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REVIEW



# Fifteen years of patient reporting –what have we learned and where are we heading to?

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## ABSTRACT

**Introduction:** In April 2003, the Netherlands Pharmacovigilance Centre Lareb successfully implemented patient reporting to their spontaneous reporting system. The number of reports by patients rapidly grew, prompting the need to evaluate the value of the patient reporting scheme and to compare experiences with other countries. The aim of this article is to summarize our 15-year experience of working with direct patient reporting in pharmacovigilance and to discuss necessary steps in order to optimize the use of patient reports in the future.

**Areas covered:** This article is based on Lareb studies on patient reporting from 2004 onwards and covers the evolution of the Dutch patient reporting system, the value of patient participation in pharmacovigilance, the impact of patient reporting on the spontaneous reporting system and future steps to strengthen patient reporting.

**Expert opinion:** After 15 years of experience with patient reporting we conclude that patients can add value to pharmacovigilance. We recognize that there is a big leap between allowing patients to report and actual patient involvement in pharmacovigilance. It is our belief that increased patient involvement in pharmacovigilance is a way to improve pharmacovigilance, enhancing the general public's trust in medicines.

## ARTICLE HISTORY

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## KEYWORDS

Patient reporting; patient participation; spontaneous reporting system; pharmacovigilance; signal detection

## 1. Introduction

It is important that patients can be confident that their medications are as effective and as safe as possible. Therefore it is important that safety risks are detected, evaluated and that appropriate action is taken as soon as possible to minimize harm to patients [1]. Spontaneous reporting of suspected adverse drug reactions (ADRs) remains a very useful method in this process. Incorporating patients as reporters of suspected ADRs to spontaneous reporting systems increases our knowledge about the harmful effects of medication [2].

Fifteen years ago – in April 2003, the Netherlands Pharmacovigilance Centre Lareb started with a pilot to add direct patient reporting to their spontaneous reporting system [3]. The implementation of patient reporting in the Netherlands was successful, and the number of reports by patients rapidly grew. Also in other countries, patient reporting was introduced, especially after the a change in the European pharmacovigilance legislation in 2012 [4]. This prompted the need to evaluate the value of the patient reporting scheme in the Netherlands and to compare experiences with other countries [2].

### 1.1. Aim

The aim of this article is to summarize our 15-year experience of working with direct patient reporting in pharmacovigilance and

to discuss necessary steps in order to optimize the use of patient reports in the future and to enhance patient involvement.

## 2. The evolution of the dutch patient reporting system

When Lareb started with its direct patient reporting pilot in 2003, there were doubts whether patients would be able to provide reports with a high enough quality to be useful for pharmacovigilance purposes. However, experiences from the pilot were favorable. In that first year, 276 reports were submitted by patients and 3,131 by health-care professionals (HCPs). The administrative- and clinical documentation in reports from patients was deemed sufficient for assessment. The reports by patients more frequently referred to serious ADRs than reports by HCPs and relatively more often concerned psychotherapeutic agents, notably antidepressants [3].

The number of patient reports rapidly grew, and in the end of 2018, the Netherlands Pharmacovigilance Centre Lareb had received a total of 124,502 direct reports from patients. During the same period, the number of reports from HCPs has remained stable, see Figure 1. Noteworthy peaks in the reporting by patients occurred in 2009, when the pandemic influenza vaccine for influenza H1N1 was given to a large part of the Dutch population [5] and in 2015 after media attention of problems occurring after a change in levothyroxine packaging from a glass

### Article highlights

- In the last 15 years, the Dutch patient reporting system has grown in numbers and evolved to make better use of patient-reported information on adverse drug reactions.
- Patients are able to report clinical information at a similar level as their health-care professional.
- Reporting of safety issues by Health-care professionals remains a cornerstone in pharmacovigilance but patient's direct contribution to signal detection has grown over the years and proved to be valuable.
- National pharmacovigilance center should enhance their collaboration with patient organizations to make the interaction with patients a two-way communication.
- Methods used in pharmacovigilance need to be optimized to make the best use of patient-reported information; This also means that methods and systems used for collecting, coding and analyzing patient-reported information need to be further developed.

This box summarizes the key points contained in the article.

bottle to a blister package [6]. A smaller peak in 2007 was caused by media attention on the ADRs related to statin use [7].

