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CURRENT OPINION

Patient-Reported Safety Information: A Renaissance of Pharmacovigilance?

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Abstract The role of patients as key contributors in pharmacovigilance was acknowledged in the new EU pharmacovigilance legislation. This contains several efforts to increase the involvement of the general public, including making patient adverse drug reaction (ADR) reporting systems mandatory. Three years have passed since the legislation was introduced and the key question is: does pharmacovigilance yet make optimal use of patient-reported safety information? Independent research has shown beyond doubt that patients make an important contribution to pharmacovigilance signal detection. Patient reports provide first-hand information about the suspected ADR and the circumstances under which it occurred, including medication errors, quality failures, and 'near misses'. Patient-reported safety information leads to a better understanding of the patient's experiences of the ADR. Patients are better at explaining the nature, personal significance and consequences of ADRs than healthcare professionals' reports on similar associations and they give more detailed information regarding quality of life including psychological effects and effects on everyday tasks. Current methods used in pharmacovigilance need to optimise use of the information reported from patients. To make the most of information from patients, the systems we use for collecting, coding and recording patient-reported information and the methodologies applied for signal detection and assessment need to be further developed, such as a patient-specific form, development of a severity grading and evolution of the database structure and the signal detection methods applied. It is time for a renaissance of pharmacovigilance.

Key Points

Patient-reported safety information makes an important contribution to pharmacovigilance signal detection.

Patient-reported safety information leads to a better understanding of the patient's experiences of the adverse drug reaction.

Current methods used in pharmacovigilance need to optimise use of the information reported from patients, including the further development of a patient-specific form, development of a severity grading and evolution of the database structure and the signal detection methods applied.

1 Introduction

As the aim of all pharmacovigilance activities is to optimise the safe use of medicines, pharmacovigilance systems should be patient-focused, since patients are the

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ones actually experiencing harm associated with medicines.

In 2007, the Erice Manifesto, in which several challenges were addressed to ensure the continuing development and usefulness of pharmacovigilance, highlighted the message that patients are essential partners to be involved in all aspects of pharmacovigilance [1]. The role of patients as key stakeholders in pharmacovigilance was also acknowledged in the new EU pharmacovigilance legislation, which contains several efforts to increase the involvement of the general public, in particular making patient adverse drug reaction (ADR) reporting systems mandatory in all European Union Member States [2, 3].

Three years have passed since the introduction of the new EU pharmacovigilance legislation and the time is right to ask the following questions: has pharmacovigilance become more patient-oriented? Does the pharmacovigilance community acknowledge the contribution from patients? Is the information provided by patients used in the best possible way to improve safe use of medicines? These issues were discussed in April 2015 during the first Lareb Conference on Patient Reporting, organised by the Netherlands Pharmacovigilance Centre, a WHO Collaborating Center for Pharmacovigilance in Education and Patient Reporting. In this paper, the authors aim to give a description of the current issues concerning patient reporting and to discuss what needs to be further developed in order to fully embrace the possibilities that patients bring to pharmacovigilance.

2 Patient Reporting Adds Value to Pharmacovigilance Signal Detection

One of the major aims of pharmacovigilance is to detect new signals. A commonly used definition of a signal is "information that arises from one or multiple sources (including observations or experiments), which suggests a new, potentially causal association, or a new aspect of a known association between an intervention (e.g. administration of a medicine) and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action" [4]. Hence, both previously unknown associations and new aspects about an already known association are considered to be signals. Patient reports of suspected adverse reactions have contributed enormously to pharmacovigilance signal detection in a number of ways [5, 6]. Patient reports gave detailed descriptions of suspected ADRs, attributed reactions to specific medicines and provided information useful for assessing causality. Patient reports often had richer narratives than those of healthcare professionals (HCPs) and rarely provided irrelevant information or ambiguities. Patient reports also often contained detailed information about the impact of the suspected ADR on the patient's life, thus providing insights that were comparatively rare in HCP reports [7–11]. In some countries, patients showed some different patterns of reporting of drugs and ADRs compared with HCPs in terms of the drug–ADR combinations reported [9, 12]. Nevertheless, *similar* proportions of reports contain at least one reaction term that is classified as 'serious', demonstrating that most patients report clinically significant problems [9].

