentage* |
| **[0-17]** | **496** | **19.88%** |
| Serious | 336 | 67.74% |
| Non-Serious | 160 | 32.26% |
| **[18-24]** | **99** | **3.97%** |
| Serious | 84 | 84.85% |
| Non-Serious | 15 | 15.15% |
| **[25-34]** | **177** | **7.09%** |
| Serious | 155 | 87.57% |

| | | |
|---|---|---|
| Non-Serious | 22 | 12.43% |
| **[35-44]** | **283** | **11.34%** |
| Serious | 248 | 87.63% |
| Non-Serious | 35 | 12.37% |
| **[45-54]** | **295** | **11.82%** |
| Serious | 256 | 86.78% |
| Non-Serious | 39 | 13.22% |
| **[55-64]** | **218** | **8.74%** |
| Serious | 198 | 90.83% |
| Non-Serious | 20 | 9.17% |
| **[+65]** | **217** | **8.70%** |
| Serious | 168 | 77.42% |
| Non-Serious | 49 | 22.58% |
| **Data Not Available** | **710** | **28.46%** |
| Serious | 527 | 74.23% |
| Non-Serious | 183 | 25.77% |

### 4.2.2. Suspected medicines

Of the 2495 total cases, 2814 suspected drugs were identified. Most cases had only one suspected medicine reported, however, spontaneous reports with 5 suspected medicines were also recorded.

Table 4: Number of suspected medicinal products per report

| **Suspected medicinal products per report (n=2495)** | | |
|---|---|---|
| | *Frequency* | *Percentage* |
| 1 medicinal product | 2240 | 89.78% |

| | | |
|---|---|---|
| 2 medicinal products | 211 | 8.46% |
| 3 medicinal products | 29 | 1.16% |
| 4 medicinal products | 10 | 0.40% |
| 5 medicinal products | 5 | 0.20% |

We could verify that 62.01% (1745 drugs) of the suspected drugs identified in the reports made through the Protocols, had the brand name of the drug described.

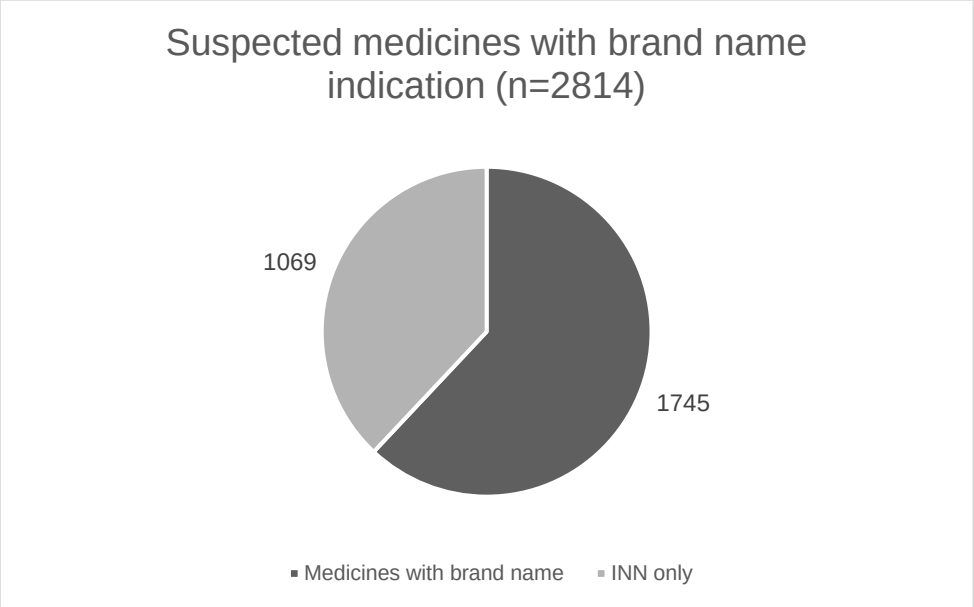


Figure 5: Number of suspected medicines with brand name description

Regarding the suspected medicinal products, the analysis was done with reference to the INN. In the table below, we can see the 10 most notified INN, the full list can be found in Appendix II.

Table 5: Top 10 suspected medicines by reporting frequency, by International Non-proprietary Names

| **Suspected medicines reporting frequency by INN, top 10 only (n=2814)** | | |
|---|---|---|
| | *Frequency* | *Percentage* |
| Amoxicillin + clavulanic acid | 482 | 17.13% |
| Ibuprofen | 330 | 11.73% |
| Amoxicillin | 228 | 8.10% |
| Diclofenac | 138 | 4.90% |

| | | |
|---|---|---|
| Acetylsalicylic acid | 83 | 2.95% |
| Paracetamol | 77 | 2.74% |
| Nimesulide | 53 | 1.88% |
| Lysine acetylsalicylate | 50 | 1.78% |
| Sulfamethoxazole + trimethoprim | 48 | 1.71% |
| Metamizole magnesium | 45 | 1.60% |

An analysis on the ATC code of the suspected medicines was also carried out, assessing each drug's 2nd and 5th ATC code levels. The top 10 most notified ATC codes, 2nd and 5th levels, can be seen in Table 6, while the complete non-descriptive data of the 5th level are shown in Appendix III.

Table 6: Most notified suspected medicines by Anatomical Therapeutic Chemical code 2nd and 5th levels

| **ATC codes 2nd level (n=2814)** | | |
|---|---|---|
| | *Frequency* | *Percentage* |
| J01 – ANTIBACTERIALS FOR SYSTEMIC USE | 1101 | 39.13% |
| M01 – ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS | 606 | 21.54% |
| N02 – ANALGESICS | 320 | 11.37% |
| L01 – ANTINEOPLASTIC AGENTS | 52 | 1.85% |
| N01 – ANESTHETICS | 52 | 1.85% |
| M03 – MUSCLE RELAXANTS | 45 | 1.60% |
| V08 – CONTRAST MEDIA | 44 | 1.56% |
| H02 – CORTICOSTEROIDS FOR SYSTEMIC USE | 38 | 1.35% |
| A02 – DRUGS FOR ACID RELATED DISORDERS | 32 | 1.14% |
| M02 – TOPICAL PRODUCTS FOR JOINT AND MUSCULAR PAIN | 30 | 1.07% |

| | | |
|---|---|---|
| Other | 494 | 17.56% |

**ATC codes 5th level (n=2814)**

| | *Frequency* | *Percentage* |
|---|---|---|
| J01CR02 – amoxicillin and beta-lactamase inhibitor | 481 | 17.09% |
| M01AE01 – ibuprofen | 302 | 10.73% |
| J01CA04 – amoxicillin | 229 | 8.14% |
| M01AB05 – diclofenac | 129 | 4.58% |
| N02BA01 – acetylsalicylic acid | 116 | 4.12% |
| N02BE01 – paracetamol | 76 | 2.70% |
| M01AX17 – nimesulide | 52 | 1.85% |
| J01EE01 – sulfamethoxazole and trimethoprim | 47 | 1.67% |
| J01MA02 – ciprofloxacin | 33 | 1.17% |
| J01FA09 – clarithromycin | 33 | 1.17% |
| Other | 1316 | 46.77% |

#### 4.2.3. Suspected ADR

Suspected ADR for each case were assessed on the seriousness, the reaction progression, and the Preferred Term (PT) and System Organ Class (SOC) classification of the Medical Dictionary for Regulatory Activities (MedDRA). As mentioned before, a single case could comprise of more than one single ADR, and in total, from the 2495 cases originated from the Protocols, 7577 suspected ADR were recorded. Three of the study metrics, the seriousness, the progression, and the prior knowledge of the reaction, were analysed on the basis of the spontaneous report case, and not each individual suspected ADR.

While most cases had only 1 suspected ADR (24.05%), 2 cases (0.08%) reported 12 suspected ADR. On average, each case had 3.03 suspected ADR reported.

Table 7: Number of Adverse Drug Reactions per spontaneous report case

| **ADR per case (n=2495)** | | |
|---|---|---|
| | *Frequency* | *Percentage* |
| 1 ADR | 600 | 24.05% |
| 2 ADR | 558 | 22.36% |
| 3 ADR | 516 | 20.68% |
| 4 ADR | 332 | 13.31% |
| 5 ADR | 221 | 8.86% |
| 6 ADR | 123 | 4.93% |
| 7 ADR | 84 | 3.37% |
| 8 ADR | 23 | 0.92% |
| 9 ADR | 20 | 0.80% |
| 10 ADR | 10 | 0.40% |
| 11 ADR | 6 | 0.24% |
| 12 ADR | 2 | 0.08% |

As mentioned previously, most of the recorded reactions were considered as serious, 1972 (70.04%). Table 8 allows us to understand the criteria for considering the reaction as serious. Most ADR were classified as “Clinically significant” (80.12%). In only 2.03% (40) cases, two seriousness criteria were selected.

Table 8: Seriousness criteria for reported Adverse Drug Reactions

| **Seriousness criteria (n=2495)** | | |
|---|---|---|
| | *Frequency* | *Percentage* |
| Clinically significant | 1580 | 80.12% |
| Death | 1 | 0.05% |
| Disability | 14 | 0.71% |
| Disability & Hospitalisation | 1 | 0.10% |

| | | |
|---|---|---|
| Hospitalisation | 257 | 13.03% |
| Hospitalisation & Clinically significant | 16 | 0.81% |
| Life-threatening | 80 | 4.06% |
| Life-threatening & Clinically significant | 1 | 0.05% |
| Life-threatening & Hospitalisation | 21 | 1.06% |

Reaction progression was also analysed, based on the individual cases. The vast majority of patients recovered, 2432 (97.47%) out of the total 2495 cases reported, while only 1 (0.04%) death was recorded. In cases where more than one reaction was reported, the analysis was based on a worst-case scenario, meaning that if a patient recovered from an ADR, but was still in recovery from another, we considered the case as *In recovery*.

Table 9: Adverse Drug Reactions progression

| **Reaction progression (n=2495)** | | |
|---|---|---|
| | *Frequency* | *Percentage* |
| Recovered | 2432 | 97.47% |
| In recovery | 10 | 0.40% |
| Persists without recovery | 2 | 0.08% |
| Death | 1 | 0.04% |
| Not Available | 50 | 2.00% |

We were also able to analyse whether the reported suspected ADR were previously described in the medicinal product Summary of Product Characteristics (SmPC). The results showed that while most ADR were *Previously known*, 70.34% (1755 cases), 740 reports (29.66%) were assessed as *Unknown*. The cases were considered as *Unknown* if one or more reactions reported in that case were not previously described.

The relationship between *Serious* and *Unknown* reported ADR was also analysed. Most *Unknown* ADR were considered *Serious* – 626 out of 740 cases, while most *Non-serious* ADR reported, were *Previously known* – 409 out of 1755 cases. The full analysis is descripted in Table 10 below.

Table 10: Reported Adverse Drug Reactions according to their previous description and seriousness

| **Reported ADR according to their previous description and seriousness (n=2495)** | *Frequency* | *Percentage* |
|---|---|---|
| **Unknow** | **740** | **29.66%** |
| Serious | 626 | 84.59% |
| Non-serious | 114 | 15.41% |
| **Previously known** | **1755** | **70.34%** |
| Serious | 1346 | 76.70% |
| Non-serious | 409 | 23.30% |

With regard to the suspected reaction, the SOC and PT of these were analysed in order to understand whether it would be possible to identify a pattern. When it comes to the SOC of the suspected ADR, almost half (49.48%) of suspected reactions were related to *Skin and subcutaneous tissue disorders*. The most commonly associated SOC with suspected ADR are shown in Figure 6. An exhaustive list can be found in Appendix IV.

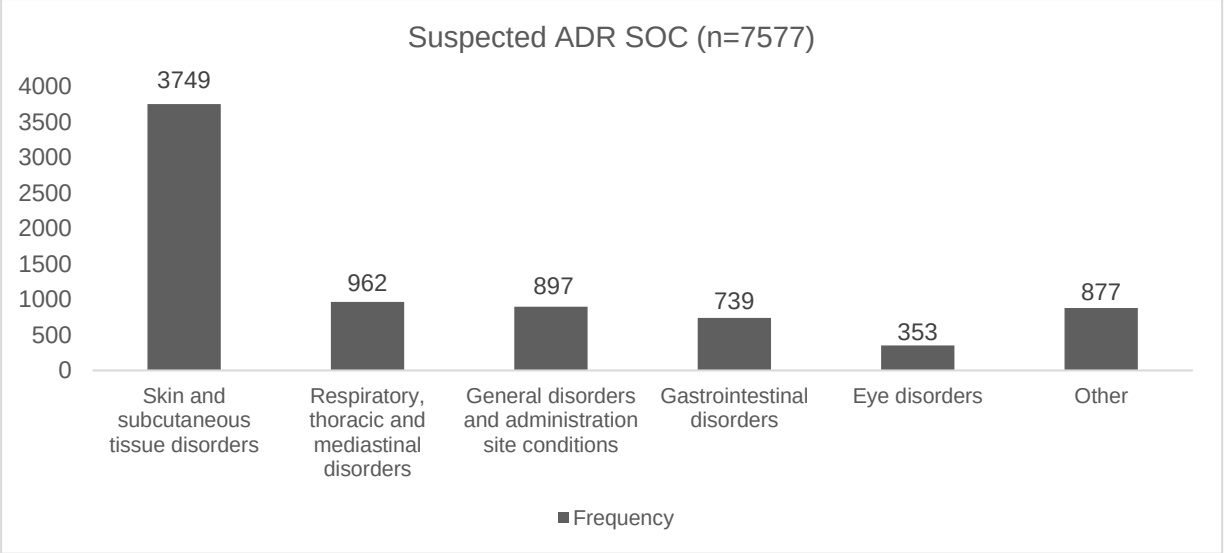


Figure 6: Suspected Adverse Drug Reactions by System Organ Class

The top 10 PT reported can be seen in Table 11, and the full list is available in Appendix V. In this top 10, seven PT related to the SOC *Skin and subcutaneous tissue disorders*, and

one to each of *Respiratory, thoracic and mediastinal disorders*, *General disorders and administration site conditions*, and *Gastrointestinal disorders*.