Comparison of patient reports and reports from HCPs received in the first 3 years after the introduction of patient reporting, showed similarities in age, sex, most frequently reported ADRs, most frequently reported drugs, and seriousness (19.5% of the patient versus 21.0% of HCP reports) [8]. Differences were however found in the categories of seriousness [8]. When analyzing and comparing reports received from patients and HCPs over the past 15 years a change in the reporting pattern is noticed; HCPs reported significantly more serious reports than patients (21.5% versus 10.4% *two-sided Pearson*  $\chi^2$   $p < 0.00$ ). However, there are also clear differences between the groups of HCPs in the percentage of serious reports, see Figure 2.

Overall, in the reports received over 15 years, the proportion of females is higher in patient reports 66.9% versus 59.9% in reports from HCPs (*two-sided Pearson*  $\chi^2$ -test  $p < 0.00$ ). The

mean age for patients is statistically lower with 38.4 years in patient reports compared to 47.8 years for HCP reports (*independent samples T-test*  $p < 0.00$ ).

In the period from 2004 to 2007, the five drug categories most frequently reported by patients were successively HMG Co-A reductase inhibitors ('statins'), selective serotonin reuptake-inhibitors, beta-adrenoceptor antagonists (beta-blockers), anticoagulants and proton pump inhibitors [8]. This top five has somewhat changed over the years, mostly due to the fact that since 2011, the Netherlands Pharmacovigilance Centre Lareb is responsible for the safety monitoring of vaccines given in the national immunization programs. Nowadays, many of those drugs which are most often reported by patients (or their caretakers) are vaccines (given in the national immunization programs) and commonly used drugs such as thyroid hormones (levothyroxine), SSRIs, oral contraceptives with estrogen, and statins. In the past, when patient reports were compared with HCP there were many similarities in the reported drugs [8]. However, when looking at the individual top 10 of the most commonly reported drugs for all reporting groups for the past 15 years, clear differences can be seen, see Table 1. There are drugs in the top 10 of some reporters, which are not in the top 10 for other reporters at all. The top 10 per reporting group is a reflection of the drugs most prescribed or dispensed by them. The reports by specialist doctors and nurses, however, include those received through a registry for patients with rheumatoid arthritis (RA) [9]. In the past, the most often reported ADRs were also similar between patient and HCP reports. Today there is more differentiation in the type of drugs patients report about, so the pattern of most often reported ADRs will also differ; 22.6% of patient reports relates to the MedDRA® System Organ Class 'General disorders and administration site conditions'. This is due to the fact that many ADRs related to injection site reactions (due to vaccines) fall in this SOC. Also, issues related to (generic) drug substitution are caught in this SOC. However, all the other reporting groups also report many ADRs that fall under this SOC.

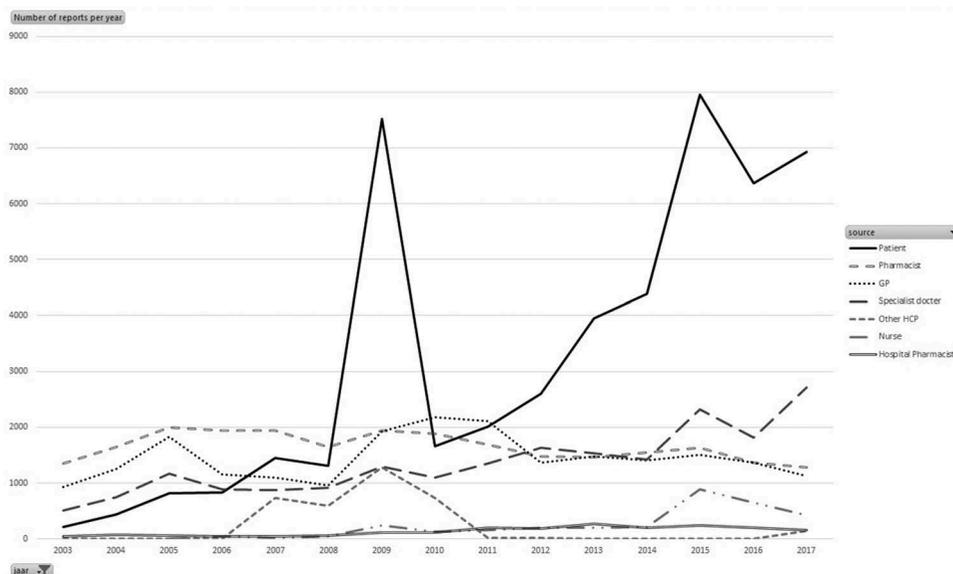


Figure 1. A number of reports (serious and non-serious) per reporting group (including the 2009 peak in reports on the pandemic influenza vaccine).

