SCOPE Work Package 4
Patient Reporting

An Active Approach to Comparisons of Adverse Drug Reaction Reports from Patients and Healthcare Professionals

SCOPE

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An Active Approach to Comparisons of ADR Reports from Patients and HCPs

Contents

Acknowledgments

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This white paper was prepared by the members of SCOPE team of the Agency for Medicinal Products and Medical Devices of Croatia (HALMED).

Acknowledgements

The authors gratefully acknowledge the Consumers, Health and Food Executive Agency (CHAFEA) of the European Commission for funding the SCOPE Joint Action and the MS partners for their contribution.

We would like to kindly thank our colleagues across EU MSs for completing the questionnaire within the Patient Reporting survey of the SCOPE Joint Action WP4 ADR Collection.

We thank the authors of all published papers on patient ADR reporting presented or cited in this white paper for their contribution to the knowledge of patient reporting across EU.

It has been our privilege to collaborate with our colleagues from Agenzia Italiana del Farmaco (AIFA), Lægemiddelstyrelsen (DKMA), Netherlands Pharmacovigilance Centre Lareb and the Medicines and Healthcare Products Regulatory Agency (MHRA), who have actively contributed to the development of this document.

1. Introduction

1.1 Purpose of the document

The purpose of this document is to advocate for an active approach to performing comparisons of adverse drug reaction (ADR) reports from healthcare professionals (HCPs) and patients across European Union Member States (MSs) and to provide national competent authorities (NCAs) with case studies as examples of different approaches to research. The case studies were chosen to illustrate different settings in which the research was performed. By using these studies as a reference point, NCAs can choose the most suitable approach they wish to take to perform their own studies.

The insights from such research can be used in other pharmacovigilance (PV) activities, primarily in signal management. Scientific knowledge enables NCAs to take evidence-based regulatory decisions and to therefore preserve and protect public health based on sound data deriving from their own population. Better understanding of the contribution of patient reporting in the European Union would offer an advantage in providing valuable insights about the characteristics of these reports and their PV impact. NCAs would thus be able to preserve and protect public health not only in medical terms, but also in the terms of what matters to the patients and public themselves.

Views presented and practices described in this document may not cover all relevant issues and may not be suitable for every NCA, since the purpose of the document is the sharing of experience and dissemination of good practices across MSs, rather than providing exhaustive guidance.

1.2 Definitions and abbreviations

Terminology	Description
ADR	Adverse Drug Reaction
AIFA	Italian Medicines Agency
ATC	Anatomical Therapeutic Chemical Classification
CIOMS	Council for International Organisations of Medical Sciences
DKMA	Danish Medicines Agency
EU	European Union
GP	General Practitioner
HCP	Healthcare Professional
HTA	Health Technology Assessment
Lareb	Netherlands Pharmacovigilance Centre
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare Products Regulatory Agency
MS	Member State
NIHR	National Institute for Health Research
NCCRM	National Coordinating Centre for Research Methodology
NCA	National Competent Authority
OR	Odds Ratio
PV	Pharmacovigilance
SAS	Statistical Analysis Software
SCOPE	Strengthening Collaboration for Operating Pharmacovigilance in Europe
SOC	System Organ Class
SPSS	Statistical Package for the Social Sciences
UK	United Kingdom
WEB-RADR	Recognising Adverse Drug Reactions
WHO-ART	World Health Organisation Adverse Reaction Terminology
WP	Work Package
YCS	Yellow Card Scheme

1.3 Background

The Strengthening Collaboration for Operating Pharmacovigilance in Europe (SCOPE) Joint Action has been created to support operations of pharmacovigilance (PV) in the European Union (EU) following the requirements introduced by the 2010 European PV legislation[1,2,3], which came into force in June 2012. Information and expertise on how regulators in Member States (MSs) run their national PV systems was gained in order to develop and deliver guidance and training in key aspects of PV, with tools, templates and recommendations. The aim of the SCOPE Joint Action was to support consistent approach across the EU network for all PV operations, in order to benefit medicines safety monitoring and communications to safeguard public health.

SCOPE was divided into eight separate work packages (WPs), with five WPs focusing on PV topics to deliver specific and measureable objectives, ranging from improvements in adverse drug reaction (ADR) reporting to assessment of quality management systems.

WP4 ADR Collection was focused on national schemes for the spontaneous reporting of ADRs and was aimed to provide NCAs with a full understanding of and good practices within national systems for collecting ADRs. Information was gathered from European MS institutions to understand their national ADR system, PV IT system capabilities, as well as implementation of patient reporting, types of reporting forms developed, and electronic reporting developments, including those from clinical healthcare systems. This information was used to create best practice guidelines, performance indicators and a media toolkit for raising awareness of ADR reporting systems which will be supported through delivery of a training course for institutions.

[1] Directive 2010/84/EU of the European Parliament and of the Council

[2] Regulation (EU) No 1235/2010 of the European Parliament and of the Council

[3] Commission Implementing Regulation (EU) No 520/2012

2. SCOPE survey results

With the aim of empowering patients through reporting and participation, the 2010 European PV legislation introduced the right of individual European citizens to report suspected ADRs directly to NCAs and marketing authorisation holders (MAHs). Results from Patient Reporting of the WP4 show that a direct patient reporting system has been in place in 14 MSs since 2012 or 2013, while for 13 MSs this system was in place before 2012. Although other MSs did receive patient ADR reports before 2012/2013, only two MSs have received these reports since before the 2000s. In contrast, collection of ADR reports from healthcare professionals (HCPs) started in 6 MSs as early as the 1960s and was introduced in 23 MSs before the 2000s. When compared to receiving HCP reports, receiving direct patient reports in EU MSs can therefore be considered a relatively new development.