Table 11: Suspected Adverse Drug Reactions by Preferred Term

| **Suspected ADR PT (n=7577)** | | |
|---|---|---|
| | *Frequency* | *Percentage* |
| Rash | 679 | 8.96% |
| Urticaria | 535 | 7.06% |
| Pruritus | 506 | 6.68% |
| Dyspnoea | 408 | 5.38% |
| Erythema | 381 | 5.03% |
| Angioedema | 371 | 4.90% |
| Rash maculo-papular | 308 | 4.06% |
| Face oedema | 290 | 3.83% |
| Rash pruritic | 260 | 3.43% |
| Lip oedema | 213 | 2.81% |
| Other | 3626 | 47.86% |

The association was made between the top five most suspected medicines, that are present in 44.81% of all cases, with the three most reported PT in these cases. The percentage attributed to the PT in Table 12 are relative to the total reports containing the INN.

Table 12: Association between top 5 suspected medicines reporting frequency by International Non-proprietary Names, and top 3 associated Adverse Drug Reactions Preferred Term

| **Association between top 5 suspected medicines reporting frequency by INN, and top 3 associated ADR PT (n=2814)** | | |
|---|---|---|
| | *Frequency* | *Percentage* |
| **Amoxicillin + clavulanic acid** | **482** | **17.13%** |
| Rash | 143 | 29.67% |
| Pruritus | 102 | 21.16% |

| | | |
|---|---|---|
| Urticaria | 100 | 20.75% |
| **Ibuprofen** | **330** | **11.73%** |
| Angioedema | 91 | 27.58% |
| Urticaria | 76 | 23.03% |
| Dyspnoea | 69 | 20.91% |
| **Amoxicillin** | **228** | **8.10%** |
| Rash | 73 | 32.02% |
| Rash maculo-papular | 62 | 27.19% |
| Urticaria | 56 | 24.56% |
| **Diclofenac** | **138** | **4.90%** |
| Pruritus | 46 | 33.33% |
| Dyspnoea | 39 | 28.26% |
| Urticaria | 37 | 26.81% |
| **Acetylsalicylic acid** | **83** | **2.95%** |
| Angioedema | 23 | 27.71% |
| Dyspnoea | 21 | 25.30% |
| Urticaria | 20 | 24.10% |

#### 4.2.4. Causality assessment

Data for causality assessment was available for 97.07% (2422) of cases. It is important to note that only the assessment performed by the NCA is considered as relevant, so cases with causality assessment performed only by the notifier weren't considered as valid.

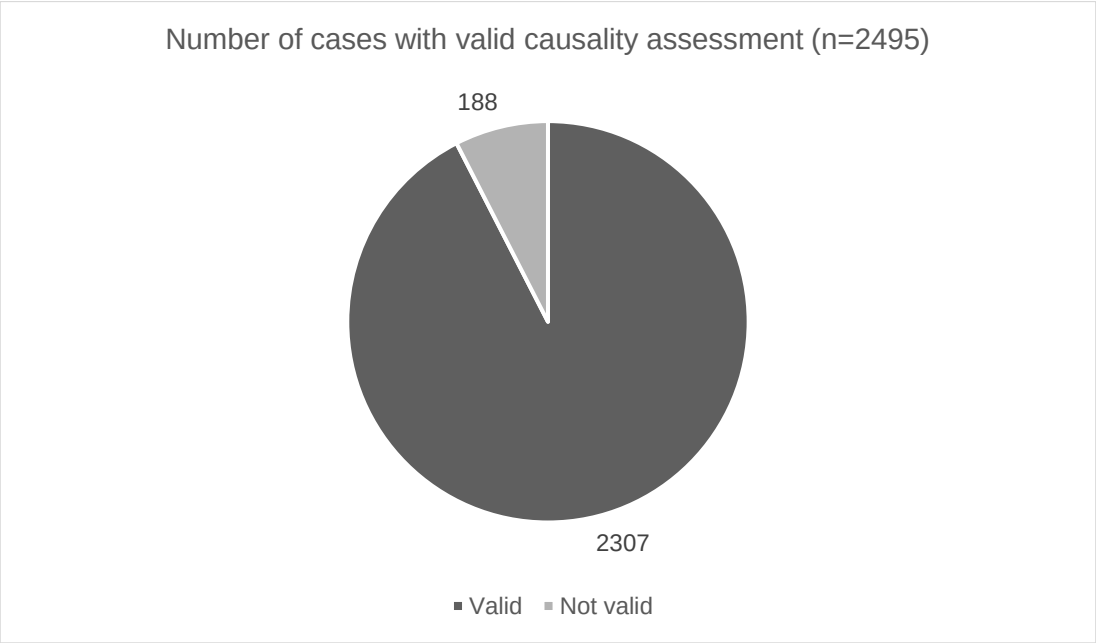


Figure 7: Number of cases with valid causality assessment

The results of the causality assessment were analysed on the basis of the spontaneous report case, and are presented in Table 13, according to the WHO scale, ranging from *Certain* – the most likely represent an association between drug and ADR – to *Unassesseable/Unclassifiable*. The below analysis was performed on a case basis, where the classification that had most likelihood of the suspected drug causing the suspected ADR was chosen.

Table 13: Causality assessment results

| **Causality assessment results (n=2307)** | | |
|---|---|---|
| | *Frequency* | *Percentage* |
| Certain | 252 | 10.92% |
| Probable | 1852 | 80.28% |
| Possible | 190 | 8.24% |
| Unlikely | 3 | 0.13% |
| Conditional | 10 | 0.43% |
| Unassesseable/Unclassifiable | 0 | 0.00% |

As we can see, suspected ADR stemming from Protocols was assessed with a classification of *Probable* or higher in 91.20% of instances, 2104 cases out of 2307 with a valid final causality assessment.

Lastly, we analysed the association between causality, previous knowledge, and seriousness of the reported ADR, as in Table 14. The proportions attributed to the previous knowledge are relative to the causality assessment, while the proportions attributed to the seriousness, are relative to the previous knowledge, of each case.

Table 14: Suspected Adverse Drug Reactions by causality assessment, previous knowledge, and seriousness

| **Suspected ADR by causality assessment, previous knowledge, and seriousness (n=2495)** | | |
|---|---|---|
| | *Frequency* | *Percentage* |
| **Certain** | **252** | **10.10%** |
| *Unknown* | *54* | *21.43%* |
| Serious | 47 | 87.04% |
| Non-serious | 7 | 12.96% |
| *Previously known* | *198* | *78.57%* |
| Serious | 170 | 85.86% |
| Non-serious | 28 | 14.14% |
| **Probable** | **1852** | **74.23%** |
| *Unknown* | *563* | *30.40%* |
| Serious | 499 | 88.63% |
| Non-serious | 64 | 11.37% |
| *Previously known* | *1289* | *69.60%* |
| Serious | 1055 | 18.15% |
| Non-serious | 234 | 81.85% |
| **Possible** | **190** | **7.62%** |
| *Unknown* | *73* | *38.42%* |
| Serious | 70 | 95.89% |
| Non-serious | 3 | 4.11% |
| *Previously known* | *117* | *61.58%* |

| | | |
|---|---|---|
| Serious | 108 | 92.31% |
| Non-serious | 9 | 7.69% |
| **Unlikely** | **3** | **0.12%** |
| *Unknown* | *0* | *0.00%* |
| Serious | 0 | 0.00% |
| Non-serious | 0 | 0.00% |
| *Previously known* | *3* | *100.00%* |
| Serious | 3 | 100.00% |
| Non-serious | 0 | 0.00% |
| **Conditional** | **10** | **0.40%** |
| *Unknown* | *8* | *80.00%* |
| Serious | 5 | 37.50% |
| Non-serious | 3 | 62.50% |
| *Previously known* | *2* | *20.00%* |
| Serious | 1 | 50.00% |
| Non-serious | 1 | 50.00% |
| **Unassesseable/Unclassifiable** | **0** | **0.00%** |
| **Invalid causality assessment** | **188** | **7.54%** |
| *Unknown* | *42* | *22.34%* |
| Serious | 5 | 11.90% |
| Non-serious | 37 | 88.10% |
| *Previously known* | *146* | *77.66%* |
| Serious | 9 | 6.16% |
| Non-serious | 137 | 93.84% |

## 5. Discussion

In our study, we intended to characterise the Protocols established between the Porto, Coimbra, and Lisboa, Setúbal e Santarém PC, and the Immunoallergology Departments of the Central Hospitals in their regions, and analyse their differences, both in the implementation, and operationalisation. To this end, interviews were conducted with the PC in study, following a script that allowed us to collect information more uniformly. Moreover, we also proposed to characterise the ADR data resulting from the Protocols, in regards to their seriousness and previous knowledge, to identify and characterise the medicinal products involved in the reported cases, and analyse the causality assessment of the cases stemming from the Protocols. Data on spontaneous report originating from the Protocols were provided by Infarmed, and comprised the period of January 2000 to December 2020.

Throughout the interviews it was possible to understand that, in addition to the collection of drug safety data, other of the main objectives of the implementation of these Protocols was to increase the rate of spontaneous reporting in the regions of their implementation. In fact, when the Protocols were implemented, we could perceive an increase in the reporting by the Immunoallergologists, as in 2004, the year when the first Protocol in the Porto PC was established, in which the reports by these HCP represented 10.15% of the total reports received by the SNF.[17,31]

We can also note that the reporting of suspected ADR by Immunoallergologists does not follow the observed evolution on the rest of the SNF – while in the SNF, the numbers seem to be constantly growing over the years, the number of reports by this class of HCP is mostly related to the date of implementation of the Protocols.[17,31] We can consequently see a peak in reporting by Immunoallergologists in 2004 (152 *vs.* 1 in 2003), probably due to the establishment of the first Protocol in an Hospital Centre in Porto, since it was possible to collect retrospective ADR data from this Hospital Centre. Although the Porto PC celebrated two more protocols, in 2007 and 2009, we can only see an increase in reports from these Protocols in 2010. It should be considered that, on average, from 2000 to 2010, outside the scope of the Protocols, only 4.6 reports per year from Immunoallergologists were registered.

In 2014 we may see another spike in reports by Immunoallergologists, and via Protocols. This could be because in that year another Protocol was established, this time between the Porto PC and an Hospital in Guimarães. However, with the creation of the Guimarães PC, on the 1st of January 2017, the responsibility of the Protocol with this institution migrated from the Porto PC, to this new Centre. Thus, the discrepancy that can be observed in the years 2017 to 2020, between the reports associated with the Protocols and the reports stemming from Immunoallergologists in general, could also correlate to the creation of the

Guimarães PC, since as of 2017 we no longer consider the data from this Hospital for our study, as it is not part of any of the PC under analysis.[46]

There were also 202 reports from the Coimbra PC, between 2017 and 2020, which were registered in the front office of the Portal RAM. From the available data, it was not possible to analyse if it was the Coimbra PC members, or the physicians themselves making the report, and having collected the data after the interviews had been conducted, there was no opportunity to personally query the members of the Coimbra PC about the origin of it. As described in the Methods section of this study, it was decided not to consider these reports as originating from the Protocol.

Lastly, the generalised increase in reported cases from 2017 could also be attributed to the restructuring of the SNF, which, with the creation of PC more evenly dispersed throughout the national territory, brought the Pharmacovigilance Professionals closer to the general population, and in this case to HCP, thus allowing for greater awareness of this topic and for the reporting of ADR to Portal RAM.[46–48]

At this moment, Porto PC, Coimbra PC, and Lisboa, Setúbal e Santarém PC have six active Protocols, with Hospital Centres with well-established Immunoallergology Departments.

From an operational point of view, all Protocols work in a similar way. Following the signing of an agreement with the Institution, where the workflow is also defined, data are collected from the clinical files of patients with suspected ADR, and are then entered in Portal RAM, to follow the course of a spontaneous report.

It should be noted that only at the time of collection and entry of data in Portal RAM these reports are different from any other, following then the normal flow of reports, *i.e.*, submitting the information to the European database (EudraVigilance), the analysis of the variables of the case, and the assessment of causality between the ADR and the suspected medicinal products.[49]

Paradoxically, it was mentioned by the Centres' members that, the increase in the number of Protocols that their PC establish, and thus the increase in suspected ADR, makes the reporting of these become challenging, due to the lack of human resources and availability of the members of the PC. Combined with complacency and insufficient knowledge on Pharmacovigilance, the lack of availability of HCP in Hospitals is considered as a crucial limitation to spontaneous reporting, thus causing it to be one of the major causes for underreporting.[50,51] It was also described as one of the crucial motivations that led to the search for the implementation of the Collaboration Protocols.

