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ORIGINAL REPORT

Adverse drug reaction reports of patients and healthcare professionals—differences in reported information†

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ABSTRACT

Purpose This study aims to explore the differences in reported information between adverse drug reaction (ADR) reports of patient and healthcare professionals (HCPs), and, in addition, to explore possible correlation between the reported elements of information.

Methods This retrospective study compared the reported information between 200 ADR reports of patients and HCPs. Reports were rendered anonymous and scored for the presence or absence of predefined elements of information. These elements can be objective (e.g. start date of the ADR) or subjective (e.g. the impact or severity of the ADR).

A two-sided Pearson's Chi-square test was used to detect statistically significant differences in the reported information. A Bonferroni correction was used to correct for multiple comparisons. Correlation between the elements of information was explored using categorical principal components analysis (CATPCA).

Results Overall, HCPs had a higher score for the presence of objective and patients for subjective elements of information. Elements that were statistically significant more often reported by patients are the impact of the ADR and the patient's weight and height. HCPs statistically significant more often reported the medical history and the route of administration of the drug. CATPCA showed four clusters of elements of information that have fair correlation.

Conclusions This study demonstrates the differences in reported information between ADR reports of patients and HCPs. Patient reports are more focused on patient-related information and the impact of the reported ADRs, whereas reports from HCPs provide more clinically related information.

KEY WORDS—adverse drug reactions (ADRs); pharmacovigilance; patient reporting; pharmacoepidemiology

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INTRODUCTION

Detection of new adverse drug reactions (ADRs) after marketing is often based on clinical observations in daily practice. Spontaneous reporting of ADRs is one of the main methods of detection of post-marketing drug safety issues.[1] Traditionally, reporting of possible ADRs was reserved for healthcare professionals (HCPs). Patients of only a few countries were able to report their ADR directly to the competent authority, for example, in the USA since 1969, Denmark and the Netherlands since 2003, the UK since 2005 and Sweden since 2008.[2] This altered after changes in the European pharmacovigilance legislation, allowing patients of all European member states to report drug concerns directly.[3]

Patient reporting in pharmacovigilance

Previous research demonstrated that patients may have a positive complementary contribution to that of HCPs by identifying different drug-ADR associations.[4] Besides, patients may report different information compared with HCPs, resulting in broader information of the ADR. Over time, several studies were conducted to explore differences in reported information between reports of patients and HCPs.[5–10] These studies mainly focused on directly measurable differences, for example, the kind of ADR and seriousness of the ADR. Less attention has been paid to subjective differences, for example, the extent to which clinical

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aspects has been reported or the impact of the ADR on the patient's daily life. A study by Avery *et al*. in the UK comparing patients' descriptions of their ADRs to HCPs demonstrated that detailed information about the impact of the ADR on the patient's daily life was given by patients, but was comparatively rare in HCP reports.[6] Information about subjective matters about the ADR can be useful in the understanding of the tolerability of ADRs[11] and provides insight into the perception of the ADR by the patient. Insight in similarities and differences between reports of patients and HCPs, including objective as well as subjective elements of information, is helpful in order to clarify the potential value of direct patient reporting to pharmacovigilance.

Correlation between reported elements of information

When comparing reports of patients and HCPs, it is interesting to take into consideration a possible correlation in reported elements of information. When the severity of the ADR is reported, it may be expected that the reporter also gives information about the impact. The same applies, for example, for information about to the suspected drug, for example, dosage unit, pharmaceutical form, or indication. To the best of our knowledge, possible correlation in reported elements of information has not been explored before.

This study aims to explore the differences in reported information between ADR reports of patient and HCPs, and, in addition, to explore possible correlation between the reported elements of information.

METHOD

A retrospective study of 200 ADR reports from patients and HCPs was performed, which looked at similarities and differences in reported information and possible correlation between reported elements of information. Reports of patients were compared with those of HCPs in general and to the individual groups on the basis of reported elements of information.