The practice of HCPs reporting ADRs is well established across the EU and it makes a robust base for further PV activities. Because direct patient reporting in the majority of EU MSs was introduced only recently, the scientific and practical knowledge about these reports is more modest than the knowledge about HCP reports. Specifically, not much is known about what type of ADRs patients tend to report, the groups/classes of medicines patients report more frequently, how the form and content of the ADR reports differs in this reporter group when compared to HCP reports, and what motivates patients to report ADRs. More research on patient ADR reporting is therefore needed for NCAs to be able to make the most of these reports.

In Patient Reporting of the SCOPE Joint Action WP4, the information about EU MSs practices in direct patient ADR reporting was collected through a questionnaire completed by EU MSs. In a specific question the MSs were asked if they performed any comparison of patient ADR reports to HCPs' reports in terms of completeness, seriousness or other aspects; respondents were also asked to describe their findings. The responses included information about completeness, seriousness and other performed comparisons performed by eight, seven and six MSs, respectively.

Six MSs provided general comments regarding the completeness of patient versus HCP reports. Out of these, four MSs answered that the narratives of the patient reports contain more details, are more informative and provide more information on the impact of the ADR on quality of life, while two MSs answered that patient reports tend to contain less information in the structured parts of ADR reports.

Four MSs provided general comments regarding the seriousness of patient versus HCP reports. One MS answered that the proportion of serious reports is higher in patient reports than in overall reports from all reporters, while another MS answered that HCPs report serious ADRs more frequently than patients. One MS reported that there is no difference in seriousness between patient and physician reports, but that the patients report serious ADRs more frequently than pharmacists. One MS answered that the perception of seriousness is different for patients and perhaps not always in line with the PV definition of seriousness.

Four MSs provided general comments on other comparisons, which included proportion of patient reports in total number of reports, gender, age, time lag between suspect ADR and reporting, number of ADRs, System Organ Classes (SOCs), ADR-terms, drugs, drug-ADR combinations, causality, categories of seriousness and outcomes. No specific data were provided.

In addition, four references to relevant articles were obtained from MSs, namely Italy, Denmark, Netherlands and United Kingdom (UK)[4,5,6,7]. These articles are briefly described in this white paper as case studies – examples of different approaches to research in this field. The focus of these case studies is on description of the setting the study was performed in and a brief description of the main research question, methods and design in general terms. By using these case studies as a reference point, MSs can choose the most suitable approach they wish to take to perform their own studies.

[4] Leone R, Moretti U, D'Incau P, Conforti A, Magro L, Lora R, Velo G. Effect of pharmacist involvement on patient reporting of adverse drug reactions: first Italian study. Drug Saf. 2013 Apr;36(4):267-76.

[5] Aagaard L, Lars Hougaard N, Ebba Holme H. 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.

[6] 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(6):515-24.

[7] Avery AJ, Anderson C, Bond CM, Fortnum H, Gifford A, Hannaford PC, Hazell L, Krska J, Lee AJ, McLernon DJ, Murphy E, Shakir S, Watson MC. 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 May;15(20):1-234, iii-iv.

3. Case studies of an active approach to scientific research into comparison of ADR reports from HCPs and patients

The case studies were chosen to illustrate different settings in which the research was performed. Specifically, studies from Denmark and Netherlands were the first studies in this field in the respective MSs; the study from Italy is an example of research performed at a regional level, while the study from the UK is an example of complex research suitable for more mature direct patient reporting systems. NCAs can take these studies into consideration when choosing the most suitable approach they wish to take to perform their own studies.

The insights from such research can be used in other PV activities, primarily in signal management. Scientific knowledge enables NCAs to take evidence-based regulatory decisions and to therefore preserve and protect public health based on sound data deriving from their own population.

For brief summaries of these articles, including their results, the readers are invited to consult the annexes to this document or to consult the respective published articles. For a reference to most relevant research in this field, the readers are referred to Section 4: Call for action and conclusions, and are also invited to consult available scientific databases for up-to-date information.

3.1. Case study – Italy

3.1.1. Description of the research

The main objectives of this study performed by Leone and his colleagues[8] were to assess the potential impact of an intervention to promote patient reporting in community pharmacies in the Veneto region of Italy and to compare the characteristics of patients' and general practitioners' (GPs) reports of ADRs collected over a one year-period (April 2010–March 2011).

Regarding the methodology, this study involved 211 pharmacists working in 118 community pharmacies. Each pharmacist was asked to select, during the 4-month period, about 250 patients who had received at least one drug, and then to present the spontaneous reporting form to those who had experienced a suspected ADR. Patients were asked to complete the ADR report form and either give it back to the pharmacist, send it by fax or mail, or else to fill in the form online.

All the 'citizen's reporting forms' were sent to the pharmacovigilance centre of the Veneto region. In agreement with Agenzia Italiana del Farmaco (AIFA), the ADR reporting forms in which all the mandatory fields had been filled in were entered into the Italian PV Database. The characteristics of ADR reports sent by patients were compared with those sent over the same one year-period (April 2010–March 2011) by GPs in the Veneto region, since they derived from the same setting, i.e. primary care.