In fact, this was one of the concerns heightened with the implementation of this type of Protocols with other Hospital Departments, the more that are established, the greater the burden on the PC staff, which causes them to become overwhelmed, making data collection impossible. In Denmark, the use of a specialised and exclusive ADR reporting manager in specific Departments of an Hospital was studied for a 12-month period. This allowed for a five-fold increase in reports received by the NCA, when comparing to the year previous to its implementation.[52] This methodology has since then been extended to include other Departments and other Hospitals.[53] Even though the use of a reporting manager in Denmark and the implementation of the Protocols in Portugal are based on the communication of a HCP of a suspected ADR to a Pharmacovigilance professional that then reports it to the respective NCA, the fact that this manager's main responsibility is reporting ADR that are communicated to them, makes the high number of cases not as challenging and not as much of a burden for this Professional, contrary to what happens with Protocols in the Portuguese PC.[52,53]

Several studies have found that one way to stimulate ADR reporting is through spontaneous reporting methods with intervention, such as training and communications aimed at raising awareness among Health Professionals.[54–56] One of the limitations found in these studies, which is also mentioned by Ribeiro-Vaz *et al*, in a study carried out by the Porto PC, is that as time passes, these methodologies start to lose relevance and a decrease in the reporting rate can be observed.[33,55] We can then conclude that one of the greatest advantages of the implementation of these Protocols is the continuous collaboration that the members of the PC maintain with the HCP of the involved Hospitals, promoting a know-how sharing culture between Pharmacovigilance Professionals and HCP.

Nevertheless, other improvements to increase spontaneous reporting to the SNF were identified to collect data of suspected ADR during clinical practice. The main proposals were based on the collection of information directly from the electronic health record of each patient, which would be applicable to all HCP, or the implementation of cross-reporting of CPARA Portal records to Portal RAM, since Immunoallergologists tend to prioritise the report in the former.[38,45]

A study conducted in Portugal reported that between 2000 and 2009, 116720 hospitalisations were caused or prolonged by ADR. In the same period, the spontaneous reporting data to the SNF comprised of only approximately 10% of this figure, coming from all channels, and not only from the hospital environment.[57] We were thus able to perceive the potential for ADR collection methods from electronic health records, in real time, given the increasing computerisation of them. As such, the implementation of systems that allow the collection of these data in an automatic way, directly from the electronic health records to the

Pharmacovigilance Systems, should assume greater relevance as a methodology for collecting real-world data on drug safety, bridging some of the limitations of spontaneous reporting.[55,58,59]

Nevertheless, the perceived impact of the Protocols by PC members, both on their Centre and on the SNF as a whole, was overwhelmingly positive. In part, this is because these Protocols have allowed a better engagement of the PC with the medical community in their region, thus creating closer relationships, which ultimately leads to an increase in Pharmacovigilance awareness. They have also allowed the PC to reach the objectives on the number of suspected ADR reported in their region, to meet the required reporting rate established by Infarmed.[60] Finally, we were conveyed the importance of collecting any information that would otherwise be lost, particularly in suspected ADR that are perceived to be mostly serious. As a matter of fact, from our analysis we were able to conclude that 79.04% of suspected ADR originating from the Protocol were classified as serious.

When we compare this figure with the available spontaneous reporting data in Portugal, where serious reactions represent around 55% to 63% of the total reports, we can see that suspected ADR from the Protocol are more often classified as serious.[34,61–69]

With regard to patient data, according to the reports published by Infarmed for the period 2014 to 2020, we were able to see that the proportion of female patients (60.26% of the total number of reports) is also in line with what is expected, as we were able to observe 60.56% of female individuals with suspected ADR by the Protocols.[67–69]

The same data also allows us to observe that, in terms of reports per age group, the greatest differences are related to children and adolescents under 17 years of age – which represent 8.40% of the SNF cases, compared to 19.88% of the Protocol cases –, and with the elderly population (over 65 years of age), where there is a representation of 8.70% in the Protocols and 22.85% in the public data published by Infarmed. However, it is important to note that the Protocols have a similar proportion of cases where it is not possible to identify the patients' age, 28.46% of Protocols versus 24.97% of Infarmed data, therefore proximity to HCP has not helped to improve this metric.[63–69]

Generally, the suspected medicinal products reported had the brand name indication (62.01%). Literature data show quite variable values, from 38% to 98%, thus, it is not possible to draw conclusions about the easiest collection of these data by the Protocols.[70,71]

In analysing the ATC codes of these medicines, we can see a tendency, as the medicines with the codes *J01 – Antibacterials for systemic use*, *M01 – Antiinflammatory and Antirheumatic Products* and *N02 – Analgesics* represent 72.04% of all suspected ADR

medicines across the Protocols, thus meeting what was considered by PC members to be the medicines most likely to cause adverse reactions. In fact, these classes of drugs are those described as having the highest predictability of causing allergic-type ADR.[38,72,73]

When compared with the rest of the country's reality, analysing the public data published by Infarmed, we see that the medicines with the 2nd level ATC codes *L01 – Antineoplasic Agents*, *L04 – Immunosuppressants* and *J05 – Antivirals for systemic use* are the most reported in 8 of the last 9 years (data from 2012 to 2020).[61–69] In contrast, in the reports collected through the Protocols, these were reported only 52 (1.85%), 7 (0.25%), and 3 (0.11%) times, respectively.

With regard to the suspected ADR reported through the Protocols, we see an overwhelming majority belonging to SOC *skin and subcutaneous tissue disorders*, 49.48% – corresponding to 3749 suspected ADR out of 7577 – which is as expected, as most allergic ADRs are manifested by skin reactions. Since these reactions are on the skin, and widely visible, they are often associated with the first signs of systemic allergy. This can be a factor that leads patients to seek specialised medical help, in this case in a hospital environment.[74,75] The three most commonly reported PT are also skin manifestations, *rash*, *urticaria* and *pruritus*.

The causal relationship was also analysed, taking into account that, at the time of collecting the information to complete the reporting of suspected ADR, the relevant clinical data of the patient is also gathered, and may be of relevance at this stage of the case assessment. Data revealed that 91.20% of the reported cases resulted in a degree of causality of *Probable* or *Certain*. A study conducted by the Coimbra PC revealed that in the first six years of activity of this Centre, 73% of the spontaneous report cases received were classified as *Certain* or *Probable*.[76] Another study by the same Centre, concluded that hypersensitivity notifications received by this Centre in the period 2010 to 2017 were classified as *Certain* in 64.6% of cases.[39] Lastly, a study carried out in the Porto PC, which analyses the 20 years of activity of this Centre, including the data of all the spontaneous reports under its responsibility, concludes that 81.6% of the cases were assessed as to the causality of the ADR-drug reaction as either *Certain* or *Probable*.[77] We were thus able to observe that ADR-suspected medicine relationships reported through the Protocols have a higher probability of being assessed as *Certain* or *Probable* as to their causality.

Seriousness of an ADR is a significant factor when considering signal generation. Other important variables to consider are the previous knowledge we have of an ADR related to a suspected medicine, and the causality assessment.[78] In our study we concluded that 25.09% (626 cases) of ADR stemming from the Protocols are simultaneous serious, and unknow.

Furthermore, we identified 617 cases (24.73%), which were previously unknow, not previously described, and had a causality assessment of *Certain* or *Probable*. These cases provide new information to the SNF, potentially originating new safety signals. This figure is slightly higher when compared to the published literature of Portuguese data, representing in this way the potential value that the Protocols have in signal generation.[76]

### 5.1. Limitations and future research

The present study is affected by limitations that can be identified, and that may influence the interpretation of the results. First of all, by interviewing only the members of the PC, who are the great driving forces behind the implementation and maintenance of these Protocols, the results obtained might have a certain degree of bias, especially when dealing with interview data, *i.e.*, data that may be considered as subjective. Thus, it would be of added value to collect these data for all stakeholders involved in the Collaboration Protocols, in addition to the PC, Immunoallergologists and the NCA itself, adapting the script to encompass all the themes applicable to these stakeholders.

Additionally, to be able to truly measure the impact that suspected ADR data stemming from the Protocols has on the Portuguese SNF, a full analysis of these data would be of utmost relevance. This would entail the analysis of the 77945 suspected ADR reported to the SNF in the study period, from 2000 to 2020.[17,31] As it was not possible to obtain these data, we believe that the importance of its study lies in the standardisation of the analysis of the various parameters, allowing better conclusions to be reached on the true impact that the Protocols could potentially have on the SNF. To summarise, the analysis of these data would allow a study with less variability in the intermediate analyses, allowing more robust results.

## 6. Conclusions

Spontaneous reporting represents one of the best opportunities for collecting real-world safety data on approved medicines. The establishment of Collaboration Protocols between the Porto, Coimbra, and Lisboa, Setúbal e Santarém PC, and the Immunoallergology Departments of the Central Hospitals in these regions aimed to collect information obtained during clinical practice, for the SNF.

In fact, these Protocols allowed the collection of safety information that would otherwise be lost. It is possible to verify, in the three PC, that there was an increased proximity between PC members and HCP, which contributes to improve Pharmacovigilance awareness, and to promote a culture of notification of suspected ADR. These Protocols help strengthening the SNF, since HCP make a greater contribution to this System, both by reporting suspected ADR and by sharing know-how with the PC.

Since this information is collected from patients' clinical records, it is prone to be more complete than in other spontaneous reports, whether reported by patients or by other HCP. Additionally, these data include many assessments that would otherwise not be considered, such as provocation test, that allow the causality assessor to infer a better assessment of the relationship between the suspected drug and the ADR reported. This is illustrated by the high number of cases with a causality grade of *Certain* or *Probable*, from the suspected ADR resulting from the Protocol.

The information obtained from these Protocols feeds the SNF with suspected ADR that are mainly serious, previously described, and with mainly allergic origin characteristics. Nevertheless, the impact perceived by the PC in this study is quite positive. Its generalised implementation would allow a greater standardisation of the data collected, enabling a better characterisation of the Portuguese population with drug allergies, and the benefit-risk balance of the most reported drugs, such as antibacterial, anti-inflammatory, and analgesic drugs, and thus outlining mitigation strategies for this type of ADR.

Based on the information gathered from the interviews, we can further conclude that it is necessary to re-evaluate the methods of collecting suspected ADR. With the increasing automation of our everyday activities, there is also a demand to automate the process of collecting this information through patients' electronic health records, thus alleviating the burden on HCP and contributing to the overall decrease in underreporting.

Considering the limitations identified for this study, especially regarding the missing data on suspected ADR notified to the SNF, conducting a study to analyse the complete data is of the utmost importance, as from this study we can draw benefits from the implementation

of these Protocols for ADR data collection, but without the ADR reports data from all notifiers, we cannot measure their true impact on the SNF.

## 7. References


1. World Health Organization. *The Importance of Pharmacovigilance - Safety Monitoring of Medicinal Products*.; 2002. doi:10.1002/0470853093
2. Directive 2010/84/EU of The European Parliment and of The Council of 15 December 2010.
3. Coleman J, Pontefract S. Adverse drug reactions. *Clin Med (Northfield Il)*. 2016;16(5):481-485. doi:10.7861/clinmedicine.16-5-481
4. Kaufman G. Adverse drug reactions: classification, susceptibility and reporting. *Nurs Stand*. 2016;30(50):53-63. doi:10.7748/ns.2016.e10214
5. Edwards IR, Aronson JK. Adverse drug reactions: Definitions, diagnosis, and management. *Lancet*. 2000;356(9237):1255-1259. doi:10.1016/S0140-6736(00)02799-9
6. Uppsala Monitoring Centre. Glossary of pharmacovigilance terms. https://www.who-umc.org/global-pharmacovigilance/publications/glossary/. Published 2020. Accessed November 29, 2021.
7. World Health Organization. Briefing Note Safety of medicines – adverse drug reactions Key facts. :1-3. https://www.who.int/docs/default-source/medicines/safety-of-medicines--adverse-drug-reactions-jun18.pdf?sfvrsn=4fcaf40_2. Accessed February 8, 2021.
8. Sultana J, Cutroneo P, Trifirò G. Clinical and economic burden of adverse drug reactions. *J Pharmacol Pharmacother*. 2013;4(SUPPL.1):73-78. doi:10.4103/0976-500X.120957
9. Wester K, Jönsson AK, Spigset O, Druid H, Hägg S. Incidence of fatal adverse drug reactions: A population based study. *Br J Clin Pharmacol*. 2008;65(4):573-579. doi:10.1111/j.1365-2125.2007.03064.x
10. Teixeira F. Aspetos Históricos da Farmacovigilância. In: *Farmacovigilância Em Portugal: 25 Anos*. ; 2018:15-29.
11. Beninger P. Pharmacovigilance: An Overview. *Clin Ther*. 2018;40(12):1991-2004. doi:10.1016/j.clinthera.2018.07.012
12. Herdeiro MT, Ferreira M, Ribeiro-Vaz I, Junqueira Polónia J, Costa-Pereira A. O sistema Português de farmacovigilância. *Acta Med Port*. 2012;25(4):241-249.
13. Santoro A, Genov G, Spooner A, Raine J, Arlett P. Promoting and Protecting Public Health: How the European Union Pharmacovigilance System Works. *Drug Saf*. 2017;40(10):855-869. doi:10.1007/s40264-017-0572-8
14. Borg JJ, Tanti A, Kouvelas D, et al. European Union pharmacovigilance capabilities: Potential for the new legislation. *Ther Adv Drug Saf*. 2015;6(4):120-140. doi:10.1177/2042098615591802
15. Regulation (EU)1235/2010 of the European Parliament and of the Council of 15 December 2010.
16. Commission Implementing Regulation (EU) 520/2012 of 19 June 2012.
17. INFARMED - Autoridade Nacional do Medicamento e Produtos de Saúde I.P. Notificações RAM recebidas no SNF. https://www.infarmed.pt/documents/15786/2522033/Notificacoes%2BRAM%2B2017/b0cdcfd7-627b-45eb-a0ee-134d8673b37d. Accessed March 14, 2021.