Studies from the UK and the Netherlands have found that patient reports have strengthened rather than hampered signal detection [5, 6]. Patient reports add weight to HCP reports by creating new and important potential signals. These studies provide reassurance regarding initial worries that an increase in the number of patient reports would only increase distracting 'noise' in signal detection [7].

Patient reports have been key in identifying certain signals that would not otherwise have been identified and in the causality analysis of others. Examples include a signal of electric shock-like sensations associated with the use of selective serotonin reuptake inhibitors (SSRIs) and duloxetine [13–16], prolonged sexual dysfunction after discontinuation of SSRIs [17, 18], SSRIs and aggression [19, 20], thyroid dysregulation after packaging change of a levothyroxine preparation from a bottle to a blister [21, 23], vitamin B6 and polyneuropathy [22], amlodipine and interaction with grapefruit juice, donepezil and unusual dreams including nightmares, medroxyprogesterone and infertility, and fentanyl and product adhesion issues [23].

Despite these convincing data, a recent survey conducted in 143 countries worldwide showed that patient reporting is not accepted in 24.1 % of the countries [24].

3 Making Best Use of Patient Reports

The role of patient reports in strengthening signal detection is therefore not in doubt. Patient reports provide first-hand information about the ADR and the circumstances under which it occurred (Table 1), leading to enhancement of pharmacovigilance systems in a number of ways.

Patient reports lead to a better understanding of the patient's experiences of the ADR and are better at explaining the nature, personal significance and consequences of ADRs than HCPs' reports on similar associations, and give more detailed information regarding impact on quality of life including psychological effects and effects on everyday tasks [7, 8, 25–27].

In view of the substantial additional value from patient reports, the question now needs to be asked whether current methods used in pharmacovigilance today make best use of the information reported from patients. Some key issues

Table 1 Areas in which patient reports in particular contribute to pharmacovigilance

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

worthy of further consideration are discussed in the following sections.

3.1 Capturing Information from Patients in ADR Reporting Forms

The first question to ask is whether the information obtained in a patient report could be improved. It is important to optimise ADR reporting forms for patients so they capture fully all the relevant information that the specific type of reporter can provide. In the past, when patient reporting was new, much emphasis was put on the perceived advantage of having similar forms for HCPs and patients, with only the wording of the questions being different. This was also one of the key recommendations of independent research carried out in the UK [9]. However, if we want to make better use of patient ADR reports as a valuable source of information, it needs to be considered whether ADR reporting forms for HCPs and patients should be clearly differentiated in order to better capture the different kinds of information that the reporter can provide. We believe that differences should be accepted and efforts made to develop reporter-specific forms, taking into account the type of information each reporter can contribute.

To know what items to include in a patient-specific form, one can draw from experience (what have patients reported in free text in the old reporting form?) or consultation with a patient organisation might provide valuable insight in to what kind of information the patient can contribute in a reporting form. Patients should also be involved in the phrasing of the questions and deciding on the answer options to make sure that the questions are easy to understand and answer.

3.2 Categorisation—Seriousness Versus Severity

Currently, reports of suspected adverse drug reactions are divided into two categories, serious and non-serious, using the CIOMS (Council for International Organizations of Medical Sciences) definition of seriousness [28]. Serious reports have the highest priority for investigation since these are considered to have the highest potential to cause harm to patients. However, with the introduction of patient reports, the division of reports based on seriousness only might need re-thinking. The concept of 'seriousness' of an adverse drug reaction was introduced at a time when primarily HCPs were reporting. For patients, an ADR might be of importance, not only based on medical seriousness but also taking severity into account. Many ADRs would be regarded as non-serious by HCPs while nevertheless being intolerable and causing severe problems or having major impact on a patient's life, showing that there might be a difference in the perceived importance of an ADR between the medical community and patients [20, 26]. An example of how patients describe the severity and the impact of the ADR on their daily functioning can be seen in the following description, in a report received by the Netherlands Pharmacovigilance Centre Lareb, by a patient who experienced aggression during citalopram use:

> Since stopping the drug [citalopram], due to an allergic reaction, the aggression and agitation disappeared almost instantly. I can enjoy life and I have not had any aggressive episodes again. When using citalopram I could shake my daughter back and forth, I did not have myself under control during the aggressive episodes.
>
> Female, 37, reported in February 2010

Severity and seriousness describe different aspects of an ADR [26]. Patient reports are helpful in evaluating severity. A more consistent or structured approach to this elicitation of the severity of the adverse reaction in the patient reporting form, similar to the CIOMS serious classification of seriousness, could help in the evaluation of the severity of the reaction from a patient's perspective. Questions about the impact of an ADR on the quality of life are asked in the reporting forms used in Italy and the UK, but they all use different ways of asking the question (see Table 2). However, it should be borne in mind that research has found no significant differences between patients and HCPs

Table 2 Questions about the impact of an ADR asked in the UK and Italian reporting forms

UK reporting form	Italian reporting form
Please describe how the side effects affected the patient by selecting from the options below (select all that apply):	How serious was the reaction?
Mild or slightly uncomfortable	Non-serious
Uncomfortable, a nuisance or irritation, but able to carry on with everyday activities	Hospital admission
Had short-term effect that was bad enough to affect everyday activities	Life-threatening
Caused significant or long-term incapacity	Permanent disability
Significant enough to lead you to seek advice from a healthcare professional	Birth defect
Bad enough to be admitted to hospital	Death
Caused an abnormality in an unborn child	
Life threatening	
Caused death	
Not serious	
	How much the reaction influenced your quality of life? Specify a value from 1 (not at all) to 10 (very much)

in the proportion of adverse reaction reports containing at least one reaction term classified as 'serious' [9], and the effort to improve clarity in terminology could create complexity which could itself result in deterring patients from reporting.

3.3 Coding and Database Structure

In some countries, patients are asked to choose the term describing the suspected adverse event which they experienced from a pre-defined list; for example, a MedDRA® term [29]. However, MedDRA® and other terminologies were not developed with the aim of being used by patients. Therefore, coding terminologies need to be further developed to better suit the needs of the patients. This has, for example, been done with the Common Terminology Criteria for Adverse Event (CTCAE), which is used for detecting and documenting AEs commonly encountered in oncology [30]. In other countries, patients' narratives are collected and translated into a code by experienced assessors, who are in turn supported by training, quality management systems and audit. However, when translating a patient narrative into a code, there is nevertheless a risk of loss of information and misinterpretation, as illustrated below by a narrative from a patient who used carmellose eye drops. The associated adverse effect was then coded with the MedDRA® term 'pruritus facial'.

> Strong pruritus, in particular on the cheeks and neck, but also in the ears, nose and the skin on the head which is covered by hair.

Pharmacovigilance database structures have mainly been developed in a time where HCPs were the primary reporters, and are therefore adjusted to the type of information often provided in HCP reports. Research has shown that there are both similarities and differences in what patients and HCPs report [9–12, 31, 32] and the current databases are not structured and operated with regard to information which is specific for patient reports. Below, two examples are given of signals identified by Lareb in a case-by-case review and where identification of the reports in the database was made manually since these cases, due to the current database structures, were not easily identified. The first signal concerns persistent sexual dysfunction after stopping SSRI treatment and is illustrated by the patient narrative in one report.

> The problems started after withdrawal of the drug, when I did not use the drug anymore. When using the drug, I had a slightly decreased libido, but that was nothing compared to the libido decrease I felt when I did not use fluoxetine anymore.