Reporting to the Netherlands Pharmacovigilance Centre

In the Netherlands, patients and HCPs can report by means of an electronic or paper reporting form. Almost 95% of all reports are performed by means of the electronic form. The reporting form contains standardized questions of which some are mandatory in the electronic form. Besides, reporters can give additional information in a free text field. With exception of the question about medical history, which is only present on the HCP reporting form, both reporting forms obtain the same information.

Study population

From 1 March 2012, the first 100 reports of patients and the first 100 reports of HCPs (pharmacists, general practitioners, and specialist doctors) were selected from the database of the Netherlands Pharmacovigilance Centre. For each reporter, only one ADR report was included.

Rating of ADR reports

Reports were scored for the presence or absence of predefined elements of information. A list of elements of information was obtained from a previous study in our center, exploring information that was found to be important regarding ADR reporting by reporters and assessors of ADRs.[12] Seriousness of the reports was scored according to the international Council for International Organizations of Medical Sciences criteria. ADRs considered serious include reactions leading to (prolongation of) hospitalization, life-threatening events, reactions leading to death, disabling events or congenital abnormalities.[13]

All included reports were blinded by removing the type of source (either patient or HCP). Reports were rendered anonymous and scored by one of five experienced ADR assessors (FH, IO, MH, PH, and SK). ADR assessors are professionals that are trained to do a causality assessment of ADR reports. At the Netherlands Pharmacovigilance Centre, these assessors are mainly medical doctors or (hospital)pharmacists. In assigning the reports, none of the assessors received reports they had previously seen before.

Prior to the study, the assessors were trained to score the reports. After training, the assessors scored 10 reports individually. The degree of agreement in scoring was determined by calculation of the Fleiss Kappa coefficient (κ). Training was continued until substantial agreement (κ of 0.60) was achieved.[14]

Statistical analysis

A Pearson's Chi-square (X^2)-test was used to study differences in the number of reported elements of information. Significance was based on a two-sided Pearson's X^2-test; $p < 0.05$. To correct for multiple comparisons, a Bonferroni correction was conducted (corrected $\alpha = \alpha$/number of independent significance tests).[15] It adjusted for 52 independent tests leading to the corrected p-value for significance of <0.001.

Correlation testing of pharmacovigilance data can be performed using categorical principal components analysis (CATPCA). CATPCA is mostly used in

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social and behavioral sciences in order to reduce large numbers of variables to a small number of uncorrelated linear combinations that represent most of the information found in the original variables.[16,17]

The CATPCA based on two dimensions was conducted to investigate which elements of information possibly correlate. In CATPCA, the variance account for (VAF)-score can be used to determine the degree of correlation. The following rules of thumb for VAF can be used: 10% is poor, 20% is fair, 30% is good, 40% is very good, and 50% is excellent.[16] For this study, elements with at least fair correlation were selected. Elements of information that were 100% reported were excluded from the CATPCA, because no differences between both study groups exist.

Data were analyzed using the statistical software program SPSS Statistics, version 20.0 (SPSS, Chicago, IL).

RESULTS

Differences in reported information

An overview of the number of elements of information reported by patients and HCPs is shown in Table 1. Six elements of information are statistically differently reported by patients and HCPs. Patients more often reported the impact of the ADR (17% versus 2%) and patient's weight and height (respectively, 94% versus 52% and 93% versus 54%). HCPs more often reported the route of administration of the drug (92% versus 41%) and the medical history (61% versus 9%). Further, a statistically significant difference was seen for the seriousness of the ADR between reports of patients and specialist doctors (10% versus 42%).

Although not statistically significant, some elements showed a difference in reporting worth mentioning. The course and outcome of the ADR, a detailed description of what happened, the severity of the ADR, contact with or between HCPs, and patient's thoughts about causality were more often reported by patients compared with HCPs. Elements related to the drug use, drug dosage, the pharmaceutical form of the drug, and other suspect medication, were more often reported by HCPs. Further, a diagnosis confirmed with clinical tests was more often reported by specialist doctors compared with patients. The registration number for drugs was more often reported by pharmacists followed by patients, which subsequently reported more often than general practitioners and specialist doctors.