18. Mousinho C, Bragança F, Hergy F. Portal RAM. In: *Farmacovigilância Em Portugal: 25 Anos*. ; 2018:79-92.

19. European Medicines Agency. Module VI – Collection, management and submission of reports of suspected adverse reactions to medicinal products (Rev 2). *Guidel good Pharmacovigil Pract*. 2017;Revision 2(July). http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2017/08/WC500232767.pdf. Accessed 14 March 2021.

20. Härmark L, Van Grootheest AC. Pharmacovigilance: Methods, recent developments and future perspectives. *Eur J Clin Pharmacol*. 2008;64(8):743-752. doi:10.1007/s00228-008-0475-9

21. Steurbaut S, Hanssens Y. Pharmacovigilance: empowering healthcare professionals and patients. *Int J Clin Pharm*. 2014;36(5):859-862. doi:10.1007/s11096-014-0004-0

22. Inácio P, Cavaco A, Allan E, Airaksinen M. Key pharmacovigilance stakeholders' experiences of direct patient reporting of adverse drug reactions and their prospects of future development in the European Union. *Public Health*. 2018;155:119-128. doi:10.1016/j.puhe.2017.11.023

23. Inácio P, Cavaco A, Airaksinen M. The value of patient reporting to the pharmacovigilance system: a systematic review. *Br J Clin Pharmacol*. 2017;83(2):227-246. doi:10.1111/bcp.13098

24. Mascolo A, Scavone C, Sessa M, et al. Can causality assessment fulfill the new European definition of adverse drug reaction? A review of methods used in spontaneous reporting. *Pharmacol Res*. 2017;123:122-129. doi:10.1016/j.phrs.2017.07.005

25. Pombal R. Imputação de Causalidade. In: *Farmacovigilância Em Portugal: 25 Anos*. ; 2018:177-200.

26. Decreto-Lei n. 41448/57 de 18/12/1957. Diário da República I Série de 18/12/1957.

27. INFARMED - Autoridade Nacional do Medicamento e Produtos de Saúde I.P. Farmacovigilância. https://www.infarmed.pt/web/infarmed/profissionais-de-saude/informacao-de-seguranca/farmacovigilancia. Accessed 14 March, 2021.

28. Decreto-Lei n.º 176/2006 - Diário da República n.º 167/2006, Série I de 2006-08-30.

29. INFARMED - Autoridade Nacional do Medicamento e Produtos de Saúde I.P. Notificação de Reações Adversas (RAM) FAQ. https://www.infarmed.pt/web/infarmed/faq. Accessed March 14, 2021.

30. Cabrita da Silva J, Soares MA, de Oliveira Martins S. Análise da base de dados do Sistema Nacional de Farmacovigilância (SVIG) 2009 - 2011. 2012:97. https://www.ff.ulisboa.pt/wp-content/uploads/2018/08/Relatorio_analise_dados_SVIG_2009_2011.pdf. Accessed March 14, 2021. Accessed March 14, 2021.

31. INFARMED - Autoridade Nacional do Medicamento e Produtos de Saúde I.P. Desempenho do SNF. https://www.infarmed.pt/web/infarmed/entidades/medicamentos-uso-humano/farmacovigilancia/desempenho-do-snf. Accessed March 14, 2021.

32. INE - Instituto Nacional de Estatística. Bases de dados - Estimativas de população. https://www.ine.pt/xportal/xmain?xpid=INE&xpgid=ine_indicadores&indOcorrCod=0006031&contexto=bd&selTab=tab2. Accessed March 14, 2021.

33. Ribeiro-Vaz I, Santos CC, Cruz-Correia R. Promoting adverse drug reaction reporting: comparison of different approaches. *Rev Saude Publica*. 2016;50:14. doi:10.1590/S1518-8787.2016050006122

34. Batel-Marques F, Mendes D, Alves C, et al. Farmacovigilância em Portugal: Atividade da Unidade Regional do Centro Pharmacovigilance in Portugal: Activity of the Central Pharmacovigilance Unit. 2015. www.actamedicaportuguesa.com.

35. Figueiras A, Herdeiro MT, Polónia J, Gestal-otero JJ. An Educational Intervention to Improve Physician Reporting. *Jama*. 2006;296(9):1086-1093. doi:296:1086-1093

36. Martins AP, Alves R. Unidade de Farmacovigilância de Setúbal e Santarém. In: *Farmacovigilância Em Portugal: 25 Anos*. ; 2018:137-147.

37. INFARMED - Autoridade Nacional do Medicamento e Produtos de Saúde I.P. Boletim de Farmacovigilância Volume 22, Números 11 e 12. 2018. https://www.infarmed.pt/documents/15786/2506612/Boletim+de+Farmacovigilância%2C+Volume+22%2C+nº11+e+12%2C+novembro+e+dezembro+de+2018/7da353bc-c466-48b2-bd40-00af3e4ee40b?version=1.1. Accessed March 14, 2021.

38. Mendes D, Alves C, Loureiro M, Fonte A, Batel-Marques F. Drug-induced hypersensitivity: A 5-year retrospective study in a hospital electronic health records database. *J Clin Pharm Ther*. 2019;44(1):54-61. doi:10.1111/jcpt.12752

39. Mendes D, Oliveira AR, Alves C, Batel Marques F. Spontaneous reports of hypersensitivity adverse drug reactions in Portugal: a retrospective analysis. *Expert Opin Drug Saf*. 2020;19(6):763-769. doi:10.1080/14740338.2020.1743262

40. SPAIC - Sociedade Portugesa de Alergologia e Imunologia Clínica. Alergia a medicamentos. https://www.spaic.pt/publicacoes-folhetos?id=37. Accessed March 14, 2021.

41. Audicana A, Ortega N, Lobera T, et al. Spanish Society Vision of Drug challenge tests. *J Investig Allergol Clin Immunol*. 2021;31(5):6. doi:10.18176/jiaci.0681

42. Costa MJ, Herdeiro MT, Polónia JJ, et al. Type B adverse drug reactions reported by an immunoallergology department. *Pharm Pract (Granada)*. 2018;16(1):1-6. doi:10.18549/PharmPract.2018.01.1070

43. Alves C, Romeira AM, Abreu C, Carreiro-Martins P, Gomes E, Leiria-Pinto P. Non-steroidal anti-inflammatory drug hypersensitivity in children. *Allergol Immunopathol (Madr)*. 2017;45(1):40-47. doi:10.1016/j.aller.2016.04.004

44. Atanaskovic-Markovic M, Gomes E, Cernadas JR, et al. Diagnosis and management of drug-induced anaphylaxis in children: An EAACI position paper. *Pediatr Allergy Immunol*. 2019;30(3):269-276. doi:10.1111/pai.13034

45. Mota I, Pereira AM, Pereira C, et al. Abordagem e Registo da Anafilaxia em Portugal. *Acta Med Port*. 2015;28(6):786. doi:10.20344/amp.6802

46. Vila Real de Araújo A. Unidade de Farmacovigilância de Guimarães. In: *Farmacovigilância Em Portugal: 25 Anos*. ; 2018:93-101.

47. Duarte AP, Monteiro C. Unidade de Farmacovigilância da Beira Interior. In: *Farmacovigilância Em Portugal: 25 Anos*. ; 2018:123-128.

48. Marques N, Melo H. Unidade de Farmacovigilância do Algarve e Alentejo. In: *Farmacovigilância Em Portugal: 25 Anos*. ; 2018:149-151.

49. Barão Sousa-Ferreira P, Torre C. Notificação Espontânea. In: *Farmacovigilância Em Portugal: 25 Anos*. ; 2018:163-176.

50. Hasford J, Goettler M, Munter KH, Müller-Oerlinghausen B. Physicians' knowledge and attitudes regarding the spontaneous reporting system for adverse drug reactions. *J Clin Epidemiol*. 2002;55(9):945-950. doi:10.1016/S0895-4356(02)00450-X

51. Güner MD, Ekmekci PE. Healthcare professionals' pharmacovigilance knowledge and adverse drug reaction reporting behavior and factors determining the reporting rates. *J Drug Assess*. 2019;8(1):13-20. doi:10.1080/21556660.2019.1566137

52. Lander AR, Blicher TM, Jimenez-Solem E, Jespersen M, Kampmann JP, Christensen HR. Introducing an adverse drug event manager. *Eur J Hosp Pharm*. 2013;20(2):78-81. doi:10.1136/ejhpharm-2012-000171

53. Vinther S, Klarskov P, Borgeskov H, et al. An adverse drug event manager facilitates spontaneous reporting of adverse drug reactions. *Dan Med J*. 2017;64(1):1-5.

54. Vallano A, Cereza G, Pedròs C, et al. Obstacles and solutions for spontaneous reporting of adverse drug reactions in the hospital. *Br J Clin Pharmacol*. 2005;60(6):653-658. doi:10.1111/j.1365-2125.2005.02504.x

55. Molokhia M. Improving reporting of adverse drug reactions: Systematic review. *Clin Epidemiol*. 2009:75. doi:10.2147/clep.s4775

56. Ribeiro-Vaz I, Herdeiro MT, Polónia J, Figueiras A. Strategies to increase the sensitivity of pharmacovigilance in Portugal. *Rev Saude Publica*. 2011;45(1):129-135. doi:10.1590/S0034-89102010005000050

57. Miguel A, Marques B, Freitas A, Lopes F, Azevedo L, Costa Pereira A. Detection of adverse drug reactions using hospital databases— a nationwide study in Portugal. *Pharmacoepidemiol Drug Saf*. 2013;22(8):907-913. doi:10.1002/pds.3468

58. Ribeiro-Vaz I, Silva AM, Costa Santos C, Cruz-Correia R. How to promote adverse drug reaction reports using information systems - A systematic review and meta-analysis. *BMC Med Inform Decis Mak*. 2016;16(1):1-10. doi:10.1186/s12911-016-0265-8

59. Lavertu A, Vora B, Giacomini KM, Altman R, Rensi S. A New Era in Pharmacovigilance: Toward Real-World Data and Digital Monitoring. *Clin Pharmacol Ther*. 2021;109(5):1197-1202. doi:10.1002/cpt.2172

60. Moreira A, Pêgo A, Bragança F, Carvalhal J. 25 anos de SNF: Principais Resultados. In: *Farmacovigilância Em Portugal: 25 Anos*. ; 2018:63-77.

61. INFARMED - Autoridade Nacional do Medicamento e Produtos de Saúde I.P. *Relatório Anual 2012 Notificações e Casos de RAM Espontâneos Recebidos No SNF (Sistema Nacional de Farmacovigilância)*.; 2012. https://www.infarmed.pt/documents/15786/17838/Relatorio_casuistica_2012_anual_v2_versao_publicacao+_2_.pdf/9fd6b4da-d66a-4005-960a-f9a889c9446a. Accessed November 23, 2021.

62. INFARMED - Autoridade Nacional do Medicamento e Produtos de Saúde I.P. *Relatório Anual 2013 Notificações e Casos de RAM Recebidos No SNF (Sistema Nacional de Farmacovigilância)*.; 2015. https://www.infarmed.pt/documents/15786/2099374/Relatório+Anual_2013/2a2f57d6-e044-4efd-8bea-8ed4fcdb7c30. Accessed November 23, 2021.

63. INFARMED - Autoridade Nacional do Medicamento e Produtos de Saúde I.P. *Sistema Nacional de Farmacovigilância (SNF): Notificações e Casos de RAM - Ano/2014*.; 2014. https://www.infarmed.pt/documents/15786/17838/Relatorio_casuistica_anual_2014_V2_final_graficos_ordem_alterada.pdf/c3b2892b-9b33-4a48-809e-b8a13b2161c2.

Accessed November 23, 2021.

64. INFARMED - Autoridade Nacional do Medicamento e Produtos de Saúde I.P. *Sistema Nacional de Farmacovigilância (SNF): Notificações e Casos de RAM - Ano/2015*.; 2015. https://www.infarmed.pt/documents/15786/17838/Relatorio_casuistica_anual_2015_V2.pdf/c1721fca-3ee5-4a04-ba0b-2056048fb6da. Accessed November 23, 2021.

65. INFARMED - Autoridade Nacional do Medicamento e Produtos de Saúde I.P. *Sistema Nacional de Farmacovigilancia (SNF) - Notificações e Casos de RAM - Ano 2016*.; 2016. https://www.infarmed.pt/documents/15786/2099374/Notificações+e+Casos+de+RAM+-+Ano+2016/f86216ad-009b-4855-9021-1c54f3534ca8. Accessed November 23, 2021.

66. INFARMED - Autoridade Nacional do Medicamento e Produtos de Saúde I.P. *Sistema Nacional de Farmacovigilancia (SNF) - Notificações e Casos de RAM Ano 2017*.; 2017. https://www.infarmed.pt/documents/15786/2099374/Notificações+e+Casos+de+RAM+-+Ano+2017/f60bdace-f08d-4d85-928d-f9b22ca5d7f1. Accessed November 23, 2021.