This narrative was coded with MedDRA® as 'libido decreased' as there was no possibility to code that the problem increased when stopping the drug (it does not fall into the category 'withdrawal symptoms' as the symptoms persist for months and sometimes even years). Since the symptoms were present both during and after stopping the drug, the latency would be based on the start of the initial symptoms and would probably not be very different compared with reports that describe sexual dysfunction during the use of SSRIs which disappears when withdrawing the drug. Also, the fact that the symptoms persist from months to years after cessation cannot be captured in structural fields (unless recovered at the time of notification). Since many countries rely on statistical signal detection, and sexual dysfunction is a well known ADR of SSRIs, this signal would probably not have been identified because of the structure of the current databases and the signal detection methods applied to these databases. We recommend that the structure of databases should evolve to maximise the value of patient reports.

The second signal is illustrated by this quote from a patient who reported adverse events during levothyroxine use:

> The events began after the packaging of the drug changed [from a glass bottle to a blister]. Talking to the pharmacist was useless, according to them everything should be the same, but I felt that I was feeling worse and worse.

In the beginning it was thought that these reports were similar to reports when patients experience generic substitution. However, since there was no substitution in this case (manufacturer had changed the packaging) it could not be coded as such. After receiving a few more reports, the Netherlands Pharmacovigilance Centre Lareb started to think that this was a quality issue, and started to code 'pharmaceutical product complaint' in addition to the physical complaints the patients experienced.

Statistical signal detection, based on different forms of statistical disproportionality algorithm, is in many settings the standard approach to detect new signals in a dataset, followed up by detailed case causality assessment. In most cases of statistical signal detection, a measure of disproportionality is calculated for every report, despite the (quality of) information it contains. New approaches to statistical signal detection try to take the (quality of) the information into account [33]. However, a limitation of statistical signal detection is that it only takes structured fields into account, not making use of data in unstructured fields. Data in unstructured text fields can be examined using text analysis, but this field is in its infancy. Since text fields provide so much more clinically useful information, this area should be developed and tested rapidly.

3.4 New Ways of Collecting Safety Information from Patients

In the US, about half of all adverse incident reports received by the FDA come from patients [34–36]. Mobile technology can help bring ADR reporting closer to patients, as seen in the pilot of a mobile app for adverse drug reaction reporting which started in 2015 in the UK and in 2016 in the Netherlands and Croatia as part of the WEB-RADR (Recognising Adverse Drug Reactions) project. This pilot has the advantage of enabling direct feedback to reporters, and further interaction with the reporter is facilitated [35, 37]. In the US, the FDA's Medwatcher app has been key in identifying problems with the Essure® device [38].

A prerequisite for submitting a report of a suspected adverse drug reaction to a spontaneous reporting system is that the patient knows that the system exists and that he or she can use it to report. A major issue to be addressed if the potential of patient reporting is to be realised is that awareness about ADR reporting systems is in general quite low among the general public. Furthermore, even if patients know about the ADR reporting system, they might not want to report in a formal way [9, 39, 40].

One way of coming to terms with this is to actively approach patients; for example, collecting data directly from patients as is done in Lareb Intensive Monitoring (LIM) [41–47]. Cohorts of consecutive exposed patients can be identified in various ways (e.g. through the patients' longitudinal case records), and patients can be prompted to report themselves. These data are different from spontaneous reporting data as these have more focus on extending knowledge on already known ADRs, which will hopefully be useful in detecting, understanding and treating ADRs in clinical practice. Results from a study in patients using metformin illustrates what kind of information can be obtained by LIM. In the study population, the incidence of ADRs was 34.5 %. A higher proportion of females reported the occurrence of an ADR (39.6 %) compared with the proportion in males (30.9 %). Some patients (11.4 %) stopped using metformin within 1 year after start. More than half of the patients (50.8 %) undertook no action regarding metformin after the occurrence of ADRs. A high number of patients (77.7 %) recovered or were still recovering from ADRs despite continuation of metformin. Most ADRs occurred shortly after the beginning of the treatment, with a median latency time of 1–6 days. The study revealed some ADR-specific differences in occurrence rate, latency time, management and outcome [47].