The Italian PV Database was also used to calculate the spontaneous reporting rate for the Veneto region. All the percentages in the article were shown with their 95% confidence intervals. The Chi-square test was used to compare patient and GP reports. All calculations were made using Epi Info, a standard statistical software program developed by the Centers for Disease Control and Prevention, Atlanta, United States of America (http://wwwn.cdc.gov/epiinfo/).

The results of this study included a general description of consumer data and a comparison between patient and GP reports. The description of consumer data included the total number and, where applicable, percentages of patients interviewed, patients with ADRs, ADR forms accepted and sent by patients and distribution by sex and age groups. The comparison between patient and GP reports was with regard to causality, sex and age distribution, distribution of ADR reports by reporter type, expectedness and seriousness of reaction, type of reaction according to the World Health Organisation Adverse Reaction Terminology (WHO-ART) and suspected drugs according to the first level of the Anatomical Therapeutic Chemical Classification (ATC).

[8] Leone R, Moretti U, D'Incau P, Conforti A, Magro L, Lora R, Velo G. Effect of pharmacist involvement on patient reporting of adverse drug reactions: first Italian study. Drug Saf. 2013 Apr;36(4):267-76.

3.1.2. Discussion of the research

In this study, which was based on stimulated ADR reporting, the parameters for comparisons which were measured are the ones that would be easy to extract from any national ADR database. However, aspects where the patient is very knowledgeable, such as the severity of a reaction (which does not always correspond to the seriousness) and the impact of the ADR on daily functioning were not taken into account, since the current database model does not accommodate this type of information. This information can be very valuable for PV, since the impact on daily functioning will probably influence patient adherence to treatment.

The methodology applied and the fact that the study was performed at a regional level enabled additional information to be collected, which allowed the calculation of reporting rates and ADR incidence in this cohort. Performing this type of research at a national level would probably be more time- and resource-consuming and might not be feasible. Therefore, performing the study at a regional level could be considered feasible for MSs in which regional PV centres are in place, for MSs who receive very large number of reports or for MSs who have estimated that it is possible to establish a productive study collaboration at a certain region.

This study showed a remarkable difference in the causality between patient and GP reports (causality for 87.6% of GP reports was probable, compared to 87.1% of patient reports for which the causality was possible), which could be of interest for further research. Although this difference might also be due to the design of the study (patients were stimulated to report, while GPs were not, which might have led to patients being more willing to report only a suspicion of an ADR and GPs to remain more conservative), it would be interesting to investigate if this difference might also be due to the fact that GPs are better at recognising a symptom as an ADR or if the reason for the higher causality is that GP reports contain other types of information that accounts for the higher causality. If the last scenario is the case, it would be interesting to see what kind of information this is and if possible use this information when designing a reporting form for patients in order to enhance collection of relevant information for causality assessment.

The method of using pharmacists in recruiting patients to report proved to be very successful in the Italian setting. This indicates that NCAs could consider involving pharmacists (or GPs) to motivate patients to report. However, in some MSs pharmacists are also a large group of reporters themselves and it is important to maintain reporting from them as well. Such an intervention would need a carefully designed framework and consideration could be needed on employing adequate incentives for pharmacists. Nevertheless, the positive response by patients in this study indicates their willingness to play an active role in PV.

3.2. Case study – Denmark

3.2.1. Description of the research

The objective of this study by Aagaard et al.[9] was to compare ADRs reported by consumers with ADRs reported from other sources, in terms of their type, seriousness and the suspected medicines involved.

This retrospective study comprised all serious ADR reports submitted to the Danish Medicines Agency (DKMA) from 2004 to 2006, which covers the first three years after the introduction of consumer reporting in Denmark. The reports were analysed in terms of category of reporter, category of seriousness, category of ADRs by SOC and the suspected medicines on the first level of the ATC classification system. ADR reports from consumers were compared with reports from other sources (physicians, pharmacists, lawyers, pharmaceutical companies and other HCPs). The unit of analysis was ADRs.

The main thrust of the statistical analysis was the investigation of dependence between the individuals submitting the ADR report and the reported ADRs (classified by ATC code or SOC), which was analysed using a chi-squared test for independence. In the event, the test for independence was rejected, the dependence between the reporter and category of ADRs for each category of ATC or SOC were investigated in further detail. Each odds ratio (OR) was calculated using a 2x2 table for the categories of reporters (consumers and other sources) and each ATC group or SOC. Confidence intervals were calculated for all ORs (95% level). The statistical analyses were performed with the Statistical Analysis Software (SAS) version 9.1. (SAS Institute Inc., Cary, North Carolina, United states of America).

The results of this study included distribution of ADRs by reporters and seriousness according to the Council for International Organisations of Medical Sciences (CIOMS) criteria, distribution of serious ADRs by SOC and type of reporter and distribution of serious ADRs by the type of medicine (ATC groups) and type of reporter.

3.2.2. Discussion of the research

This study retrospectively described reporting of serious ADRs among consumers compared with other reporters and was the first study performed since the introduction of consumer reporting in Denmark in 2003. The authors have chosen to analyse only serious ADRs as being the primary focus of the spontaneous reporting systems and of particular public health interest.

[9] Aagaard L, Lars Hougaard N, Ebba Holme H. 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.

The results of this study showed some differences between consumers and other sources with regard to reported ADRs (SOC) and therapeutic categories. Performing a similar type of study could be considered useful for MSs in which consumer reporting was introduced more recently (i.e. MSs in which this reporting was introduced in 2012 or 2013), with the aim of obtaining a first systematic overview of their own national data.