Correlation between reported elements of information

Of all 56 elements included in this study, 52 were included in the CATPCA. In Table 2, the 20 elements with a VAF-score of $\geq 20\%$ are shown.

Roughly, a distinction can be made for four clusters of correlated elements as shown in Figure 1. The first clusters refer to patient-related information; patient's weight and height. Elements of this cluster are statistically significant more often reported by patients. Elements in the second cluster are mostly related to the patient's perception of the ADR, for example, the impact and severity of the ADR. Although not all statistically significant, these elements are more often reported by patients. The third cluster contains additional Information on the ADRs, for example, test results in relation with the ADR and past drug therapy. With the exception of the test results, there is no difference in reporting between patients and HCPs for elements in cluster C. The final cluster refers to drug-related information; for example, drug dosage and dosage unit. Although not all statistically significant, most of these elements are more often reported by HCPs.

DISCUSSION

This study demonstrates the differences in information reported by patients and HCPs. The Netherlands Pharmacovigilance Centre has long-time experiences with patient reporting, and previous studies learned that there are differences in reported information between both groups.[6–10,18] However, the exact nature of the differences was not yet clarified. By including a large number of elements of information, we aimed to give a comprehensive view of the differences in reported information between reports of patients and HCPs. Besides, correlation between the included elements of information was explored to obtain a deeper insight in the nature of the reported information.

This study found differences in both objective and subjective elements of information. HCPs more often reported objective information compared with patients. Probably, they might recognize the importance of these elements more or are more equipped to provide this information. It is remarkable that clinical information like test results were not more often reported by HCPs. A general idea about reporting by HCPs is that they report additional information to clinically support their ADR report. This idea was not supported by this study. Test results are reported, albeit minimal.

Distinguishing the different groups of HCPs and comparing them with patients, only specialist doctors more often reported a diagnosis, which was confirmed with test results. However, the reporting of addition information to clinically support the ADR reports might be associated with the specific drug-ADR associations, which was not included in this study design.

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Table 1. Comparison of elements of information reported by patients and healthcare professionals