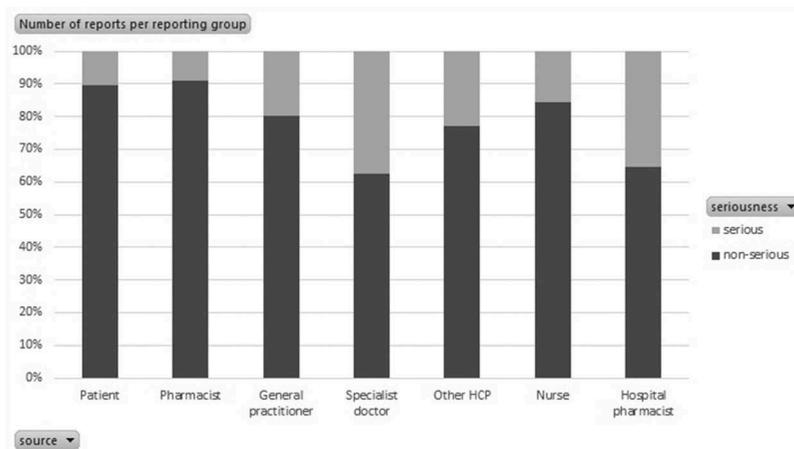


Figure 2. Percentage of serious and non-serious reports per reporting group.

### 2.1. The value of patient participation in pharmacovigilance

In our opinion, a well-functioning pharmacovigilance system, where patients are actively included, helps to increase the trust that the general public has in drugs. Studies have shown that patients are valuable contributors to pharmacovigilance [10]. Since patients are the ones that suffer from ADRs they can provide first-hand information about their experience. This also includes more detailed information about under which circumstances the drug was used, adherence, where the drug was bought in case of non-prescription medication. Also, patient reporting might be helpful in the detection of issues such as medication errors, quality failures of products and the detection of counterfeit products [10]. In the past, there were doubts about the quality of the reports patients might provide [11]. When comparing ADRs reported by both patients and HCPs, we found that the level of clinical documentation was similar between patients and HCP reports [12].

In addition, we can use this patient-reported information to get a better understanding of the patient's experiences with ADRs. Patients are in a better position than HCPs to give information about how they ADR affected them and what consequences the ADRs had, for instance on their well-being, absence from work, costs involved etc. compared to HCP reports on similar associations. Patient reports can provide more detailed information regarding the quality of life, including practical examples of how the ADR can be a barrier in performing everyday tasks [7,10]. In a comprehensive comparison between patient and HCP reports, we found that patients in their reports focused more on so-called patient-related information which included their own thoughts about causality and the impact of the reported ADRs on their daily life, whereas HCPs in their reports focused more objective elements of information such as the route of administration of the drug. However, importantly, between the groups of HCPs themselves, there were also differences in the information reported; for instance, pharmacists provide more drug-related information than medical doctors because this information is more readily available to them [13]. This highlights that patients are in a better position to describe to what

extent ADRs influence their health-related quality of life than HCPs and this information can be used for pharmacovigilance purposes [6].

Patients can also report on different types of drugs and ADRs than HCPs. Nowadays, most commonly reported products for patients include many vaccines, given in the national immunization program, where most often a parent reports adverse reactions in their children. Without patient reports, vaccine pharmacovigilance in the Netherlands would be less effective. Patients can also be used to cover blind-spots in pharmacovigilance systems, such as over-the-counter medication, herbal drugs and issues with counterfeit drugs [14].

In the Netherlands, many reports on drug-ADR associations that eventually became signals were reported by patients. In the period 2010–2015 26.3% of all ADR reports in Dutch drug safety signals were reported by patients, and 30.5% of the patient reports in the signals contained one or more terms listed as important medical events [15]. Our study showed that patients especially contributed to signals for ADRs related to generic drug substitution and psychiatric ADRs [15]. Most signals comprised of a mix of HCP and patient reports, however, there were some signals comprising almost solely from HCP reports and vice versa. An example of a signal that could not have been detected without patient reports is 'High dose vitamin B6 products and the development of neuropathy' which led to a regulatory action in the Netherlands, restricting the maximum dosage of vitamin B6 in vitamin supplements [16]. Encouraging patients to participate more actively could strengthen signal detection. More so, because we found that certain signals would not have been detected without the direct reports from patients [15,17].