Another approach is to go looking for the information on drug safety experiences where patients usually share it. Patients are increasingly using social media to search for and exchange information about their health status [48]. At the moment, much research is ongoing to see if social media data mining can contribute to signal detection [49–52] and whether it does so in a way that enables early detection of signals, including geographical trends.

Social media data mining uses information for pharmacovigilance purposes which were not primarily shared by the patient for this purpose. This raises a number of ethical questions which must be addressed as well. The ethical issues about identification of individuals by utilising additional information (such as the geocode location on posting, username and other potentially personally identifiable information) need to be further debated. How would patients using social media react when approached for additional information by organisations that collect pharmacovigilance data? [50] Since this is a new area, ethically sound policy guidance needs to be developed.

4 Engaging with the General Public

Raising public awareness of the existence and purpose of pharmacovigilance systems in general is vitally important to increase patient involvement in pharmacovigilance.

Surveys show that public awareness of ADR reporting systems is low, ranging from 8.5 % in the UK to 17 % in the Netherlands [9, 39]. In contrast to HCPs, the general public is more difficult to target regarding promotional activities, being a larger and more diverse demographic group. Building partnerships is one way to approach this problem, involving other stakeholders in efforts to promote pharmacovigilance. Possible partners for promoting pharmacovigilance and patient engagement are the patients' organisations.

When raising awareness about pharmacovigilance, it is important to show the general public what is done with their information and how that contributes ultimately to safer use of medicines and better patient care; for example, by sharing information pro-actively about reports submitted and signals that have been raised on the basis of the reports. At the moment, more and more organisations have opened up their databases to the general public [53–55].

Patients should be actively engaged, not only as a source of information, but also when it comes to decision making in pharmacovigilance: they are the ones who ultimately will be affected by the decisions. Patient representatives are included in the Pharmacovigilance Risk Assessment Committee at the European Medicines Agency (EMA), the central decision-making body concerning pharmacovigilance issues in Europe since its establishment in 2012 [2, 3]. In 2016, public hearings will begin to be held by the EMA, when the evaluation of a drug safety issue and the relevant risk minimisation options will be enhanced by listening to patients' views. To maximise the input of patient participation, it is important to increase the capacities and capabilities of well informed patients and patient organisations so that they can be effective advocates and advisors. The consortium project 'European Patients' Academy on Therapeutic Innovation' (EUPATI), funded by the Innovative Medicines Initiative, will help patients and patients' organisations in this matter by providing scientifically reliable, objective, comprehensive information on medicines research and development [56]. Not for pharmacovigilance in particular, but to incorporate more patient focus, the EMA has also established a Patient Engagement Forum supporting the agency to access experiences of diseases, their management and information on current use of medicines and to contribute to more efficient and targeted communication with patients and consumers [57].

Patient focus is a topic that is gaining more and more attention, not only in Europe but worldwide. In the US, The Patient-Centered Outcomes Research Institute (PCORI) conducts patient-centred outcomes research that addresses the questions and concerns most relevant to patients, and also involves patients, caregivers, clinicians and other healthcare stakeholders, along with researchers, throughout the process [58].

5 A Renaissance in Pharmacovigilance?

Although the new EU pharmacovigilance legislation has made the implementation of patient-oriented ADR reporting systems mandatory, that alone does not necessarily mean that all countries have fully embraced patient reporting and the great value that it offers for pharmacovigilance. In some countries, actively promoting patient reporting might not be undertaken wholeheartedly because of fear of suddenly being flooded with reports. However, if we want to use the additional value that patients bring to pharmacovigilance, active promotion is necessary and those organisations responsible for the processing and assessing of these reports should develop the means to do this. At the moment, the full potential of patient-reported safety information and its role in contributing to public health protection is yet to be realised. To make the most of information from patients, the systems we use for collecting, coding and recording patient-reported information and the methodologies applied for signal detection need to be further refined and adapted, such as a patient-specific form, development of a severity grading and evolution of the database structure and the signal detection methods applied. It is time for a renaissance of pharmacovigilance.