In this study, just as in the Italian study, parameters were measured that are easy to extract from the database. As discussed for the Italian study, other aspects, such as the severity of a reaction and the impact of the ADR on daily functioning were not investigated. In addition, for an individual report to be valuable for PV, it needs to contain good-quality information. Recent developments in this field, specifically the VigiGrade tool developed by the Uppsala Monitoring Centre[10] and the ClinDoc tool developed to measure the clinical quality of an ADR report, which was developed by Lareb in the Recognising Adverse Drug Reactions (WEB-RADR) project[11], could be employed in the research on the quality of reports.

It is of note that in 2013 the DKMA published a comprehensive report on ADRs reported by consumers compared with reports from HCPs, which covers the period from 2003 to 2011[12]. This report showed that consumer reports contribute significantly to the total number of ADR reports, quantitatively as well as qualitatively and that, in general, consumer reports provide important, well-documented information contributing to increased patient safety. This type of more comprehensive research, which can provide a deeper understanding of the differences between reports from consumers and HCPs, can be considered suitable for MSs where consumer reporting was introduced in the 2000s, providing that the number of reports is sufficient for statistical analysis.

More mature patient reporting schemes, like the Danish one, since Denmark now has more than 10 years of data from patients, can be suitable for studying the contribution patient reports make to signal detection. In such systems it can be interesting to investigate if patients contribute to different type of signals as compared to HCPs.

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[10] Bergvall T, Norén GN, Lindquist M. vigiGrade: A tool to identify well-documented individual case reports and highlight systematic data quality issues. Drug Safety, 2014, 37(1):65-77.

[11] Rolfes L, Oosterhuis I, Ekhart C, Muller-Hansma A, Härmark L. Development and testing of a Clinical Documentation tool to assess Individual Case Safety Reports in an international setting. 2016. Manuscript submitted for publication.

[12] Adverse Drug Reactions Reported by Consumers in Denmark – Compared with Reports from Healthcare Professionals. DKMA, 2013. Available from: http://sundhedsstyrelsen.dk/en/publications/2015/~/media/B71CB7AF2879471ABE9DCF23BF853B18.ashx. Accessed on November 25th 2015.

3.3. Case study – The Netherlands

3.3.1. Description of the research

The study by de Langen et al.[13] covered 3 years of experience with patient reporting in daily practice and compared patient reports with reports from HCPs. Being published in 2008, it was the first study to describe long-term experiences with patient reporting as part of a spontaneous reporting system, to the knowledge of the authors.

In this study, the number of reports received, age and sex of the reporters, characteristics of the most frequently reported drugs (according to the first three levels of the ATC classification system) and characteristics of the ADRs (most frequently reported ADRs, seriousness, outcome) in a 3-year period (April 2004-April 2007) were compared between patient reports and reports from HCPs (GPs, specialist doctors and pharmacists).

The authors used a chi-square test to establish possible significant differences. To establish possible significant differences in the male-female ratio between reports from patients and HCPs a t-test was used. Statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS) (Chicago, Illinois, United States of America).

The results included the number of reports and ADRs stratified by source, patient characteristics, type of reported drugs and associations (with the five most frequently reported drug classes, stratified by source), characteristics of the reported ADRs (including the ten most frequently reported ADRs for patients and for HCPs) and a case report of an example of a duplicate report from a pharmacist and a patient.

3.3.2. Discussion of the research

As the authors themselves state, this study was the first to describe long-term experiences with patient reports as part of a spontaneous reporting system. Similar to the studies presented earlier, the data used for the statistical analysis was easy to extract from the national ADR database. In addition to this, a brief case report of a duplicate report from an HCP and a patient was presented. Taking a qualitative approach to the research can be useful for gaining a deeper understanding of the differences between patient and HCP reports. In addition, qualitative research might be a useful method of investigation for those MSs who do not receive numbers of reports from patients large enough to allow statistical analysis.

[13] 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(6):515-24.

In addition to the analyses performed in this study, the authors also reflect on their, at that point in time, recent experience with signals generated mainly from patient reports: isotretinoin and inflammatory bowel disease[14], lithium and hyperparathyroidism[15] and the impact of gambling addiction related to pergolide on a patient's daily life[16]. Their experience shows that a qualitative approach to analysis of ADR reports generates relevant safety signals and therefore contributes to signal detection.

The authors of this study conclude that interpretative differences by patients and HCPs may have caused the observed differences with respect to the seriousness and outcome of the reported ADRs. They also conclude that direct patient reporting is feasible and that it significantly contributes to reliable PV.

From this first study, the research into patient ADR reporting led to investigating other relevant topics, including the motives for reporting by patients[17], the proportion of patient reports of suspected ADRs to signal detection[18] and a recent study into differences in reported information between patient and HCP reports[19]. In addition, on their website, Lareb maintains a list of downloadable international publications related to patient reporting[20].

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[14] Passier JLM, Srivastava N, van Puijenbroek EP. Isotretinoin-induced inflammatory bowel disease. Neth J Med 2006; 64 (2): 52-4.

[15] Passier JLM. Lithium and hyperparathyroidism. Geneesmiddelenbulletin 2005; 39 (11): 131-2.

[16] van Grootheest AC, de Graaf L. Pergolide en gokverslaving. Geneesmiddelenbulletin 2006; 40 (8): 86-7.

[17] van Hunsel F, van der Welle C, Passier A, van Puijenbroek E, van Grootheest K. Motives for reporting adverse drug reactions by patient-reporters in the Netherlands. Eur J Clin Pharmacol. 2010 Nov;66(11):1143-50.