Elements of information	% patient reports	% HCP reports	X^2-test *p*-value	% General practitioners^ (X^2-test *p*-value)	% Pharmacists+ (X^2-test *p*-value)	% Specialist doctors^ (X^2-test *p*-value)
ADR						
ADR**	100	100	NA	100 (NA)	100 (NA)	100 (NA)
Start date of the ADR**	98	97	1.00#	97 (1.00#)	97 (0.75)	97 (1.00#)
Time to onset	95	96	1.00#	91 (1.00#)	97 (0.62)	97 (1.00#)
Outcome ADR**	91	81	0.04	85 (0.32#)	68 (0.01)	91 (0.99#)
Treatment of the ADR**	37	39	0.77	45 (0.34)	32 (0.63)	40 (0.81)
ADR occurred after use of a similar drug**	12	10	0.65	9 (0.76#)	12 (1.00#)	9 (0.76#)
No ADR after use of a similar drug	7	1	0.07#	3 (0.67#)	0 (0.19#)	0 (0.19#)
Other aspects that could have caused the ADR**	15	14	0.84	12 (0.78#)	12 (0.71#)	18 (0.66)
Seriousness**	**10**	25	0.01	12 (0.75)	21 (0.14#)	**42** (<**0.001**)
Detailed description of the ADR	49	30	0.01	42 (0.51)	21 (0.01)	27 (0.03)
Course of the ADR	30	28	0.76	12 (0.04)	35 (0.57)	36 (0.50)
ADR after increase/decrease of dose, after withdrawal of drug	5	4	1.00*	0 (0.33#)	3 (1.00)	9 (0.41#)
Dechallenge	10	12	0.65	9 (1.00#)	21 (0.14#)	6 (0.73#)
Rechallenge	9	3	0.07	3 (0.45#)	3 (0.51#)	3 (0.45#)
Recurrence	5	5	1.00	9 (0.41#)	0 (0.39#)	6 (1.00#)
Recovery date**	0	4	0.12#	3 (0.25#)	3 (0.25#)	6 (0.06#)
Time to recover	4	8	0.23	6 (0.64#)	6 (0.64#)	12 (0.11#)
Impact of the ADR on the patient's daily life	**17**	**2**	<**0.001**	0 (0.07#)	3 (0.29#)	3 (0.29#)
Severity of the ADR	30	12	0.01	12 (0.04)	12 (0.04)	12 (0.04)
Drug						
Suspect drug**	100	100	NA	100 (NA)	100 (NA)	100 (NA)
RVG code*	27	19	0.18	6 (0.01)	47 (0.03)	3 (0.01)
Interaction*	2	3	1.00#	3 (1.00)	9 (1.00#)	3 (1.00#)
Start date drug**	98	100	0.50#	100 (1.00#)	100 (1.00)	100 (1.00#)
Stop date drug*	58	66	0.24	73 (0.13)	59 (0.9)	67 (0.38)
Drug dosage*	77	93	0.01	90 (0.08)	100 (0.01)	88 (0.18)
Dosage unit*	77	87	0.07	88 (0.18)	91 (0.18)	82 (0.56)
Route of administration*	**41**	**92**	<**0.001**	**90** (<**0.001**)	**97** (<**0.001**)	**88** (<**0.001**)
Pharmaceutical form*	74	86	0.03	82 (0.37)	94 (0.013)	82 (0.36)
Indication*	86	89	0.52	90 (0.56)	79 (0.36)	97 (0.12#)
Actions after occurrence of ADR	94	95	0.76	94 (0.99#)	97 (0.49#)	94 (0.99#)
Other suspect drugs*	4	14	0.01	12 (0.11#)	9 (0.37#)	21 (0.01#)
Concomitant drugs**	36	46	0.15	33 (0.78)	62 (0.01)	42 (0.51)
Batch number	1	2	1.00#	6 (0.15#)	0 (1.00#)	0 (1.00#)
Contra indication	1	0	1.00#	0 (1.00#)	0 (1.00#)	0 (1.00#)
Extra information about the drug use	10	5	0.18	3 (0.29#)	9 (1.00#)	3 (0.29#)
Patient's characteristics						
Sex**	100	100	NA	100 (NA)	100 (NA)	100 (NA)
Date of birth**	100	100	NA	100 (NA)	100 (NA)	100 (NA)
Patient's weight*	**94**	**52**	<**0.001**	**61** (<**0.001**)	**24** (<**0.001**)	**73** (<**0.001**)
Patient's height*	**93**	**54**	<**0.001**	**52** (<**0.001**)	**24** (<**0.001**)	**61** (<**0.001**)
Medical history/co-morbidity/ allergy*	**9**	**61**	<**0.001**	**56** (<**0.001**)	**47** (<**0.001**)	**79** (<**0.001**)
Past drug therapy	8	10	0.62	3 (0.45#)	15 (0.31#)	12 (0.49#)
Life style (occupation, diet, sports)	4	2	0.68#	0 (0.57#)	6 (0.64#)	0 (0.57#)
Compliance	0	1	1.00#	0 (NA)	3 (0.25#)	0 (NA)
Additional information						
Test results in relation with the ADR	8	10	0.62	6 (1.00#)	9 (1.00#)	15 (0.31)
Diagnosis confirmed with clinical test	2	8	0.05	3 (1.00#)	9 (0.10#)	12 (0.03#)
Discharge letter	1	2	1.00#	0 (1.00#)	0 (1.00#)	6 (0.15#)
Literature	2	4	0.68#	3 (1.00#)	6 (0.27#)	3 (1.00#)
Incidence	2	1	1.00#	0 (1.00#)	3 (1.00#)	0 (1.00#)
ADR present/absent in SmPC	3	0	0.25#	0 (0.57#)	0 (0.57#)	0 (0.57#)
Confounding by indication	3	4	1.00#	0 (0.57#)	6 (0.60#)	6 (0.60#)
Information about specific groups of patients	5	3	0.72#	3 (1.00#)	3 (1.00#)	3 (1.00#)
ADR seen before by the reporter	6	1	0.12#	3 (0.68)	0 (0.34#)	0 (0.34#)