Compliance with Ethical Standards

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References

1. The Erice Manifesto. for global reform of the safety of medicines in patient care. Drug Saf. 2007;30:187–90.
2. Directive 2010/84/EU. Official Journal of the European Union 2010; L. 348-74-99.
3. Regulation 1235/2010. Official Journal of the European Union 2010; L. 348-1-16.
4. CIOMS Working group VIII. Practical aspects of signal detection in pharmacovigilanc: report of CIOMS Working group VIII. Geneva: CIOMS; 2010.
5. van Hunsel F, Talsma A, van Puijenbroek E, de Jong-van den Berg L, van Grootheest K. The proportion of patient reports of suspected ADRs to signal detection in the Netherlands: case-control study. Pharmacoepidemiol Drug Saf. 2011;20:286–91.
6. Hazell L, Cornelius V, Hannaford P, Shakir S, Avery AJ. How do patients contribute to signal detection?: a retrospective analysis of

spontaneous reporting of adverse drug reactions in the UK's Yellow Card Scheme. Drug Saf. 2013;36:199–206.
7. Blenkinsopp A, Wilkie P, Wang M, Routledge PA. Patient reporting of suspected adverse drug reactions: a review of published literature and international experience. Br J Clin Pharmacol. 2007;63:148–56.
8. Medawar C, Herxheimer A. A comparision of adverse drug reaction reports from professionals and users, relating to risk of dependence and suicidal behaviour with paroxetine. Int J Risk Saf Med. 2004;16:5–19.
9. Avery AJ, Anderson C, Bond CM, Fortnum H, Gifford A, Hannaford PC, Hazell L, Krska J, Lee AJ, McLernon DJ, et al. Evaluation of patient reporting of adverse drug reactions to the UK 'Yellow Card Scheme': literature review, descriptive and qualitative analyses, and questionnaire surveys. Health Technol.Assess. 2011;15:1–iv.
10. Rolfes L, van Hunsel F, Wilkes S, van Grootheest K, van Puijenbroek E. Adverse drug reaction reports of patients and healthcare professionals-differences in reported information. Pharmacoepidemiol Drug Saf. 2015;24:152–8.
11. de Langen J, van Hunsel F, Passier A, de Jong-van den Berg L, van Grootheest K. Adverse drug reaction reporting by patients in the Netherlands: three years of experience. Drug Saf. 2008;31:515–24.
12. Danish Health and medicines Authority. Adverse Drug Reactions reported by consumers in Denmark compared with reports from Healthcare Professionals. 2013. https://laegemiddelstyrelsen.dk/~/media/B71CB7AF2879471ABE9DCF23BF853B18.ashx. Accessed 20 June 2016.
13. de Graaf L, van Puijenbroek EP. Serotonin reuptake inhibitors and shocklike paresthesia. J Clin Psychiatry. 2003;64:969–71.
14. Frost L, Lal S. Shock-like sensations after discontinuation of selective serotonin reuptake inhibitors. Am J Psychiatry. 1995;152:810.
15. Netherlands Pharmacovigilance Centre Lareb. Serotonin re-uptake inhibitors (SSRIs) and Shocklike Paraesthesia. 2002. http://www.lareb.nl/Signalen/kwb_2002_2_ssris. Accessed 21 Jan 2016.
16. Netherlands Pharmacovigilance Centre Lareb. Duloxetine and Electric Shock Sensations. 2011. http://www.lareb.nl/Signalen/kwb_2011_2_dulox. Accessed 21 Jan 2016.
17. Kennedy SH, Rizvi S. Sexual dysfunction, depression, and the impact of antidepressants. J Clin Psychopharmacol. 2009;29:157–64.
18. Ekhart CG, van Puijenbroek EP. Does sexual dysfunction persist upon discontinuation of selective serotonin reuptake inhibitors? Tijdschr Psychiatr. 2014;56:336–40.
19. Netherlands Pharmacovigilance Centre Lareb. SSRIs and aggression. 2009. http://www.lareb.nl/Signalen/kwb_2009_3_ssris. Accessed 21 Jan 2016.
20. Netherlands Pharmacovigilance Centre Lareb. SSRI's and aggression an update. 2014. http://www.lareb.nl/Signalen/KWB_2014_2_SSRI. Accessed 21 Jan 2016.
21. Netherlands Pharmacovigilance Centre Lareb. Overview of reports of adverse drug reactions associated with changes of the package of Thyrax (levothroxine) from a bottle to a blister. 2014. http://www.lareb.nl/Signalen/KWB_2014_4_Thyrax_bottle_2. Accessed 21 Jan 2016.