67. INFARMED - Autoridade Nacional do Medicamento e Produtos de Saúde I.P. *Relatório Casuística 2018*.; 2018. https://www.infarmed.pt/documents/15786/2099374/Relat%FF%FFrio%2BAnual%2BCasu%FF%FFstica%2B2018/b3b74cab-d176-4c6a-adb9-9371589d75e9. Accessed November 23, 2021.

68. INFARMED - Autoridade Nacional do Medicamento e Produtos de Saúde I.P. *Relatório Casuística 2019*.; 2019. https://www.infarmed.pt/documents/15786/2522033/relat%FF%FFrio%2Bde%2Bcasu%FF%FFstica%2Brelativo%2Bao%2Bano%2Bde%2B2019/432c673f-74d0-84d0-62a8-11724d7fec7e. Accessed November 23, 2021.

69. INFARMED - Autoridade Nacional do Medicamento e Produtos de Saúde I.P. *Relatório Casuística 2020*.; 2020. https://www.infarmed.pt/documents/15786/2099374/Relatório+casuística++-Anual+2020/5f7b15bf-6367-fce5-5669-4b35f5499794. Accessed November 23, 2021.

70. Vermeer NS, Spierings I, Mantel-Teeuwisse AK, et al. Traceability of biologicals: Present challenges in pharmacovigilance. *Expert Opin Drug Saf*. 2015;14(1):63-72. doi:10.1517/14740338.2015.972362

71. Cutroneo PM, Isgrò V, Russo A, et al. Safety Profile of Biological Medicines as Compared with Non-Biologicals: An Analysis of the Italian Spontaneous Reporting System Database. *Drug Saf*. 2014;37(11):961-970. doi:10.1007/s40264-014-0224-1

72. Warrington R, Silviu-dan F. Immunology Drug allergy. *Allergy, Asthma Clin Immunol*. 2011;7(Suppl 1):S10. http://www.aacijournal.com/content/7/S1/S10.

73. Minaldi E, Philips EJ, Norton A. Immediate and Delayed Hypersensitivity Reactions to Beta-Lactam Antibiotics. *Clin Rev Allerg Immunol*. 2021. doi:10.1007/s12016-021-08903-z

74. Mockenhaupt M. Drug Allergy and Cutaneous Adverse Reactions. In: *Allergic Diseases – From Basic Mechanisms to Comprehensive Management and Prevention. Handbook of Experimental Pharmacology, Vol 268*. ; 2021:195-212. doi:978-3-030-84048-8

75. Ardern-Jones MR, Friedmann PS. Skin manifestations of drug allergy. *Br J Clin*

*Pharmacol*. 2011;71(5):672-683. doi:10.1111/j.1365-2125.2010.03703.x

76. Batel-Marques F, Penedones A, Mendes D, Alves C. Outcomes from the first 6 years of operation of the central Portugal pharmacovigilance unit. *J Patient Saf*. 2020;16(3):E136-E142. doi:10.1097/PTS.0000000000000273

77. Ferreira-Da-Silva R, Ribeiro-Vaz I, Silva AM, Marques J, Polónia JJ. Looking back on 20 years of work at the Porto Pharmacovigilance Centre, Portugal. *Cad Saude Publica*. 2021;37(10). doi:10.1590/0102-311X00304420

78. European Medicines Agency. Module IX - Signal Management (Rev 1). *Eur Med Agency*. 2017;44(April):1-6.

## Appendices

### I. Script used in interviews conducted with PC members

"Regarding the Protocols your Centre has established with the Immunoallergology Department of certain Hospitals, we would kindly ask for your help to characterise them, by describing the following elements:

- What is the essence of these Protocols?
- What was the motivation behind seeking its implementation?
- What are the main goals of these Protocols?
- How many of these partnerships does your PC have? With what Hospitals?
- From where did the initiative to implement these Protocols arise? From the Hospital or from the PC?
- How where the Protocols first established?
- Since when are they in force?
- How is data collection handled?
    - How frequently is it collected?
    - Is it collected by the PC personnel, or is it collected directly by the Hospitals' personnel?
    - How is the data selection carried out?
- Do you consider the Protocols to have a positive impact on your PC? Why?
- And in the Portuguese National Pharmacovigilance System? Why?
- What positive and negative aspects do you highlight from these Protocols?
- What are the improvements you consider to be necessary in order to strengthen the Protocols and the resulting data?
- Would it make sense to implement these Protocols with other [Hospital] Departments? Which ones?
- Do you consider this to be a project that should be implemented throughout Portugal?
- The originating data has any peculiarity?
- Is clinical data [from each patient's clinical history] taken into account in each ADR causality assessment?"

## II. Suspected medicinal products reported, by INN

| INN | Frequency | Percentage |
|---|---|---|
| Aceclofenac | 3 | 0.11% |
| Acemetacin | 4 | 0.14% |
| Acetylcysteine | 3 | 0.11% |
| Acetylsalicylic acid | 83 | 2.95% |
| Acetylsalicylic acid + Ascorbic acid | 6 | 0.21% |
| Acetylsalicylic acid + Ascorbic acid + Caffeine | 2 | 0.07% |
| Acetylsalicylic acid + Caffeine | 2 | 0.07% |
| Acetylsalicylic acid + Citric acid + Sodium bicarbonate | 1 | 0.04% |
| Acetylsalicylic acid + Codeine + Caffeine | 2 | 0.07% |
| Acetylsalicylic acid + Codeine + Caffeine + Ascorbic acid | 1 | 0.04% |
| Agomelatine | 1 | 0.04% |
| Albendazole | 1 | 0.04% |
| Alendronic acid + Cholecalciferol | 1 | 0.04% |
| Alfentanil | 1 | 0.04% |
| Allergens | 3 | 0.11% |
| Allopurinol | 26 | 0.92% |
| Alprazolam | 1 | 0.04% |
| Ambroxol | 3 | 0.11% |
| Aminocaproic acid | 2 | 0.07% |
| Amiodarone | 1 | 0.04% |
| Amitriptyline | 1 | 0.04% |
| Amlodipine | 1 | 0.04% |
| Amlodipine + Valsartan | 1 | 0.04% |
| Amoxicillin | 228 | 8.10% |
| Amoxicillin + Clavulanic acid | 482 | 17.13% |
| Ampicillin | 3 | 0.11% |
| Amylase | 3 | 0.11% |
| Apixaban | 1 | 0.04% |
| Articaine | 1 | 0.04% |
| Articaine + Adrenaline | 2 | 0.07% |
| Atorvastatin | 1 | 0.04% |
| Atovaquone | 1 | 0.04% |
| Atracurium besylate | 1 | 0.04% |
| Atropine | 3 | 0.11% |
| Azathioprina | 3 | 0.11% |
| Azilsartan medoxomil | 1 | 0.04% |
| Azithromycin | 28 | 1.00% |
| Beclometasone | 1 | 0.04% |
| Benzathine benzylpenicillin | 9 | 0.32% |
| Benzathine benzylpenicillin + Benzylpenicillin potassium + Procaine benzylpenicillin | 3 | 0.11% |
| Benzylpenicillin | 3 | 0.11% |
| Benzylpenicillin sodium + Clemizole penicillin | 1 | 0.04% |
| Betahistine | 1 | 0.04% |
| Betamethasone | 11 | 0.39% |
| Betamethasone + Fusidic acid | 1 | 0.04% |
| Bezafibrate | 2 | 0.07% |
| Bilastine | 4 | 0.14% |
| Bioflavonoids | 1 | 0.04% |
| Bisoprolol | 1 | 0.04% |

| INN | Frequency | Percentage |
|---|---|---|
| Brivudine | 1 | 0.04% |
| Bromhexine | 1 | 0.04% |
| Budesonide | 10 | 0.36% |
| Budesonide + Formoterol | 1 | 0.04% |
| Bupivacaine | 1 | 0.04% |
| Bupropiom | 1 | 0.04% |
| Butylscopolamine | 3 | 0.11% |
| Butylscopolamine + Paracetamol | 2 | 0.07% |
| Calcitonin salmon | 1 | 0.04% |
| Calcium carbonate | 1 | 0.04% |
| Calcium folinate | 1 | 0.04% |
| Candesartan + Hydrochlorothiazide | 1 | 0.04% |
| Capsaicin | 1 | 0.04% |
| Captopril | 1 | 0.04% |
| Carbamazepine | 7 | 0.25% |
| Carboplatin | 6 | 0.21% |
| Cefaclor | 14 | 0.50% |
| Cefatrizine | 20 | 0.71% |
| Cefazolin | 25 | 0.89% |
| Cefixime | 8 | 0.28% |
| Cefoxitin | 4 | 0.14% |
| Cefprozil | 5 | 0.18% |
| Ceftazidime | 2 | 0.07% |
| Ceftriaxone | 23 | 0.82% |
| Cefuroxime | 18 | 0.64% |
| Celecoxib | 11 | 0.39% |
| Cetirizine | 3 | 0.11% |
| Cetuximab | 1 | 0.04% |
| Chlorhexidine | 1 | 0.04% |
| Chlortalidone | 1 | 0.04% |
| Cholecalciferol | 2 | 0.07% |
| Ciprofloxacin | 42 | 1.49% |
| Cisatracurium besylate | 1 | 0.04% |
| Cisplatin | 2 | 0.07% |
| Citicoline | 1 | 0.04% |
| Clarithromycin | 33 | 1.17% |
| Clemastine | 1 | 0.04% |
| Clindamycin | 12 | 0.43% |
| Clobazam | 1 | 0.04% |
| Clobutinol | 1 | 0.04% |
| Clomipramine | 1 | 0.04% |
| Clonazepam | 1 | 0.04% |
| Clonidine | 1 | 0.04% |
| Clonixin | 24 | 0.85% |
| Cloreto de tróspio + Echinacea angustifolia + Sabal serulata | 1 | 0.04% |
| Clotrimazole | 1 | 0.04% |
| Coagulation factor VIII + Von Willebrand factor human | 1 | 0.04% |
| Cobamamide | 3 | 0.11% |
| Codeine | 1 | 0.04% |
| Codeine + Phenyltoloxamine | 2 | 0.07% |
| Cyanocobalamin | 2 | 0.07% |

| INN | Frequency | Percentage |
|---|---|---|
| Cyanocobalamin + Pyridoxine + Thiamine | 1 | 0.04% |
| Cyclobenzaprine | 1 | 0.04% |
| Cyclopentolate | 1 | 0.04% |
| Cyclophosphamide | 1 | 0.04% |
| Deflazacort | 10 | 0.36% |
| Dequalinium chloride | 1 | 0.04% |
| Desflurane | 1 | 0.04% |
| Dexibuprofen | 3 | 0.11% |
| Dexketoprofen | 2 | 0.07% |
| Dextromethorphan | 1 | 0.04% |
| Diazepam | 1 | 0.04% |
| Dichlorobenzyl alcohol + Amylmetacresol | 1 | 0.04% |
| Dichlorobenzyl alcohol + Benzydamine | 1 | 0.04% |
| Diclofenac | 138 | 4.90% |
| Diclofenac + Misoprostol | 4 | 0.14% |
| Diflunisal | 1 | 0.04% |
| Diltiazem | 1 | 0.04% |
| Dimetindene | 2 | 0.07% |
| Diosmin | 1 | 0.04% |
| Diphteria and tetanus vaccine | 1 | 0.04% |
| Diphteria, tetanus and pertussis vaccine | 1 | 0.04% |
| Diphteria, tetanus, pertussis, and poliomyelitis vaccine | 1 | 0.04% |
| Disodium levofolinate | 1 | 0.04% |
| Docetaxel | 5 | 0.18% |
| Domperidone | 1 | 0.04% |
| Dosulepin | 1 | 0.04% |
| Doxycycline | 1 | 0.04% |
| Duloxetine | 1 | 0.04% |
| Ebastine | 1 | 0.04% |
| Enalapril | 4 | 0.14% |
| Enalapril + Lercanidipine | 1 | 0.04% |
| Enoxaparin sodium | 7 | 0.25% |
| Ergotamine + Paracetamol + Belladonna (alkaloids) + Caffeine | 1 | 0.04% |
| Ergotamine + Propyphenazone | 2 | 0.07% |
| Ertapenem | 2 | 0.07% |
| Erythromycin | 3 | 0.11% |
| Escitalopram | 1 | 0.04% |
| Esomeprazole | 5 | 0.18% |
| Estradiol + Norethisterone | 1 | 0.04% |
| Ethambutol | 1 | 0.04% |
| Ethyl loflazepate | 1 | 0.04% |
| Etodolac | 9 | 0.32% |
| Etofenamate | 1 | 0.04% |
| Etoricoxib | 21 | 0.75% |
| Fenofibrate | 3 | 0.11% |
| Fentanyl | 10 | 0.36% |
| Ferric carboxymaltose | 5 | 0.18% |
| Filgrastim | 2 | 0.07% |
| Flavoxate | 1 | 0.04% |
| Flucloxacillin | 12 | 0.43% |
| Fluconazole | 4 | 0.14% |