### 2.2. Impact of patient reporting on the spontaneous reporting system

The introduction of patient reporting and the experiences over the years have led to new developments in our way of working. Approximately 85% of all reports directly reported to the Netherlands Pharmacovigilance Centre Lareb comes through an electronic reporting form on the Lareb website. There are different forms for both drugs and vaccines and for each type

Table 1. Top 10 most reported drugs per reporting group.

	Reporter													
	top 10 most reported drugs (% of total)													
Patient	%	Pharmacist	%	GP	%	Specialist doctor	%	Nurse	%	Hospital Pharmacist	%	other HCP	%	
1	Influenza vaccines	14.8%	Statin	5.5%	Bacterial and viral vaccines, combined	15.4%	Tumor Necrosis Factor-alpha-antagonists	4.7%	Folic acid derivatives	9.3%	Platina substances	6.9%	Bacterial and viral vaccines, combined	32.0%
2	Bacterial and viral vaccines, combined	8.6%	Proton pump inhibitors	3.8%	Pneumococcal vaccine	7.8%	Other immunosuppressants	4.2%	Influenza vaccines	7.5%	Iron, parenteral preparations	4.5%	Pneumococcal vaccine	18.5%
3	Thyroid hormones	7.0%	ACE-inhibitors	2.5%	Influenzavaccines	5.7%	Mesalazin and related substances	3.2%	Tumor Necrosis Factor-alpha-antagonists	6.5%	Taxans	3.3%	Papilloma virusvaccines	8.7%
4	Pneumococcal vaccine	4.1%	Selective serotonin reuptake inhibitors	2.5%	Statins	3.7%	Folic acid derivatives	2.8%	Bacterial and viral vaccines, combined	4.9%	Tumor Necrosis Factor-alpha-antagonists	3.3%	Measles vaccines	5.0%
5	Statins	3.2%	Selective beta-blockers	2.4%	Measles vaccines	3.1%	Selective serotonin reuptake inhibitors	2.7%	Mesalazin and related substances	4.6%	Pyrimidine-derivates	3.1%	Meningococcal vaccine	4.6%
6	Selective serotonin reuptake inhibitors	2.8%	Other anti-epileptics	2.3%	Meningococcal vaccine	2.4%	Amino-chinolines	2.3%	Amino-chinolines	3.3%	Selective serotonin reuptake inhibitors	2.5%	Vitamin k-antagonists	1.93%
7	Measles vaccines	2.4%	Other antidepressants	2.2%	Selective serotonin reuptake inhibitors	2.1%	Other antidepressants	2.3%	Other immuno-suppressants	2.8%	Antivirals for treatment of hiv infections, combinations	2.5%	Thrombocyte aggregation inhibitors excluding heparine)	1.3%
8	Other antidepressants	1.7%	Thrombocyte aggregation inhibitors excluding heparine)	2.0%	ACE-inhibitors	1.9%	Diazepines, oxazepines, thiazepines and oxepines	2.0%	Pneumococcal vaccine	2.8%	Monoclonal antibodies	2.1%	Glucocorticoids	1.2%
9	Proton pump inhibitors	1.5%	Dihydropyridine derivatives	1.8%	Proton pump inhibitors	1.6%	Other anti-epileptics	2.0%	Direct inhibitors of factor xa	2.4%	Diazepines, oxazepinen, thiazepinen and oxepines	1.9%	Sulfonamides	1.2%
10	Progestogens and estrogens in combination	1.4%	Angiotensine-II-antagonists	1.8%	Other antidepressants	1.5%	Centrally acting sympathomimetics	1.8%	Selective immunosuppressants	2.3%	Proton pump inhibitors	1.9%	Selective beta-blockers	0.9%

there is a special form for both HCPs and patients. The form includes certain mandatory fields, ensuring that at least basic information needed for causality assessment will be present in the report. In the beginning of our work with patient reports, we were very careful that the forms should be equal, but nowadays we more and more recognize that each reporting group is good at reporting different things. Patients can be asked things only they know, for example, the place a drug was obtained (including online shops) in case it was an over-the-counter product (including herbals and supplements) and the impact of the ADR on daily their daily life [18].

Studies demonstrated that patients want to be informed after they reported a possible ADR to a pharmacovigilance center [14,19]. Patients, for example, would like to know what will happen with their reports or they would like information about the ADR. Due to the rising number of patient reports in pharmacovigilance, the manner in which feedback is provided to patients is an element to be considered. In the past we provided a personalized feedback to all reporters however with the growing number of reports this is no longer feasible. Research has shown that patients are as satisfied with a general acknowledgment letter as with personalized feedback [20]. This led to an improvement of our acknowledgment letter to provide as much necessary information as possible without having to write individual feedback to each reporter.