[18] 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 Mar;20(3):286-91.

[19] 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 Feb;24(2):152-8.

[20] Patient reporting – Publications. Lareb, http://www.lareb.nl/Informatie-bijwerkingen/Publicaties. Accessed on November 14th 2016.

3.4. Case study – United Kingdom

3.4.1. Description of the research

This research by Avery et al.[21] was a multifaceted evaluation of patient and HCP reporting of suspected ADRs to the Yellow Card Scheme (YCS) in the UK. The research consisted of a literature review, descriptive and qualitative analyses, and questionnaire surveys, comprising a total of eight separate studies. The objectives were to:

- Evaluate the PV impact of patient reporting of ADRs by analysing reports of suspected ADRs from the UK YCS and by comparing reports from patients and HCPs
- Elicit the views and experiences of patients and the public about patient reporting of ADRs.

The objectives and research questions relate to:

- A review of the literature
  - Study 1: Review of the world literature describing and comparing patient and HCP reporting of ADRs
- Studies based on the analysis of YCS data for patients and health professionals, evaluating the pharmacovigilance impact of patient reporting of suspected ADRs
  - Study 2: Description of the characteristics of reports from patients and HCPs
  - Study 3: Assessment of the PV impact of reports from patients and HCPs using signal generation analysis and clinical assessment of reports
  - Study 4: Qualitative analysis of reports from patients and HCPs
- Studies considering the views and experiences of patients and members of the public regarding patient reporting
  - Study 5: Questionnaire survey to capture the views and experiences of patients who have made reports
  - Study 6: Telephone interviews to explore further the views and experiences of patients who have made reports
  - Study 7: Focus groups and usability testing with members of the public regarding patient reporting
  - Study 8: Omnibus survey to assess public awareness of the YCS.

The methodologies used in these eight studies, as well as brief description of the results, are presented in Annex 4 to this document.

[21] Avery AJ, Anderson C, Bond CM, Fortnum H, Gifford A, Hannaford PC, Hazell L, Krska J, Lee AJ, McLernon DJ, Murphy E, Shakir S, Watson MC. 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 May;15(20):1-234, iii-iv.

3.4.2. Discussion of the research

The authors of these studies consider that, compared with HCPs, patient reports to the YCS contained a higher median number of suspected ADRs per report, and described reactions in more detail. The proportions of reports categorised as 'serious' were similar; the patterns of drugs and reactions reported differed. Patient reports were richer in their descriptions of reactions than those from HCPs, and more often noted the effects of ADRs on patients' lives. Combining patient and HCP reports generated more potential signals than HCP reports alone; some potential signals in the 'HCP-only' data set were lost when combined with patient reports, but fewer than those gained; the addition of patient reports to HCP reports identified 47 new 'serious' reactions not previously included in 'Summaries of Product Characteristics'. Most patient reporters found it fairly easy to make reports, although improvements to the scheme were suggested, including greater publicity and the redesign of web- and paper-based reporting systems. Among members of the public, 8.5% were aware of the YCS in 2009.

The authors conclude that patient reporting of suspected ADRs has the potential to add value to PV by reporting types of drugs and reactions different from those reported by HCPs; generating new potential signals; and describing suspected ADRs in enough detail to provide useful information on likely causality and impact on patients' lives. These findings suggest that further promotion of patient reporting to the YCS is justified, along with improvements to existing reporting systems. In order of priority, the authors consider that future work should include further investigation of:

- The PV impact of patient reporting in a longer-term study
- The optimum approach to signal generation analysis of patient and HCP reports
- The burden of ADRs in terms of impact on patients' lives
- The knowledge and attitudes of HCPs towards patient reporting of ADRs
- The value of using patient reports of ADRs to help other patients and HCPs who are seeking information on patient experiences of ADRs
- The impact of increasing publicity and/or enhancements to reporting systems on the numbers and types of Yellow Card reports from patients.

This type of comprehensive and complex study can be considered suitable for more mature direct patient reporting systems, e.g. for those MSs where patient reporting was introduced before the 2000s or during the early 2000s. The complexity of performing this type of research is expected to require the availability of a range of expertise beyond that available at the level of the NCA, such as the expertise of a consortium of researchers. Besides this, and depending on the areas that are to be investigated, the results of this type of research would be of importance for health policy makers at the national level, who would, if not initiating the research themselves, at least be included as a major stakeholder. The similar setting was in fact the case in this UK study, performed by a consortium of researchers, which was commissioned by the National Coordinating Centre for Research Methodology (NCCRM), and was formally transferred to the Health Technology Assessment (HTA) programme (part of the National Institute for Health Research (NIHR)) afterwards.

In order to further the science of PV, and in particular patient reporting, it is important to continuously look with a critical eye at how and what we as NCAs do and also to try to improve it. Sharing this information through publications enables others to learn from experiences gained elsewhere.

4. Call for action and conclusions

The 2010 European PV legislation[22,23,24] introduced the right of individual European citizens to report suspected ADRs directly to NCAs and MAHs, with the aim of empowering patients through reporting and participation. This has led to the introduction of direct patient reporting schemes in all EU MSs. To assess the extent to which patient reports contribute to pharmacovigilance, comparison with reports from HCPs is necessary.