| INN | Frequency | Percentage |
|---|---|---|
| Flunarizine | 1 | 0.04% |
| Fluoresceine | 2 | 0.07% |
| Fluorometholone | 1 | 0.04% |
| Fluorouracil | 1 | 0.04% |
| Flupirtine | 1 | 0.04% |
| Flurbiprofen | 18 | 0.64% |
| Fluticasone | 2 | 0.07% |
| Fluticasone + Salmeterol | 1 | 0.04% |
| Fluticasone furoate + Vilanterol | 2 | 0.07% |
| Fluvoxamine | 1 | 0.04% |
| Folic acid | 1 | 0.04% |
| Formoterol | 1 | 0.04% |
| Fosfomycin | 3 | 0.11% |
| Furosemide | 2 | 0.07% |
| Fusidic acid | 3 | 0.11% |
| Gabapentin | 2 | 0.07% |
| Gadobutrol | 2 | 0.07% |
| Gelatin + Calcium chloride + Sodium chloride | 1 | 0.04% |
| Gemcitabine | 1 | 0.04% |
| Gentamicin | 5 | 0.18% |
| Glatiramer acetate | 1 | 0.04% |
| Gliclazide | 1 | 0.04% |
| Glucosamine | 1 | 0.04% |
| Human normal immunoglobulin | 1 | 0.04% |
| Hydrocortisone | 5 | 0.18% |
| Hydroxocobalamin | 1 | 0.04% |
| Hydroxychloroquine | 2 | 0.07% |
| Hydroxyzine | 1 | 0.04% |
| Ibuprofen | 330 | 11.73% |
| Imidapril | 1 | 0.04% |
| Imipenem | 1 | 0.04% |
| Imipenem + Cilastatin | 2 | 0.07% |
| Indapamide | 1 | 0.04% |
| Indometacin | 2 | 0.07% |
| Infliximab | 4 | 0.14% |
| Influenza vaccine | 3 | 0.11% |
| Iobitridol | 4 | 0.14% |
| Iodixanol | 2 | 0.07% |
| Iomeprol | 7 | 0.25% |
| Iopromide | 22 | 0.78% |
| Ioversol | 5 | 0.18% |
| Ipratropium bromide | 1 | 0.04% |
| Irinotecan | 2 | 0.07% |
| Iron | 1 | 0.04% |
| Iron-dextran complex | 1 | 0.04% |
| Isoniazid | 6 | 0.21% |
| Isoniazid + Pyrazinamide + Rifampicin | 1 | 0.04% |
| Itraconazole | 1 | 0.04% |
| Ketoprofen | 8 | 0.28% |
| Ketorolac | 11 | 0.39% |
| Lamotrigine | 2 | 0.07% |

| INN | Frequency | Percentage |
|---|---|---|
| Lansoprazole | 2 | 0.07% |
| Letrozole | 1 | 0.04% |
| Leuprorelin | 1 | 0.04% |
| Levetiracetam | 3 | 0.11% |
| Levodopa + Carbidopa | 1 | 0.04% |
| Levodopa + Carbidopa + Entacapone | 1 | 0.04% |
| Levodropropizine | 1 | 0.04% |
| Levofloxacin | 16 | 0.57% |
| Lidocaine | 7 | 0.25% |
| Lidocaine + Adrenaline | 9 | 0.32% |
| Linezolid | 1 | 0.04% |
| Lisinopril | 1 | 0.04% |
| Lisinopril + Hydrochlorothiazide | 1 | 0.04% |
| Loperamide | 1 | 0.04% |
| Lornoxicam | 1 | 0.04% |
| Losartan | 1 | 0.04% |
| Lysine acetylsalicylate | 50 | 1.78% |
| Macrogol and other associations | 1 | 0.04% |
| Measles, mumps, and rubella vaccine | 2 | 0.07% |
| Mefenamic acid | 1 | 0.04% |
| Meloxicam | 8 | 0.28% |
| Meningococcus vaccine | 2 | 0.07% |
| Mepivacaine | 2 | 0.07% |
| Mepivacaine + Adrenaline | 1 | 0.04% |
| Meropenem | 2 | 0.07% |
| Mesalazine | 1 | 0.04% |
| Metadoxine | 1 | 0.04% |
| Metamizole magnesium | 45 | 1.60% |
| Metamizole sodium | 1 | 0.04% |
| Metformin | 5 | 0.18% |
| Metformin + Dapagliflozin | 1 | 0.04% |
| Methylergometrine | 1 | 0.04% |
| Methylprednisolone | 6 | 0.21% |
| Metoclopramide | 12 | 0.43% |
| Metronidazole | 6 | 0.21% |
| Midazolam | 6 | 0.21% |
| Minocycline | 2 | 0.07% |
| Mirabegrom | 1 | 0.04% |
| Mirtazapine | 1 | 0.04% |
| Mitomycin | 1 | 0.04% |
| Mometasone | 1 | 0.04% |
| Montelukast | 5 | 0.18% |
| Morphine | 2 | 0.07% |
| Moxifloxacin | 11 | 0.39% |
| Multivitamins + Minerals | 1 | 0.04% |
| Multivitamins + Minerals + Folic acid | 1 | 0.04% |
| Naproxen | 23 | 0.82% |
| Nebivolol | 1 | 0.04% |
| Nifedipine | 1 | 0.04% |
| Nimesulide | 53 | 1.88% |
| Nitrofurantoin | 12 | 0.43% |

| INN | Frequency | Percentage |
|---|---|---|
| Norfloxacin | 1 | 0.04% |
| Ofloxacin | 5 | 0.18% |
| Omalizumab | 1 | 0.04% |
| Omeprazole | 12 | 0.43% |
| Ondansetrom | 6 | 0.21% |
| Oxaliplatin | 20 | 0.71% |
| Oxybuprocaine | 1 | 0.04% |
| Oxybutynin | 1 | 0.04% |
| Oxytocin | 4 | 0.14% |
| Paclitaxel | 2 | 0.07% |
| Pantoprazole | 5 | 0.18% |
| Papillomavirus vaccine (types 6,11,16,18) | 2 | 0.07% |
| Paracetamol | 77 | 2.74% |
| Paracetamol + Bromopheniramine + Caffeine + Ascorbic acid | 3 | 0.11% |
| Paracetamol + Chlorphenamine + Hesperidin + Ascorbic acid | 1 | 0.04% |
| Paracetamol + Chlorphenamine + Phenylephrine | 1 | 0.04% |
| Paracetamol + Codeine | 4 | 0.14% |
| Paracetamol + Codeine + Buclizine | 1 | 0.04% |
| Paracetamol + Dextromethorphan + Phenylpropanolamine | 1 | 0.04% |
| Paracetamol + Mepyramine + Caffeine | 1 | 0.04% |
| Paracetamol + Thiocolchicoside | 4 | 0.14% |
| Parecoxib | 3 | 0.11% |
| Paroxetine | 3 | 0.11% |
| Patent Blue V | 3 | 0.11% |
| Peginterferon alfa-2a | 1 | 0.04% |
| Peginterferon alfa-2b | 1 | 0.04% |
| Pemetrexed | 1 | 0.04% |
| Pentoxifylline | 1 | 0.04% |
| Perindopril | 3 | 0.11% |
| Perindopril + Amlodipine | 2 | 0.07% |
| Perindopril + Indapamide | 3 | 0.11% |
| Pethidine | 1 | 0.04% |
| Phenobarbital | 1 | 0.04% |
| Phenylephrine | 1 | 0.04% |
| Phenytoin | 4 | 0.14% |
| Pholcodine | 1 | 0.04% |
| Phytine + Glutamine + Thiamine | 1 | 0.04% |
| Piperacillin + Tazobactam | 17 | 0.60% |
| Piroxicam | 10 | 0.36% |
| Pitavastatin | 2 | 0.07% |
| Policresulen + Cinchocaine | 2 | 0.07% |
| Polidocanol | 1 | 0.04% |
| Potassium chloride | 1 | 0.04% |
| Potassium iodide | 1 | 0.04% |
| Povidone-iodine | 2 | 0.07% |
| Pravastatin | 1 | 0.04% |
| Prednisolone | 10 | 0.36% |
| Pregabalin | 4 | 0.14% |
| Primidone | 1 | 0.04% |
| Proglumetacin | 1 | 0.04% |
| Promethazine | 1 | 0.04% |

| INN | Frequency | Percentage |
|---|---|---|
| Propafenone | 1 | 0.04% |
| Propofol | 15 | 0.53% |
| Prulifloxacin | 3 | 0.11% |
| Pseudoephedrine + Triprolidine | 3 | 0.11% |
| Pyrantel | 1 | 0.04% |
| Pyrazinamide | 2 | 0.07% |
| Quetiapine | 2 | 0.07% |
| Racecadotril | 1 | 0.04% |
| Ramipril | 4 | 0.14% |
| Ranitidine | 8 | 0.28% |
| Ribavirin | 1 | 0.04% |
| Rifampicin | 5 | 0.18% |
| Rilmenidine | 1 | 0.04% |
| Rituximab | 5 | 0.18% |
| Rivaroxaban | 2 | 0.07% |
| Rocuronium bromide | 10 | 0.36% |
| Rofecoxib | 6 | 0.21% |
| Ropivacain | 3 | 0.11% |
| Rosuvastatin | 1 | 0.04% |
| Rupatadine | 1 | 0.04% |
| Saccharated iron oxide | 3 | 0.11% |
| Salbutamol | 1 | 0.04% |
| Salicylic acid + Rhubarb | 1 | 0.04% |
| Sertraline | 3 | 0.11% |
| Sevoflurane | 1 | 0.04% |
| Simvastatin | 3 | 0.11% |
| Spiramycin | 1 | 0.04% |
| Streptomycin | 1 | 0.04% |
| Sulbutiamine | 1 | 0.04% |
| Sulfamethoxazole + Trimethoprim | 48 | 1.71% |
| Sulfasalazine | 5 | 0.18% |
| Suxamethonium chloride | 1 | 0.04% |
| Tamoxifen | 3 | 0.11% |
| Tansulosin | 1 | 0.04% |
| Teicoplanin | 2 | 0.07% |
| Temozolomide | 2 | 0.07% |
| Tenoxicam | 1 | 0.04% |
| Terbinafine | 2 | 0.07% |
| Tetracaine + Chlorhexidine | 1 | 0.04% |
| Thiocolchicoside | 23 | 0.82% |
| Thiopental sodium | 1 | 0.04% |
| Tinidazole | 1 | 0.04% |
| Tinzaparin sodium | 3 | 0.11% |
| Tizanidine | 1 | 0.04% |
| Tolu balsam + Sodium benzoate and combinations | 1 | 0.04% |
| Topiramate | 1 | 0.04% |
| Tramadol | 10 | 0.36% |
| Tramadol + Paracetamol | 6 | 0.21% |
| Tramazoline | 1 | 0.04% |
| Trastuzumab | 2 | 0.07% |
| Triflusal | 1 | 0.04% |

| INN | Frequency | Percentage |
|---|---|---|
| Trimetazidine | 1 | 0.04% |
| Tropicamide | 1 | 0.04% |
| Trospium chloride | 2 | 0.07% |
| Trospium chloride + Echinacea angustifolia + Sabal serulata | 6 | 0.21% |
| Valaciclovir | 1 | 0.04% |
| Valproic acid | 3 | 0.11% |
| Vancomycin | 10 | 0.36% |
| Vardenafil | 1 | 0.04% |
| Vecuronium bromide | 3 | 0.11% |
| Venlafaxine | 2 | 0.07% |
| Warfarin | 1 | 0.04% |
| Zolpidem | 1 | 0.04% |

## III. Suspected medicinal products reported, by 5th level ATC code, non-descriptive

| ATC Code 5th level | Frequency |
|---|---|
| A01A | 1 |
| A01AB11 | 1 |
| A01AB17 | 1 |
| A01AD05 | 5 |
| A01AD11 | 1 |
| A02BA02 | 8 |
| A02BC01 | 12 |
| A02BC02 | 5 |
| A02BC03 | 2 |
| A02BC05 | 5 |
| A03BB01 | 3 |
| A03DB04 | 2 |
| A03FA01 | 12 |
| A03FA03 | 1 |
| A04AA01 | 6 |
| A05 | 1 |
| A07AA04 | 1 |
| A07AA09 | 2 |
| A07DA03 | 1 |
| A07EC01 | 5 |
| A07EC02 | 1 |
| A07XA04 | 1 |
| A10BA02 | 5 |
| A10BB09 | 1 |
| A10BD | 1 |
| A11AA03 | 1 |
| A11B | 1 |
| A11CC05 | 2 |
| A11DA02 | 1 |
| A11DB | 1 |
| A11JB | 1 |
| A12AA04 | 1 |
| B01AA03 | 1 |
| B01AB05 | 7 |
| B01AB10 | 3 |
| B01AC06 | 11 |
| B01AC18 | 1 |
| B01AF01 | 2 |
| B01AF02 | 1 |
| B02AA01 | 2 |
| B02BD06 | 1 |
| B03AC | 9 |
| B03AC02 | 1 |
| B03BA01 | 2 |
| B03BA03 | 1 |
| B03BA04 | 3 |
| B03BB01 | 1 |
| B05AA06 | 1 |
| B05XA01 | 1 |
| C01BC03 | 1 |
| C01BD01 | 1 |
| C01EB15 | 1 |
| C01EB16 | 4 |
| C02AC01 | 1 |
| C02AC06 | 1 |
| C03BA04 | 1 |
| C03BA11 | 1 |
| C03CA01 | 2 |
| C04AD03 | 1 |
| C05A | 2 |
| C05BB02 | 1 |
| C05CA03 | 1 |
| C05CA53 | 1 |
| C07AB07 | 1 |
| C07AB12 | 1 |
| C08CA01 | 1 |
| C08CA05 | 1 |
| C08DB01 | 1 |
| C09AA01 | 1 |
| C09AA02 | 4 |
| C09AA03 | 1 |
| C09AA04 | 3 |
| C09AA05 | 4 |
| C09AA16 | 1 |
| C09BA03 | 1 |
| C09BA04 | 3 |
| C09BB02 | 1 |
| C09BB04 | 2 |
| C09CA01 | 1 |
| C09CA09 | 1 |
| C09DA06 | 1 |
| C09DB01 | 1 |
| C10AA01 | 3 |
| C10AA03 | 1 |
| C10AA05 | 1 |
| C10AA07 | 1 |
| C10AA08 | 2 |
| C10AB02 | 2 |
| C10AB05 | 3 |
| D01AC01 | 1 |
| D01AE15 | 2 |
| D04AB01 | 1 |
| D06AX01 | 2 |
| D07AA01 | 1 |
| D07AC01 | 1 |
| D07CC01 | 1 |
| D08AC02 | 1 |
| D08AG02 | 2 |
| D11AX18 | 2 |