We believe pharmacovigilance centers should make efforts to draft at least a general acknowledgment letter, explaining, for example, how their report is handled, privacy aspects concerning reported personal information, and what patients can expect from the pharmacovigilance center. This would raise awareness about the importance of reporting of ADRs, spread knowledge about the work of a pharmacovigilance center and make the patients feel that their participation is appreciated [21].

Our research on how patients can provide information about the impact of the ADR on their quality of life has been translated to practical use by adding a question about the impact of the ADR on the patient reporting form. The answer option is a 5-point scale, ranging from 'not at all' to 'very much'. There is also an option for free text, where the patient can give an elucidation of the answer given on the 5-point scale. Analysis of the first reports in which this question was answered showed that many patients make use of this option to describe how the ADR affected their daily life. Aspects that were mostly mentioned were: the severity of the ADR, impact on mood or concentration, overall (change in) health, physical impairment, and limitations in social activities. This is valuable information in order to understand the actual impact of ADRs [21,22].

These activities have also meant that our focus has widened beyond the scope of just searching for new signals of serious, and often rare, ADRs. We are also trying to capture information on the severity of common ADRs and searching for new methodologies to capture the time course and management of ADRs. The use of patient-reported information goes beyond that of spontaneous reporting only. Cohort studies using an intensive monitoring method with web-based questionnaires have been used in the Netherlands to gather information about the frequency of ADRs and aspects such as latency time, drug withdrawal, recovery and management and impact of frequently

occurring ADRs related to the use of drugs in daily practice, for instance for the antidiabetic drug metformin [23].

As seen in Figure 1, peaks in the reporting by patients occurred during a large immunization campaign for the pandemic influenza vaccine for influenza H1N1 in 2009 [5] and can occur after media attention [6,7,24]. These peaks in reporting are often viewed as negative effects of media attention and putting a strain on a spontaneous reporting system. However, a peak in reporting can also be seen as a way to quickly gain information about possible drug-related harm, which can then be analyzed and disseminated. For instance, standardized follow-up questions were used to obtain more information about risk factors for the development of thrombosis in Diane-35® users [25] and about the height and duration of fever in children after the pandemic influenza vaccine [26].

### 2.3. Current practices and future steps

As our reporting systems for patients have matured, there have been important changes in the way we view patient-reported information, worked with their reports, and the broader output we now generate as a pharmacovigilance center. We need to optimize the methods used in pharmacovigilance to make the best use of patient-reported information. This also means that our methods and systems used for collecting, coding and analyzing patient-reported information need to be further developed. This includes further development of the methodologies applied for signal detection and the way we assess possible signals [10].

Patient reports generally contain a large amount of unstructured information in the narrative. To put this to use, the application of natural language processing/text mining of reports in a pharmacovigilance database is a potential way to make use of the richness of patient ADR experiences [27]. We now capture information on the severity of the ADR in a structured data field in the reporting form. However, although this information is now collected, strategies how it will be used for signal detection purposes have to be further developed. Also, with the growth in the number of reports, we are reaching the limits of what we can assess using our case-by-case methodology, which has been the cornerstone of our signal detection since 1991. Future steps will involve combining case-by-case analyses of a selection of cases with more statistical based methods to be able to assess and analyze the large amount of data that we receive.

Since 2012 all European Union (EU) member states are obliged to give patients the opportunity to report ADRs [4]. More familiarity with the reporting of ADRs among patients has resulted in an increase of patient reports in recent years. However, there are still large differences in the number of patient reports between the various EU member states [28] where in countries with a shorter history of accepting patient reports had lower patient reporting rates than countries who had accepted patient reports for a longer period of time. There are still many countries worldwide who do not accept reports from patients and many others who do but who struggle to use the information from patients optimally [29]. Financial restraints and a lack of information/education of patients were mentioned as important barriers to achieve this [29]. A recent study found that health investment indicators were among the relevant factors for countries that had higher patient reporting rates [30].