Research on practices and experiences with systems for direct patient reporting of ADRs has been of scientific and regulatory interest for several years now[25,26]. Informative overviews of systems for direct patient reporting in several selected EU MSs have been presented both prior to 2010 PV legislation and since its introduction[27, 28]. A more recent systematic review of studies comparing ADR reports from patients and HCPs conducted on the national PV schemes was published in 2012[29]. This review identified and included three comparative studies conducted in Denmark, the Netherlands and the UK; these studies are included in this white paper as case-studies. The authors of this systematic review conclude that only a few comparative studies have been undertaken of patient and HCP reporting and that the true value of patient ADR reports to PV will remain unknown unless more comparative evaluations are undertaken.

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[22] Directive 2010/84/EU of the European Parliament and of the Council

[23] Regulation (EU) No 1235/2010 of the European Parliament and of the Council

[24] Commission Implementing Regulation (EU) No 520/2012

[25] 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.

[26] van Hunsel F, Härmark L, Pal S, Olsson S, van Grootheest K. Experiences with adverse drug reaction reporting by patients: an 11-country survey. Drug Saf. 2012 Jan 1;35(1):45-60.

[27] Herxheimer A, Crombag R, Leonardo Alves T. Direct Patient Reporting of Adverse Drug Reactions. A Fifteen-Country Survey & Literature review. Health Action International (HAI) Europe, 2010. Available from: https://consumers.cochrane.org/sites/consumers.cochrane.org/files/uploads/10 May 2010 Report Direct Patient Reporting of ADRs.pdf. Accessed on November 25th 2015.

[28] Santos A. Direct Patient Reporting in the European Union. A snapshot of Reporting Systems in Seven Member States. Health Action International. Available from: http://haieurope.org/wp-content/uploads/2015/09/Direct-Patient-Reporting-in-the-EU.pdf. Accessed on November 25th 2015.

[29] Durrieu G et al. First French experience of ADR reporting by patients after a mass immunization campaign with Influenza A (H1N1) pandemic vaccines: a comparison of reports submitted by patients and healthcare professionals. Drug Saf. 2012 Oct 1;35(10):845-54.

The studies presented in this document as case studies investigated the patient ADR reports and compared them to HCP reports. These, along with other studies that were performed worldwide, showed that patient reports tend to contain sufficient information about the ADR and can be comparable to HCP reports in terms of seriousness, suspected drugs and suspected ADRs. Patient reports are generally considered to contain a more detailed description of the ADR and the impact of the ADR on the patients' quality of life. Comparisons can also be performed in relation to a specific context, such as following media attention to a specific drug class or following public health interventions, such as a mass immunisation campaign[30].

The impact of patient reports has been further studied in terms of their contribution to the generation of safety signals[31,32]. The results showed that patient reports generate safety signals that are different from safety signals generated based on HCP reports. Patient reports can therefore be considered as an important source of ADR reports that is complementary to reports originating from HCP reports. Other studies have shown that patients value the independence from HCPs of direct patient reporting systems[33]. This might be one of the reasons for the observed difference between signals generated based on patient versus HCP reports. Other topics relating to patient reporting have also been subject to recent interest, including the motivations of patients for reporting, how patients identify symptoms as ADRs and what patients are experiencing in broader terms in relation to an ADR[34,35,36,37].

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[30] 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 May;67(5):558-64.

[31] 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 Mar;20(3):286-91.

[32] Hazell L, Cornelius V, Hannaford P, Shakir S, Avery AJ; Yellow Card Study Collaboration. 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 Mar;36(3):199-206.

[33] Anderson C, Krska J, Murphy E, Avery A; Yellow Card Study Collaboration. The importance of direct patient reporting of suspected adverse drug reactions: a patient perspective. Br J Clin Pharmacol. 2011 Nov;72(5):806-22.

[34] van Hunsel F, van der Welle C, Passier A, van Puijenbroek E, van Grootheest K. Motives for reporting adverse drug reactions by patient-reporters in the Netherlands. Eur J Clin Pharmacol. 2010 Nov;66(11):1143-50.

[35] Krska J, Anderson C, Murphy E, Avery AJ. How patient reporters identify adverse drug reactions: a qualitative study of reporting via the UK Yellow Card Scheme. Drug Saf. 2011 May 1;34(5):429-36.

[36] Chaipichit N, Krska J, Pratipanawatr T, Uchaipichat V, Jarernsiripornkul N. A qualitative study to explore how patients identify and assess symptoms as adverse drug reactions. Eur J Clin Pharmacol. 2014 May;70(5):607-15.

[37] 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 Dec 23;13:19.

The case studies presented in this document are a good example on how the comparison between patient and HCP reports can be performed, both at regional and national level. These comparisons are needed to assess the extent to which patient reports contribute to PV. Being investigated in only several EU MSs, the scientific knowledge about national systems for direct patient reporting, the similarities and differences between patient and HCP reports and the impact of patient reports in terms of their contribution to safety signals remains modest. Due to the inherent differences between MSs' healthcare systems in general and PV systems in particular, the generalisation of the findings from the case studies presented in this white paper to other EU MSs is not possible. Therefore, more research into patient reports and national patient reporting systems is needed. This is true for national level, where the specifics of these reports and systems need to be investigated, but also for international level, where synthesis in terms of systematic reviews is also needed.

The aim of this document was to advocate for an active approach to comparisons of ADR reports from patients and HCPs across EU MSs and to provide NCAs with case studies as examples of different approaches to research. The case studies presented in this white paper illustrate different settings in which the research was performed. By taking these studies into consideration, NCAs can choose the most suitable approach they wish to take to perform their own comparisons.