| | |
|---|---|
| G01AA10 | 1 |
| G01AC05 | 1 |
| G01AF01 | 1 |
| G02AB01 | 1 |
| G02CC01 | 3 |
| G02CC02 | 4 |
| G03FB05 | 1 |
| G04BD02 | 1 |
| G04BD04 | 1 |
| G04BD09 | 3 |
| G04BD12 | 1 |
| G04BE09 | 1 |
| G04CA02 | 1 |
| H01BB02 | 4 |
| H02AB01 | 10 |
| H02AB04 | 5 |
| H02AB06 | 9 |
| H02AB09 | 4 |
| H02AB13 | 10 |
| H03CA | 1 |
| H05BA01 | 1 |
| J01AA02 | 1 |
| J01AA08 | 2 |
| J01CA01 | 3 |
| J01CA04 | 229 |
| J01CE01 | 3 |
| J01CE08 | 10 |
| J01CE30 | 3 |
| J01CF05 | 12 |
| J01CR02 | 481 |
| J01CR05 | 17 |
| J01DA04 | 1 |
| J01DA06 | 1 |
| J01DA13 | 3 |
| J01DB04 | 24 |
| J01DB07 | 20 |
| J01DC01 | 4 |
| J01DC02 | 17 |
| J01DC04 | 14 |
| J01DC10 | 5 |
| J01DD02 | 2 |
| J01DD04 | 20 |
| J01DD08 | 8 |
| J01DH02 | 2 |
| J01DH03 | 2 |
| J01DH51 | 3 |
| J01E | 1 |
| J01EE01 | 47 |
| J01FA01 | 3 |
| J01FA02 | 1 |
| J01FA09 | 33 |
| J01FA10 | 25 |

| | |
|---|---|
| J01FF01 | 11 |
| J01GB03 | 2 |
| J01MA01 | 3 |
| J01MA02 | 33 |
| J01MA06 | 1 |
| J01MA12 | 12 |
| J01MA14 | 10 |
| J01MA17 | 3 |
| J01XA01 | 8 |
| J01XA02 | 2 |
| J01XC01 | 1 |
| J01XD01 | 1 |
| J01XD02 | 1 |
| J01XE01 | 12 |
| J01XX01 | 3 |
| J01XX08 | 1 |
| J02AC01 | 4 |
| J02AC02 | 1 |
| J04AB02 | 5 |
| J04AC01 | 6 |
| J04AK01 | 2 |
| J04AK02 | 1 |
| J04AM02 | 1 |
| J05AB04 | 1 |
| J05AB11 | 1 |
| J05AB15 | 1 |
| J06BA02 | 1 |
| J07AH | 1 |
| J07AH09 | 1 |
| J07AM51 | 1 |
| J07AX | 1 |
| J07BB02 | 3 |
| J07BD | 1 |
| J07BD52 | 1 |
| J07BM01 | 2 |
| J07CA02 | 1 |
| L01AA01 | 1 |
| L01AX03 | 2 |
| L01BA04 | 1 |
| L01BC02 | 1 |
| L01BC05 | 1 |
| L01CD01 | 2 |
| L01CD02 | 5 |
| L01DC03 | 1 |
| L01XA01 | 2 |
| L01XA02 | 6 |
| L01XA03 | 20 |
| L01XC02 | 5 |
| L01XC03 | 2 |
| L01XC06 | 1 |
| L01XX19 | 2 |
| L02AE02 | 1 |

| | |
|---|---|
| L02BA01 | 3 |
| L02BG04 | 1 |
| L03AA02 | 2 |
| L03AB10 | 1 |
| L03AB11 | 1 |
| L03AX13 | 1 |
| L04AB02 | 4 |
| L04AX01 | 3 |
| M01AB01 | 2 |
| M01AB05 | 129 |
| M01AB08 | 9 |
| M01AB11 | 4 |
| M01AB14 | 1 |
| M01AB15 | 6 |
| M01AB16 | 3 |
| M01AB55 | 4 |
| M01AC01 | 8 |
| M01AC02 | 1 |
| M01AC05 | 1 |
| M01AC06 | 8 |
| M01AE01 | 302 |
| M01AE02 | 18 |
| M01AE03 | 7 |
| M01AE09 | 3 |
| M01AE14 | 3 |
| M01AE17 | 2 |
| M01AG01 | 1 |
| M01AH01 | 11 |
| M01AH02 | 6 |
| M01AH04 | 3 |
| M01AH05 | 21 |
| M01AX05 | 1 |
| M01AX17 | 52 |
| M02AA06 | 1 |
| M02AA07 | 2 |
| M02AA10 | 1 |
| M02AA12 | 1 |
| M02AA13 | 20 |
| M02AA15 | 4 |
| M02AA26 | 1 |
| M03AB01 | 1 |
| M03AC03 | 3 |
| M03AC04 | 1 |
| M03AC09 | 10 |
| M03AC11 | 1 |
| M03BX02 | 1 |
| M03BX05 | 27 |
| M03BX08 | 1 |
| M04AA01 | 26 |
| M05BB03 | 1 |
| M09AB | 3 |
| N01AB07 | 1 |

| | |
|---|---|
| N01AB08 | 1 |
| N01AF03 | 1 |
| N01AH01 | 7 |
| N01AH02 | 1 |
| N01AX10 | 15 |
| N01BB01 | 1 |
| N01BB02 | 6 |
| N01BB03 | 2 |
| N01BB08 | 1 |
| N01BB09 | 3 |
| N01BB52 | 9 |
| N01BB53 | 1 |
| N01BB58 | 2 |
| N01BX04 | 1 |
| N02AA01 | 2 |
| N02AB02 | 1 |
| N02AB03 | 3 |
| N02AJ06 | 2 |
| N02AJ13 | 3 |
| N02AX02 | 10 |
| N02AX52 | 3 |
| N02B | 22 |
| N02BA01 | 116 |
| N02BA11 | 1 |
| N02BA51 | 11 |
| N02BA71 | 2 |
| N02BB | 28 |
| N02BB02 | 17 |
| N02BE01 | 76 |
| N02BE51 | 15 |
| N02BE71 | 2 |
| N02BG | 1 |
| N02BG07 | 1 |
| N02CA52 | 3 |
| N02CX | 1 |
| N03AA02 | 1 |
| N03AA03 | 1 |
| N03AB02 | 4 |
| N03AE01 | 1 |
| N03AF01 | 7 |
| N03AG01 | 3 |
| N03AX09 | 2 |
| N03AX11 | 1 |
| N03AX12 | 2 |
| N03AX14 | 3 |
| N03AX16 | 4 |
| N04BA02 | 1 |
| N04BA03 | 1 |
| N05AH04 | 2 |
| N05BA01 | 1 |
| N05BA09 | 1 |
| N05BA12 | 1 |

| | |
|---|---|
| N05BA18 | 1 |
| N05BB01 | 1 |
| N05C | 1 |
| N05CD08 | 5 |
| N05CF02 | 1 |
| N06AA04 | 1 |
| N06AA09 | 1 |
| N06AA16 | 1 |
| N06AB05 | 3 |
| N06AB06 | 3 |
| N06AB08 | 1 |
| N06AB10 | 1 |
| N06AX | 1 |
| N06AX11 | 1 |
| N06AX16 | 2 |
| N06AX21 | 1 |
| N06AX22 | 1 |
| N06BA03 | 1 |
| N06BX06 | 1 |
| N07CA01 | 1 |
| N07CA03 | 1 |
| P01AB01 | 3 |
| P01AX06 | 1 |
| P01BA02 | 2 |
| P02CA03 | 1 |
| P02CC01 | 1 |
| R01AA09 | 1 |
| R01AD05 | 4 |
| R01AD08 | 1 |
| R01AD09 | 1 |
| R01BA52 | 2 |
| R02AA | 1 |
| R02AA03 | 1 |
| R02AX01 | 15 |
| R02AX02 | 2 |
| R03AC02 | 1 |
| R03AC13 | 1 |
| R03AK06 | 1 |
| R03AK07 | 1 |
| R03AK10 | 2 |
| R03BA01 | 1 |
| R03BA02 | 6 |
| R03BA05 | 1 |
| R03BB01 | 1 |
| R03DC03 | 5 |
| R03DX05 | 1 |
| R05CA10 | 1 |
| R05CB01 | 3 |
| R05CB02 | 1 |
| R05CB06 | 3 |
| R05DA04 | 2 |
| R05DA08 | 1 |
| R05DA09 | 1 |
| R05DB03 | 1 |
| R05DB27 | 1 |
| R05FA | 1 |
| R06A | 1 |
| R06AA04 | 1 |
| R06AB03 | 2 |
| R06AD02 | 1 |
| R06AE07 | 3 |
| R06AX | 2 |
| R06AX22 | 1 |
| R06AX28 | 1 |
| R06AX29 | 2 |
| S01AA26 | 3 |
| S01AE01 | 1 |
| S01AE05 | 4 |
| S01AE07 | 1 |
| S01BA07 | 1 |
| S01BC03 | 3 |
| S01BC05 | 5 |
| S01FA01 | 3 |
| S01FA04 | 1 |
| S01FA06 | 1 |
| S01GA05 | 1 |
| S01HA02 | 1 |
| S01JA01 | 2 |
| S02AA14 | 3 |
| S02AA15 | 9 |
| S02AA16 | 1 |
| S02BA01 | 1 |
| S02BA03 | 1 |
| V01 | 3 |
| V03AB31 | 1 |
| V03AF | 1 |
| V03AF03 | 1 |
| V07AY | 1 |
| V08 | 3 |
| V08AB05 | 22 |
| V08AB07 | 5 |
| V08AB09 | 2 |
| V08AB10 | 7 |
| V08AB11 | 4 |
| V08CA09 | 1 |

## IV. Suspected ADR by SOC, alphabetical order

| SOC | Frequency |
|---|---|
| Blood and lymphatic system disorders | 40 |
| Cardiac disorders | 60 |
| Congenital, familial and genetic disorders | 1 |
| Ear and labyrinth disorders | 10 |
| Eye disorders | 353 |
| Gastrointestinal disorders | 739 |
| General disorders and administration site conditions | 897 |
| Hepatobiliary disorders | 11 |
| Immune system disorders | 160 |
| Infections and infestations | 31 |
| Injury, poisoning and procedural complications | 9 |
| Investigations | 53 |
| Metabolism and nutrition disorders | 7 |
| Musculoskeletal and connective tissue disorders | 81 |
| Nervous system disorders | 255 |
| Pregnancy, puerperium and perinatal conditions | 1 |
| Product issues | 5 |
| Psychiatric disorders | 20 |
| Renal and urinary disorders | 11 |
| Reproductive system and breast disorders | 34 |
| Respiratory, thoracic and mediastinal disorders | 962 |
| Skin and subcutaneous tissue disorders | 3749 |
| Social circumstances | 1 |
| Surgical and medical procedures | 2 |
| Vascular disorders | 85 |