(*Continues*)

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Table 1. (Continued)

Elements of information	% patient reports	% HCP reports	X^2-test *p*-value	% General practitioners^ (X^2-test *p*-value)	% Pharmacists+ (X^2-test *p*-value)	% Specialist doctors^ (X^2-test *p*-value)
Opinion/clinical experience HCP	14	13	0.84	12 (1.00#)	9 (0.56#)	18 (0.58#)
Patient's thoughts about causality	12	2	0.01	0 (0.04#)	4 (0.52#)	0 (0.04#)
Contact with or between HCPs	23	10	0.01	9 (0.08)	4 (0.16)	9 (0.08)
Self-management patient	9	5	0.27	3 (0.26#)	12 (0.96#)	3 (0.26#)

In bold is the group that scores statistically significant better.
ADR, adverse drug reaction; HCP, healthcare professional; RVG, registration number for drugs.
*Standardized question on ADR reporting form.
**Standardized and mandatory question on ADR reporting form.
#Fishers exact test.
^Total number HCPs included is 33.
+Total number of HCPs included is 34.
NA: data not applicable.

Table 2. Elements of information in categorical principal components analysis with variance account for score ≥20%

Number	Element of information	VAF score	Cluster
1	Patient's weight	0.48	A
2	Patient's height	0.47	A
3	Impact of the ADR on the patient's daily life	0.20	B
4	Patient's thoughts about causality	0.25	B
5	Detailed description of the ADR	0.23	B
6	Severity of the ADR	0.20	B
7	Contact with or between HCPs	0.23	B
8	Opinion/clinical experience HCP	0.27	C
9	Course of the ADR	0.33	C
10	Recurrence	0.20	C
11	Test results in relation with the ADR	0.26	C
12	Contra-indication	0.35	C
13	Past drug therapy	0.22	C
14	Time to recovery	0.31	C
15	Discharge letter	0.43	C
16	Pharmaceutical form	0.31	D
17	Route of administration	0.45	D
18	Drug dosage	0.20	D
19	Dosage unit	0.24	D
20	Start date of the ADR	0.24	-

ADR, adverse drug reaction; HCP, healthcare professional; VAF, variance account for.

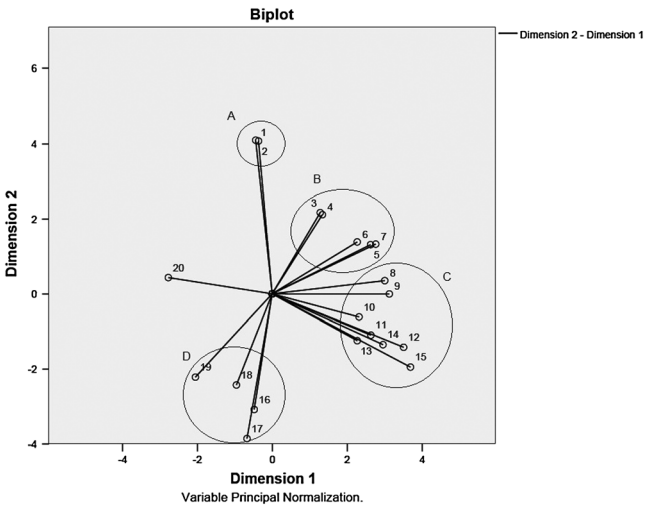

Figure 1. Categorical principal components analysis

Elements more often reported by HPCs were mainly standardized questions on the ADR reporting form, for example, route of administration of the drug and the patient's medically history. Additionally, CATPCA showed one cluster of elements of information referring to drug-related information, cluster D. Most of these elements are more often reported by HCPs. The element *medically history*, which is more often reported by HCPs, deserves special attention. This element is a standardized question on the HCP reporting form but is not on the patient reporting form. The detected difference is therefore to be expected.