In conclusion, scientific knowledge enables NCAs to take evidence-based regulatory decisions based on sound data deriving from their own population. Better understanding of the contribution of patient reporting in the European Union would provide valuable insights about the characteristics of these reports and their PV impact. NCAs would thus be able to preserve and protect public health not only in medical terms, but also in terms of what matters to the patients and public themselves.

Annexes

This section contains brief summaries of the studies presented in this document as case studies; the overview of major results is also included. For more details on these studies and their results the readers are invited to consult the respective published articles.

Annex 1

Leone and his colleagues[38] investigated the effect of pharmacist involvement on patient reporting of ADRs. The main objectives of their study were to assess the potential impact of an intervention to promote patient reporting in community pharmacies in the Veneto region of Italy, and to compare the characteristics of patients' and GPs' reports of ADRs collected over a one year-period (April 2010–March 2011).

Regarding the methodology, this study involved 211 pharmacists working in 118 community pharmacies. Each pharmacist was asked to select, during the study period, about 250 patients who had received at least one drug, and then to present the spontaneous reporting form to those who had experienced a suspected ADR. Patients were asked to complete the ADR report form and either give it back to the pharmacist, to send it by fax or mail, or else to fill in the form online.

In a 4-month period, 52,495 customers were interviewed by the pharmacists and 4,949 of them (9.4%) referred a suspected ADR. The Pharmacovigilance Centre of the Veneto region received 2,311 citizens' ADR reporting forms related to the study (from 46.7% of all patients interviewed who had experienced suspected ADRs). After quality control, 1,794 of these reports were entered into the Italian Pharmacovigilance Database and were compared with the reports (226) sent by GPs in the Veneto region in the same period.

Drugs widely used in the community setting and over-the-counter products were the drugs most frequently reported by patients. In contrast, few reports involving reactions to antineoplastic agents or contrast media-drugs, mostly used in a hospital setting, were sent by patients.

No specific completeness indicators were used in this study; the authors did discuss that the reports sent by patients were mostly adequate, since about 80 % of reports contained all the information needed for their evaluation.

Regarding the seriousness, the patients in this study reported a higher percentage of known and non-serious reactions than did GPs, with serious reports comprising only 5.1% (95% CI 4.1-6.1) of all patient reports, while 20.8% (95% CI 15.1-26.1) of GP reports were serious.

[38] Leone R, Moretti U, D'Incau P, Conforti A, Magro L, Lora R, Velo G. Effect of pharmacist involvement on patient reporting of adverse drug reactions: first Italian study. Drug Saf. 2013 Apr;36(4):267-76.

Other comparisons performed in this study include:

- Causality (according to Naranjo algorithm score): 87.1% (95% CI 85.6–88.7) of patient reports were classified as possible, while 87.6% (95% CI 83.3–91.9) of reports by GPs were classified as probable
- Sex and age distribution: in both reporter groups, more reports were made by/for female than by/for male patients, and more by/for patients aged 18–65 years compared with older people; this difference was greater in patient reports
- Type of reaction (according to the WHO-ART): patients more frequently reported gastrointestinal reactions (particularly abdominal pain, nausea and diarrhoea), whereas GPs more frequently reported systemic problems (headache, fever) and skin reactions (urticaria, pruritus and erythematous rash); the most evident differences between the two groups of reports were observed for reports of gastrointestinal, skin, application site, haematological and liver reactions
- Suspected drugs (according to first level ATC classification): drugs belonging to ATC groups M (musculoskeletal system) and N (nervous system) were more frequently reported by patients than by GPs, whereas those belonging to groups J (anti-infective drugs for systemic use), L (antineoplastic and immunomodulating agents) and V (various) were more frequently reported by GPs than patients.

The authors conclude that their study shows that patient reporting has the potential to add value to the pharmacovigilance system. The overall quality of the information provided in patients' reports was good. The differences between reports by patients and by GPs indicate different points of view that can enrich spontaneous reporting.

Annex 2

The objective of this study by Aagaard et al.[39] was to compare ADRs reported by consumers with ADRs reported from other sources, in terms of their type, seriousness and the suspected medicines involved.

The number of ADRs reported to the Danish ADR database from 2004 to 2006 was analysed in terms of category of reporter, seriousness, category of ADRs by SOC and the suspected medicines on the first level of the ATC classification system. ADR reports from consumers were compared with reports from other sources (physicians, pharmacists, lawyers, pharmaceutical companies and other HCPs). Chi-square and ORs were calculated to investigate the dependence between the type of reporter and reported ADRs (classified by ATC or SOC).

The authors analysed a total of 6,319 ADR reports corresponding to 15,531 ADRs. Consumers reported 11% of the ADRs. No specific completeness indicators were used in this study. Consumers' share of 'serious' ADRs was comparable to that of physicians (approximately 45%), but lower than that of pharmacists and other HCPs.

When consumer reports were compared with reports from other sources, consumers were more likely to report ADRs from the following SOCs: 'nervous system disorders' (OR = 1.27; 95% CI 1.05, 1.53); 'psychiatric disorders' (OR = 1.70; 95% CI 1.31, 2.20) and 'reproductive system and breast disorders' (OR = 2.02; 95% CI 1.13, 3.61) than other sources. Compared with other sources, consumers reported fewer ADRs from the SOCs 'blood and lymphatic system disorders' (OR = 0.22; 95% CI 0.08, 0.59) and 'hepatobiliary system disorders' (OR = 0.14; 95% CI 0.04, 0.57). In the SOC 'nervous system disorders', consumers reported seven categories of ADRs that were not reported by the other sources.