## V. Suspected ADR by PT, alphabetical order

| MedDRA PT | Frequency |
|---|---|
| Abdominal discomfort | 2 |
| Abdominal distension | 7 |
| Abdominal pain | 18 |
| Abdominal pain upper | 18 |
| Abnormal faeces | 1 |
| Abnormal palmar/plantar creases | 1 |
| Accidental exposure to product | 2 |
| Acidosis | 1 |
| Acne | 2 |
| Acute generalised exanthematous pustulosis | 1 |
| Acute kidney injury | 2 |
| Acute respiratory distress syndrome | 2 |
| Administration site erythema | 4 |
| Administration site oedema | 2 |
| Administration site pruritus | 2 |
| Adverse reaction | 6 |
| Agitation | 5 |
| Agranulocytosis | 1 |
| Alanine aminotransferase increased | 3 |
| Altered state of consciousness | 6 |
| Amnesia | 1 |
| Anaemia | 5 |
| Anal erythema | 2 |
| Anal pruritus | 1 |
| Anal ulcer | 1 |
| Anaphylactic reaction | 111 |
| Anaphylactic shock | 28 |
| Anaphylactoid reaction | 1 |
| Angioedema | 371 |
| Anorectal discomfort | 1 |
| Anxiety | 5 |
| Apathy | 1 |
| Aphasia | 3 |
| Aphonia | 5 |
| Aphthous ulcer | 11 |
| Apnoea | 1 |
| Application site pain | 1 |
| Arteriospasm coronary | 1 |
| Arthralgia | 17 |
| Arthritis | 4 |
| Arthropathy | 2 |
| Aspartate aminotransferase increased | 1 |
| Asthenia | 11 |
| Asthma | 12 |
| Asthmatic crisis | 2 |
| Atrial fibrillation | 2 |
| Auricular swelling | 1 |
| Back pain | 6 |
| Bicytopenia | 1 |
| Blepharitis | 1 |
| Blister | 7 |
| Blood alkaline phosphatase increased | 1 |
| Blood bicarbonate increased | 1 |
| Blood bilirubin increased | 1 |
| Blood creatinine increased | 1 |
| Blood lactic acid | 1 |
| Blood pressure increased | 2 |
| Bradycardia | 3 |
| Bradycardia foetal | 1 |
| Breast oedema | 1 |
| Bronchospasm | 31 |
| Burning sensation | 14 |
| Butterfly rash | 5 |
| Cardio-respiratory arrest | 4 |
| Cardiovascular disorder | 1 |
| Catarrh | 1 |
| Catheter site erythema | 1 |
| Catheter site pruritus | 1 |
| Cheilitis | 2 |
| Chest discomfort | 48 |
| Chest pain | 11 |
| Chills | 3 |
| Choking sensation | 1 |
| Circumoral oedema | 3 |
| Coagulopathy | 1 |
| Cold sweat | 2 |
| Condition aggravated | 12 |
| Conjunctival disorder | 1 |
| Conjunctival hyperaemia | 19 |
| Conjunctivitis | 16 |
| Conjunctivitis bacterial | 1 |
| Connective tissue disorder | 1 |
| Constipation | 1 |
| Contrast media reaction | 5 |
| Cough | 68 |
| COVID-19 treatment | 1 |
| C-reactive protein increased | 1 |
| Crying | 1 |
| Cutaneous vasculitis | 3 |
| Cyanosis | 5 |
| Deafness | 1 |
| Death | 1 |
| Decreased appetite | 1 |
| Dermatitis | 3 |
| Dermatitis acneiform | 1 |
| Dermatitis atopic | 1 |
| Dermatitis bullous | 20 |

| | |
|---|---|
| Dermatitis contact | 1 |
| Dermatitis exfoliative generalised | 7 |
| Diarrhoea | 48 |
| Diarrhoea haemorrhagic | 1 |
| Discomfort | 1 |
| Dizziness | 66 |
| Drug eruption | 3 |
| Drug ineffective | 3 |
| Drug level below therapeutic | 1 |
| Drug reaction with eosinophilia and systemic symptoms | 9 |
| Dry eye | 1 |
| Dry mouth | 8 |
| Dry skin | 1 |
| Dry throat | 2 |
| Dysarthria | 1 |
| Dyschromatopsia | 1 |
| Dysgeusia | 4 |
| Dyshidrotic eczema | 1 |
| Dyskinesia | 1 |
| Dysphagia | 38 |
| Dysphonia | 40 |
| Dyspnoea | 408 |
| Ear pruritus | 2 |
| Ear swelling | 4 |
| Ecchymosis | 3 |
| Eczema | 9 |
| Eczema infected | 1 |
| Enanthema | 3 |
| Eosinophilia | 10 |
| Epigastric discomfort | 3 |
| Epiglottic oedema | 1 |
| Epilepsy | 1 |
| Epistaxis | 2 |
| Erythema | 381 |
| Erythema multiforme | 3 |
| Erythema nodosum | 3 |
| Erythema of eyelid | 2 |
| Exfoliative rash | 6 |
| Extravasation blood | 1 |
| Eye disorder | 3 |
| Eye oedema | 23 |
| Eye pain | 1 |
| Eye pruritus | 15 |
| Eye ulcer | 1 |
| Eyelid oedema | 168 |
| Eyelids pruritus | 2 |
| Face injury | 1 |
| Face oedema | 290 |
| Fatigue | 9 |
| Fear of death | 1 |
| Feeling abnormal | 1 |
| Feeling hot | 75 |

| | |
|---|---|
| Fibrin D dimer increased | 1 |
| Fixed eruption | 8 |
| Flushing | 2 |
| Folliculitis | 1 |
| Forced expiratory volume decreased | 1 |
| Foreign body sensation in eyes | 1 |
| Formication | 5 |
| Gait disturbance | 1 |
| Gamma-glutamyltransferase increased | 2 |
| Gastritis | 1 |
| Gastrointestinal disorder | 1 |
| Generalised oedema | 18 |
| Genital erythema | 2 |
| Genital lesion | 1 |
| Genital ulceration | 1 |
| Gingival bleeding | 1 |
| Gingival oedema | 2 |
| Haemophagocytic lymphohistiocytosis | 2 |
| Hallucination | 2 |
| Hand dermatitis | 1 |
| Head discomfort | 2 |
| Headache | 13 |
| Hepatic cytolysis | 1 |
| Hepatic enzyme increased | 1 |
| Hepatic function abnormal | 5 |
| Hepatitis | 1 |
| Hepatitis toxic | 2 |
| Hepatosplenomegaly | 2 |
| Hot flush | 1 |
| Hyperaemia | 2 |
| Hypercalcaemia | 1 |
| Hyperglycaemia | 1 |
| Hyperhidrosis | 27 |
| Hypersensitivity | 10 |
| Hypertension | 5 |
| Hypertensive crisis | 1 |
| Hyperthermia | 3 |
| Hypoaesthesia | 3 |
| Hyponatraemia | 1 |
| Hypotension | 59 |
| Hypovolaemia | 1 |
| Hypoxia | 1 |
| Illness | 1 |
| Incontinence | 4 |
| Inflammatory marker increased | 1 |
| Injection site erythema | 3 |
| Injection site oedema | 2 |
| Injection site pain | 1 |
| Injection site papule | 2 |
| Injection site pruritus | 2 |
| Injection site rash | 3 |

| | |
|---|---|
| Injection site warmth | 1 |
| Insomnia | 1 |
| Irritability | 3 |
| Joint swelling | 7 |
| Lacrimation increased | 9 |
| Laryngeal discomfort | 5 |
| Laryngeal oedema | 35 |
| Laryngospasm | 1 |
| Leukocytosis | 1 |
| Leukopenia | 6 |
| Limb discomfort | 1 |
| Lip dry | 1 |
| Lip erythema | 1 |
| Lip injury | 1 |
| Lip oedema | 213 |
| Localised oedema | 50 |
| Loss of consciousness | 29 |
| Lymphadenopathy | 3 |
| Lymphopenia | 2 |
| Macule | 3 |
| Malaise | 86 |
| Manipulation | 1 |
| Medication error | 2 |
| Monocytosis | 1 |
| Monoparesis | 1 |
| Mouth haemorrhage | 2 |
| Mouth ulceration | 1 |
| Mucosal disorder | 1 |
| Mucosal exfoliation | 2 |
| Mucosal inflammation | 1 |
| Mucosal ulceration | 2 |
| Muscle spasms | 2 |
| Muscle tightness | 13 |
| Muscular weakness | 3 |
| Musculoskeletal discomfort | 7 |
| Myalgia | 6 |
| Nasal congestion | 5 |
| Nasal disorder | 5 |
| Nasal mucosal disorder | 1 |
| Nasal obstruction | 8 |
| Nasal oedema | 7 |
| Nasal pruritus | 2 |
| Nausea | 64 |
| Near death experience | 1 |
| Nephritis | 1 |
| Neutropenia | 3 |
| Neutrophilia | 1 |
| Nightmare | 1 |
| Nuchal rigidity | 1 |
| Occupational exposure to product | 2 |
| Ocular discomfort | 3 |
| Ocular hyperaemia | 7 |
| Odynophagia | 5 |
| Oedema | 11 |
| Oedema blister | 1 |
| Oedema genital | 3 |
| Oedema mouth | 4 |
| Oedema peripheral | 154 |
| Oesophageal pain | 2 |
| Oral candidiasis | 2 |
| Oral discomfort | 4 |
| Oral disorder | 3 |
| Oral mucosal erythema | 1 |
| Oral pruritus | 9 |
| Orbital oedema | 2 |
| Oropharyngeal discomfort | 111 |
| Oropharyngeal oedema | 4 |
| Oropharyngeal swelling | 2 |
| Osteoarthritis | 2 |
| Oxygen saturation decreased | 27 |
| Pain | 4 |
| Pain in extremity | 4 |
| Pain of skin | 1 |
| Palatal oedema | 8 |
| Pallor | 6 |
| Palmar erythema | 14 |
| Palmar-plantar erythrodysaesthesia syndrome | 4 |
| Palpable purpura | 1 |
| Palpitations | 14 |
| Pancreatitis | 2 |
| Pancytopenia | 2 |
| Papule | 3 |
| Paraesthesia | 19 |
| Paraesthesia oral | 12 |
| Paralysis | 1 |
| Pemphigoid | 2 |
| Penile blister | 1 |
| Penile burning sensation | 1 |
| Penile erythema | 2 |
| Penile oedema | 2 |
| Penile ulceration | 1 |
| Penis disorder | 1 |
| Penis injury | 1 |
| Perineal erythema | 3 |
| Perineal rash | 1 |
| Periorbital oedema | 81 |
| Periorbital swelling | 3 |
| Peripheral swelling | 1 |
| Petechiae | 2 |
| Pharyngeal disorder | 1 |
| Pharyngeal inflammation | 1 |
| Pharyngeal oedema | 4 |
| Pharyngeal ulceration | 1 |
| Photophobia | 1 |

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| Photosensitivity reaction | 1 |
| Physical disability | 1 |
| Pigmentation disorder | 1 |
| Plantar erythema | 2 |
| Polyarthritis | 3 |
| Polydipsia | 1 |
| Pre-existing disease | 1 |
| Presyncope | 35 |
| Product quality issue | 4 |
| Product substitution issue | 1 |
| Productive cough | 1 |
| Pruritus | 506 |
| Pruritus genital | 2 |
| Psychomotor hyperactivity | 1 |
| Purpura | 1 |
| Pustule | 1 |
| Pyrexia | 48 |
| Rash | 679 |
| Rash erythematous | 97 |
| Rash macular | 114 |
| Rash maculo-papular | 308 |
| Rash morbilliform | 7 |
| Rash papular | 176 |
| Rash pruritic | 260 |
| Rash pustular | 3 |
| Rash vesicular | 10 |
| Rectal haemorrhage | 1 |
| Renal failure | 1 |
| Renal impairment | 1 |
| Respiration abnormal | 1 |
| Respiratory arrest | 2 |
| Respiratory disorder | 2 |
| Respiratory distress | 23 |
| Respiratory failure | 1 |
| Rhinitis | 5 |
| Rhinorrhoea | 16 |
| Salivary hypersecretion | 3 |
| Scleral oedema | 2 |
| Secretion discharge | 3 |
| Seizure | 1 |
| Sense of oppression | 1 |
| Sensory disturbance | 1 |
| Sensory loss | 1 |
| Serum sickness-like reaction | 3 |
| Shock | 2 |
| SJS-TEN overlap | 1 |
| Skin burning sensation | 3 |
| Skin exfoliation | 55 |
| Skin hyperpigmentation | 1 |
| Skin lesion | 34 |
| Skin reaction | 19 |
| Sneezing | 16 |

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| Somnolence | 4 |
| Speech disorder | 2 |
| Spinal cord oedema | 1 |
| Spinal disorder | 1 |
| Status epilepticus | 1 |
| Stevens-Johnson syndrome | 4 |
| Stomatitis | 2 |
| Stridor | 30 |
| Swelling | 2 |
| Symmetrical drug-related intertriginous and flexural exanthema | 2 |
| Syncope | 22 |
| Tachycardia | 33 |
| Tachypnoea | 4 |
| Tendonitis | 1 |
| Throat irritation | 6 |
| Throat tightness | 20 |
| Thrombocytopenia | 3 |
| Tongue blistering | 1 |
| Tongue discomfort | 3 |
| Tongue disorder | 2 |
| Tongue eruption | 1 |
| Tongue erythema | 2 |
| Tongue oedema | 112 |
| Tongue pruritus | 1 |
| Toxic epidermal necrolysis | 1 |
| Toxic skin eruption | 11 |
| Transaminases increased | 5 |
| Tremor | 16 |
| Tubulointerstitial nephritis | 1 |
| Urinary incontinence | 1 |
| Urticaria | 535 |
| Urticaria papular | 2 |
| Urticarial vasculitis | 2 |
| Uterine atony | 1 |
| Vaccination site inflammation | 1 |
| Vaccination site oedema | 2 |
| Vaccination site pruritus | 1 |
| Vaccination site reaction | 2 |
| Vaccination site warmth | 1 |
| Vaginal haemorrhage | 3 |
| Vaginal infection | 1 |
| Vaginal lesion | 1 |
| Vaginal ulceration | 1 |
| Vascular purpura | 1 |
| Vasculitic rash | 2 |
| Vasculitis | 1 |
| Ventricular fibrillation | 1 |
| Vertigo | 2 |
| Vision blurred | 3 |
| Visual acuity reduced | 1 |
| Visual impairment | 2 |

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| Vomiting | 111 |
| Vulvovaginal erythema | 1 |
| Vulvovaginal inflammation | 1 |
| Vulvovaginal pain | 1 |

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| Vulvovaginal pruritus | 5 |
| Weight decreased | 2 |
| Wheezing | 70 |