22. Van Hunsel F. Examples of the role of patient reports in safety signals. 2015. http://www.lareb.nl/whocc/Conference-on-Patient-Reporting. Accessed 21 Jan 2016.
23. Raine JM. The role of patients in pharmacovigilance. 2015. http://www.lareb.nl/whocc/Conference-on-Patient-Reporting. Accessed 21 Jan 2016.
24. Matos C, Härmark L, van Hunsel FPAM. Sharing knowledge on patient reporting of adverse drug reactions. Drug Saf. 2016 (Submitted).
25. Medawar C, Herxheimer A, Bell A, Jofre S. Paroxetine, panorama and user reporting of ADRs: consumer intelligence matters in clinical practice and post-marketing drug surveillance. Int J Risk Saf Med. 2002;15:161–9.
26. Frankenfeld C. "Serious" and "severe" adverse drug reactions need defining. BMJ. 2004;329:573.
27. van Hunsel F, Passier A, van Grootheest K. Comparing patients' and healthcare professionals' ADR reports after media attention: the broadcast of a Dutch television programme about the benefits and risks of statins as an example. Br J Clin Pharmacol. 2009;67:558–64.
28. CIOMS. International reporting of adverse drug reactions. CIOMS working group report. Geneva: World Health Organisation; 1987.
29. MedDRA® and MSSO. http://www.meddramsso.com/MSSOWeb/index.htm. Accessed 21 Jan 2016.
30. Dueck AC, Mendoza TR, Mitchell SA, Reeve BB, Castro KM, Rogak LJ, Atkinson TM, Bennett AV, Denicoff AM, O'Mara AM, et al. Validity and Reliability of the US National Cancer Institute's Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). JAMA Oncol. 2015;1:1051–9.
31. Aagaard L, Nielsen LH, Hansen EH. Consumer reporting of adverse drug reactions: a retrospective analysis of the Danish adverse drug reaction database from 2004 to 2006. Drug Saf. 2009;32:1067–74.
32. Inch J, Watson MC, Anakwe-Umeh S. Patient versus healthcare professional spontaneous adverse drug reaction reporting: a systematic review. Drug Saf. 2012;35:807–18.
33. Caster O, Juhlin K, Watson S, Noren GN. Improved statistical signal detection in pharmacovigilance by combining multiple strength-of-evidence aspects in vigiRank. Drug Saf. 2014;37:617–28.
34. FDA. FAERS reporting by Heathcare Providers and Consumers by Year. FDA. 2015. http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm070456.htm. Accessed 21 Jan 2016.
35. Houyez F. SCOPE progresses- patients' views. 2015. http://www.scopejointaction.eu/_assets/files/SCOPE-Event-2015-09-21-View-from-General-Advisory-Board—Francois-Houyez,-EUORDIS.pdf. Accessed 21 Jan 2016.
36. Härmark L, van Hunsel F, Grundmark B. ADR reporting by the general public: lessons learnt from the Dutch and Swedish systems. Drug Saf. 2015;38:337–47.
37. Ghosh R, Lewis D. Aims and approaches of Web-RADR: a consortium ensuring reliable ADR reporting via mobile devices and new insights from social media. Expert Opin Drug Saf. 2015;14:1845–53.
38. Bahk CY, Goshgarian M, Donahue K, Freifeld CC, Menone CM, Pierce CE, Rodriguez H, Brownstein JS, Furberg R, Dasgupta N. Increasing patient engagement in pharmacovigilance through online community outreach and mobile reporting applications: an analysis of adverse event reporting for the Essure device in the US. Pharm Med. 2015;29:331–40.
39. Consumentenbond. Ziek van de pillen. Consumentengids. 2014;5:16–9.
40. Robertson J, Newby DA. Low awareness of adverse drug reaction reporting systems: a consumer survey. Med J Aust. 2013;199:684–6.
41. Härmark L, van Hunsel F, Hak E, van Grootheest K. Monitoring the safety of influenza A (H1N1) vaccine using web-based intensive monitoring. Vaccine. 2011;29:1941–7.
42. Härmark L, Puijenbroek E, Grootheest K. Longitudinal monitoring of the safety of drugs by using a web-based system: the case of pregabalin. Pharmacoepidemiol Drug Saf. 2011;20:591–7.