Subjective elements of information are mostly reported by patients. CATPCA showed one cluster of elements of information that are of subjective nature cluster about the perception of the ADRs. All elements of information in this cluster are more often reported by patients. Patients more often gave a detailed description about their perception of the ADR and the impact it had on their daily life. This kind of information was less frequently reported by HCPs. Information about the severity and the impact of an ADR can be useful for the understanding of the tolerability of ADRs.[19] Medical seriousness according to the Council for International Organizations of Medical Sciences criteria may differ from patients' views on what constitutes a serious problem.[20] Patients information leaflets mostly lack this kind of information.[21] When such information is documented and made available, this can be helpful for patients in the acceptance and handling of their ADRs. Because this information is rarely reported by HCPs, patients can give added value by reporting such elements of information.

Besides objective information, patients more often report their weight and height compared with HCPs.

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For patients, this kind of information is a known fact, whereas for HCPs, this information might not always be available.

Comparison with other studies

Only a few elements of information included in this study could be compared with literature. Differences in the reporting of serious ADRs has been explored in Denmark, the UK, and the Netherlands.[5,7,10] Comparing reports of patients and HCPs, no differences in seriousness of reported ADRs were found in Denmark and the Netherlands.[5,7] In the UK, HCPs statistically significant more often report serious ADRs compared with patients.[10] In the Netherlands, a statistically significant difference was only seen when comparing patients with specialist doctors.[7] As in the current study, other studies demonstrated that the impact of the ADR on the patient's daily life and a detailed description of the ADR are more often reported by patients.[6,9,18]

Since the beginning of direct patient reporting to pharmacovigilance, several studies were performed to explore their value to pharmacovigilance. A recent systematic review on patient versus HCP reporting concluded that despite the large and increasing number of national pharmacovigilance schemes that accept patient reports, only a few comparative studies have been undertaken of patient and HCPs reporting. The true value of patient reports to pharmacovigilance will remain unknown unless more comparative evaluations are undertaken.[8] This current study contributes to clarify the potential value of direct patient reporting to pharmacovigilance. The differences found in this study indicate that reports of patients as well as HCPs are needed in order to obtain a comprehensive view of the ADR.

Strengths and weakness

For this study, a large set of elements of information was included to get a comprehensive view of the essential differences between information reported by patients and HCPs. A strength of this study is that it took into account more information that only the mandatory fields in the reporting form. Also, the additional information from the narrative of the reports and added information like attached lab results, hospital discharge letters, but also subjective elements like the impact of the ADR were compared. Further, a new aspect was introduced, namely, the correlation between the reported elements of information. Because the reports had to be scored by trained assessors, a limited number of 200 reports, not matched on ADR, was selected at random. The reported information may depend on the drug-ADR association. for example, for a report about hepatitis, you would rather expect test results compared with reports about severe withdrawal syndromes or taste disorders. For these reports, you would rather expect information about the severity of impact. Further research on reported information for specific drug-ADR associations is needed.

From the results of this study, no conclusions can be drawn about the clinical relevance of the reported information between both groups. The focus was to describe the nature of the reported information. A follow-up step will be to explore differences in causality between reports of patients and HCPs. The primary aim of a spontaneous reporting system in pharmacovigilance is the timely detection of unknown ADRs. For this purpose, it is important to make a proper assessment of the drug-ADR association. Further research would be needed to determine whether the differences in reported elements between patients and HCPs affect this causality assessment.