Studies that have included experiences with patient reporting from other countries describe that the type of ADR reported and body system where the ADR occurs can differ between patient and HCPs reports [31]. Similar to the experience in the Netherlands, other countries have also found that patient reporting can help to identify novel ADRs and be useful for signal detection [31,32]. Analysis of patient reports in the UK showed that patients on the average report more ADRs per report and write more free text in their reports. Their reports were richer in description than HCPs reports and provided more information on how the ADR affected their daily life [33]. Also, similar to the Netherlands, the H1N1 pandemic influenza campaign in France leads to a large peak in reporting by patients. Analyses of the reports revealed no major difference in quality between patient and HCP reports [34]. Lack of awareness about patient reporting systems and confusion about the reporting process were found to be barriers affecting patient reporting in multiple countries [35].

While it is great that pharmacovigilance can benefit from patient reports, we should ask ourselves if pharmacovigilance can actually generate information that patients need. While it's positive that patient reporting is on the rise, pharmacovigilance centers, in turn, should undertake more efforts to identify what information patients need from them. In order to participate in decisions about their healthcare, a patient needs to receive high quality and comprehensive information about their drugs [21]. Patients can provide this information, including details on the impact on daily life, but pharmacovigilance centers should find ways to optimize the use of this information [10,21]. Based on our studies we know that patients find the impact of ADRs an important topic and that they are willing to answer questions about the impact of the ADR on their daily life. In the past, this subject remained unexplored. We believe that more efforts should be made to collect this kind of information [21].

Until now, patients have mostly been involved in pharmacovigilance as reporters of ADRs. This is in many ways a one-way communication, and we think it is important to make the interaction with patients a two-way communication, to have a dialogue with patients in matters regarding pharmacovigilance. To find out how this interaction can be established, national pharmacovigilance center should enhance their collaboration with patient organizations. Working with patient organizations can be a way for pharmacovigilance centers to have better access to the target group [36] and those active in the patient organization are also very committed. However, working with patient organizations requires time and effort on both sides. A recent European wide study shows that there is varying interest among patient organizations to be involved in pharmacovigilance. Financial restraints and lack of sources and support from National Competent Authorities are seen as the main barriers for patient organizations to being involved in pharmacovigilance [37].

### 3. Conclusion

After 15 years of experience with patient reporting, we conclude that patients can add value to pharmacovigilance. Reports from patients can provide an important complement to those from health-care professionals. Patient reports contribute to pharmacovigilance beyond numbers as they often contain more detailed

information about experienced adverse drug reactions (ADRs) and include more information on the impact on daily life, the experience of severity of the ADR (also for those which are not medically seen as 'serious') and circumstances of use. Also, it is important to recognize that patients can report information which contributes to signal detection. Involving patients will strengthen pharmacovigilance practice and ultimately can contribute to better decision-making processes.

### 4. Expert opinion

After 15 years of experience with patient reporting, we conclude that patients add value to pharmacovigilance. In general, patients are able to report clinical information at a similar level as their health-care professional and their contribution to signal detection has grown over the years. Although HCPs reported drug-ADR associations that became signals a little over a year earlier than patients, encouraging patients to participate more actively could strengthen signal detection. More so, because we found that certain signals would not have been disseminated without the direct reports from patients. Most commonly reported products for patients include many vaccines, given in the childhood vaccination programme, where most often patient report adverse reactions in their children. Without patient reports, vaccine pharmacovigilance in the Netherlands would be less effective.

Based on our studies we know that patients find the impact of ADRs an important topic and that they are willing to answer questions about the impact of the ADR on their daily life. In the past, this subject remained unexplored. We believe that more efforts should be made by pharmacovigilance centers to collect this kind of information and that ways to optimize the use of this information should be found.

Reaching patients and raising awareness about ADRs is important as many patients do not know either that they can report or where they should do this. In addition, patients should feel that their participation is appreciated. Working together with patient organizations to achieve this goal would be optimal.

We recognize that there is a big difference between allowing patients to report and actual patient involvement in pharmacovigilance. We would need to do more to really make patients partners in pharmacovigilance. On an international level, CIOMS is now having a working group dedicated to 'Patient Involvement in Drug Development and the Safe use of Drugs' [38] where guidance will be provided in which area's and how we can best involve the patient's in these matters.

The Netherlands Pharmacovigilance Centre Lareb, appointed as a WHO Collaborating Centre for patient reporting in 2013, has played an active role in disseminating information about working with patient reports in daily practice and creating knowledge on the contribution of patient participation to pharmacovigilance [2,21]. We will continue this work as it is our belief that increased patient involvement in pharmacovigilance is a way to improve pharmacovigilance and to enhance the general public's trust in medicines.

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## Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties

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## Data Availability Statement

Data associated with the paper are stored at the Netherlands Pharmacovigilance Centre Lareb

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