43. Oosterhuis I, Härmark L, van Puijenbroek E. Experiences with the use of varenicline in daily practice in the Netherlands: a prospective, observational cohort study. Drug Saf. 2014;37:449–57.
44. van Balveren-Slingerland L, Kant A, Härmark L. Web-based intensive monitoring of adverse events following influenza vaccination in general practice. Vaccine. 2015;33:2283–8.
45. Härmark L, Van Puijenbroek E, van Grootheest K. Intensive Monitoring of duloxetine, results from a web-based intensive monitoring study. Eur J Clin Pharmacol. 2013;69:209–15.
46. Härmark L, van Puijenbroek E, Straus S, van Grootheest K. Intensive Monitoring of pregabalin, results from an observational, web-based, prospective cohort study using patients as a source of information. Drug Saf. 2011;34:221–31.
47. de Jong L, Härmark L, van Puijenbroek E. Time course, outcome and management of adverse drug reactions associated with metformin from patient's perspective: a prospective, observational cohort study in the Netherlands. Eur J Clin Pharmacol. 2016;72:615–22.
48. Fox S. The social life of health information. 2011. http://www.pewinternet.org/2011/05/12/the-social-life-of-health-information-2011/. Accessed 21 Jan 2016.
49. Freifeld CC, Brownstein JS, Menone CM, Bao W, Filice R, Kass-Hout T, Dasgupta N. Digital drug safety surveillance: monitoring pharmaceutical products in twitter. Drug Saf. 2014;37:343–50.
50. Sloane R, Osanlou O, Lewis D, Bollegala D, Maskell S, Pirmohamed M. Social media and pharmacovigilance: a review of the opportunities and challenges. Br J Clin Pharmacol. 2015;80:910–20.
51. Sarker A, Ginn R, Nikfarjam A, O'Connor K, Smith K, Jayaraman S, Upadhaya T, Gonzalez G. Utilizing social media data for pharmacovigilance: a review. J Biomed Inform. 2015;54:202–12.
52. Powell GE, Seifert HA, Reblin T, Burstein PJ, Blowers J, Menius JA, Painter JL, Thomas M, Pierce CE, Rodriguez HW, et al. Social media listening for routine post-marketing safety surveillance. Drug Saf. 2016;39:443–54.
53. EMA. European database of suspected adverse reaction reports. EMA. 2015. http://www.adrreports.eu/. Accessed 22 Jan 2016.
54. UMC. VigiAccess. 2015. http://www.vigiaccess.org/. Accessed 21 Jan 2016.
55. Netherlands Pharmacovigilance Centre Lareb. 2015. http://www.lareb.nl. Accessed 21 Jan 2016.
56. European Patients' Academy on Therapeutic Innovation (EUPATI), 2016. https://www.eupati.eu/what-is-eupati/. Accessed 20 June 2016.
57. EMA. Patient Engagement Forum. 2016. http://www.ema.europa.eu/ema/index.jsp?curl=pages/partners_and_networks/general/general_content_000317.jsp&mid=WC0b01ac058003500c. Accessed 20 June 2016.
58. The Patient-Centered Outcomes Research Institute (PCORI). 2016. http://www.pcori.org/. Accessed 20 June 2016.