CONCLUSION

This study demonstrates the differences in reported information between ADR reports of patients and HCPs. Patient reports are more focused on patient-related information and the impact of the reported ADRs, whereas reports from HCPs provide more clinically related information.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

KEY POINTS
- Patient reports are more focused on the impact of the reported ADRs, whereas reports from HCPs provide more clinical related information.
- There is no difference between patients and HCPs in the reporting of additional information to clinically support their ADR.
- Patient reporting is a relatively new but very promising part of drug safety monitoring.

ETHICS STATEMENT

For this study Ethics committee approval was not required, as Dutch legislation does not request this for studies which do not affect the patient's integrity.

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REFERENCES

1. Ishiguro C, Hall M, Neyarapally GA, Dal PG. Post-market drug safety evidence sources: an analysis of FDA drug safety communications. *Pharmacoepidemiol Drug Saf* 2012; **21**(10): 1134–1136.
2. van Hunsel F, Härmark L, Pal S, *et al.* Experiences with adverse drug reaction reporting by patients; an 11-country survey. *Drug Saf* 2012; **35**(1): 45–60.
3. The EU Pharmacogivilance system. The European Commission (EM). [online]. [14 January 2014].
4. 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**(3): 199–206.
5. 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**(11): 1067–1074.
6. Avery AJ, Anderson C, Bond CM, *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**(20): 1–iv.
7. de Langen J, van Hunsel F, Passier A, de Jong- van den Berg LTW, van Grootheest AC. Adverse drug reaction reporting by patients in the Netherlands, three years of experience. *Drug Saf* 2008; **31**(6): 515–524.
8. Inch J, Watson MC, Anakwe-Umeh S. Patient versus healthcare professional spontaneous adverse drug reaction reporting: a systematic review. *Drug Saf* 2012; **35**(10): 807–818.
9. van Hunsel F, Passier A, van Grootheest AC. 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**(5): 558–564.
10. McLernon DJ, Bond CM, Hannaford PC, *et al.* Adverse drug reaction reporting in the UK: a retrospective observational comparison of yellow card reports submitted by patients and healthcare professionals. *Drug Saf* 2010; **33**(9): 775–788.
11. 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**(2): 148–156.
12. Rolfes L, Wilkes S, van Hunsel F, van Puijenbroek E, van Grootheest K. Important information regarding reporting of adverse drug reactions: a qualitative study. *IJPP* 2013;[published online] [13 June 2013].
13. CIOMS Working Groups IV. Benefit-risk Balance for Marketed Drugs: Evaluating Safety Signals. CIOMS Working Group IV: Geneva, 1998.
14. Sim J, Wright CC. The kappa statistic in reliability studies: Use, interpretation, and sample size requirements. *Phys Ther* 2005; **85**(3): 257–268.
15. Slotboom A. Statistics in Words (2nd edn). Wolters-Noordhoff bv Groningen: the Netherlands, 1996.
16. Linting M, van der Kooij A. Nonlinear principal components analysis with CATPCA: a tutorial. *J Pers Assess* 2012; **94**(1): 12–25.
17. Linting M, Meulman JJ, Groenen PJ, van der Koojj AJ. Nonlinear principal components analysis: introduction and application. *Psychol Methods* 2007; **12**(3): 336–358.
18. Vilhelmsson A, Svensson T, Meeuwisse A, Carlsten A. Experiences from consumer reports on psychiatric adverse drug reactions with antidepressant medication: a qualitative study of reports to a consumer association. *BMC Pharmacol Toxicol* 2012; **13**: 19.
19. Blenkinsopp A, Wilkie P, Routledge PA. Patient reporting of suspected adverse drug reactions: a review of published literature and international experience. *Br J Clin Pharmacol* 2007; **63**(2): 148–156.
20. van Hunsel F. The contribution of direct patient reporting to pharmacovigilance. Thesis Rijksuniversiteit Groningen, 2011.
21. European Medicines Agency. Product information. http://www.ema.europa.eu/ema/ [13 June 2013].