Consumers were more likely to report ADRs for the ATC group N (nervous system) [OR = 2.72; 95%CI 2.34, 3.17], ATC group P (antiparasitic products) [OR = 2.41; 95% CI 1.32, 4.52] and ATC group S (sensory organs) [OR = 4.79; 95% CI 2.04, 11.23] than other groups. Consumers reported fewer ADRs for the ATC group B (blood and blood-forming organs) [OR = 0.04; 95% CI 0.006, 0.32] and the ATC groups J (anti-infective for systemic use) [OR = 0.44; 95% CI 0.33, 0.58], L (antineoplastic and immunomodulating agents) [OR= 0.19; 95%CI 0.12, 0.30] and V (various) [OR = 0.03; 95% CI 0.004, 0.21] than other sources.

[39] Aagaard L, Lars Hougaard N, Ebba Holme H. 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.

This study showed that, in a national ADR reporting system, ADR reporting from consumers and other sources differed with regard to seriousness of ADRs, reported ADRs (SOC) and therapeutic categories. The authors consider that this information can give the authorities and researchers access to relevant additional information about the adverse effects of medicines. The authors conclude that consumers should be actively included in systematic drug surveillance systems, including clinical settings, and their reports should be taken as seriously as reports from other sources.

Annex 3

De Langen et al.[40] suggest that there has been discussion about the acceptance of ADRs reported by patients to spontaneous reporting systems, with the lack of experience with patient reporting in real life being one of the main drawbacks in this debate. This study covered 3 years of experience with patient reporting in daily practice and, being published in 2008, it was the first study to describe long-term experiences with patient reporting as part of a spontaneous reporting system, to the knowledge of the authors. The authors state that, although patients have the opportunity to report ADRs in several countries, little is published in the literature about the contribution that patient reports have in practice.

In this study, the number of reports received, age and sex of the reporters, characteristics of the most frequently reported drugs and characteristics of the ADRs (most frequently reported ADRs, seriousness, outcome) in a 3-year period (April 2004-April 2007) were compared between patient reports and reports from HCPs (GPs, specialist doctors and pharmacists).

During this 3-year period, the Netherlands Pharmacovigilance Centre Lareb received 2,522 reports directly from patients, concerning 5,401 ADRs. In the same period, HCPs submitted 10,635 reports, concerning 16,722 ADRs.

No specific completeness indicators were used; the authors, however, discuss that only electronic reporting, which facilitates the completeness of information, is available to patients and that the report can only be submitted to the centre if all mandatory fields are filled in. Another general comment was made about patient reports, which are considered to usually contain sufficient medical information to be useful to pharmacovigilance.

Differences were found in the categories of seriousness and outcome of the reported ADRs between patients and HCPs. Specifically, the seriousness (according to CIOMS criteria) of the reports was not significantly different between reports from patients (19.5%) and from HCPs (21%). However, patients reported a significantly higher number of life-threatening ADRs (5.2% vs 2.7%) and disability (2.3% vs 0.4%) than HCPs.

There was a significant difference between patient reports and reports from HCPs in the proportion of reports that included mention of the outcome of the ADR (87% vs 68%; $p < 0.01$). Patients reported non-recovery (35.4%) from the ADR significantly more often than HCPs (16.7%).

[40] 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(6):515-24.

Conversely, similarities between patient reports and reports from HCPs were found in age, sex, most frequently reported ADRs and most frequently reported drugs:

- Sex and age: of the reports from patients, 63% of the patients were female compared with 61% in the reports from HCPs; the mean age of patients in the reports from patients was also similar (48 years) to that in the reports from HCPs (49 years)
- Suspected drugs (according to the first three levels of the ATC classification): the five drug categories most frequently reported by patients were successively HMG Co-A reductase inhibitors ('statins'), selective serotonin reuptake inhibitors, β-adrenoceptor antagonists ('β-blockers'), anticoagulants and proton pump inhibitors; the top five drugs reported by the different groups of HCPs showed great similarity with that of patients
- Most frequently reported ADRs (according to Medical Dictionary for Regulatory Affairs MedDRA (MedDRA)): nervous system disorders, psychiatric disorders, gastrointestinal disorders, musculoskeletal disorders and general disorders/administration-site conditions were the five most involved organ systems for patients and GPs; there were strong similarities between reports received from patients and reports from other HCPs.

The authors conclude that their study clearly highlights that valuable differences between ADR reports from patients and reports from HCPs exist. The authors consider that the differences in interpretation by patients and HCPs may cause the observed disparities in seriousness and outcome of reported ADRs. However, the authors consider the similarities between patient reports and reports from HCPs with regard to the most frequently reported ADRs and the most frequently reported drugs to be striking. After three years of experience with patient reporting, the authors conclude that patient reporting in spontaneous reporting systems is feasible and that it contributes significantly to a reliable pharmacovigilance.

Annex 4

This research by Avery et al.[41], concerning the evaluation of patient reporting of ADRs to the UK YCS, was commissioned by the National Coordinating Centre for Research Methodology (NCCRM), and was formally transferred to the Health Technology Assessment (HTA) programme (part of the National Institute for Health Research (NIHR)) in 2007. This multi-faceted evaluation of patient and HCP reporting of suspected ADRs to the YCS in the UK consisted of a literature review, descriptive and qualitative analyses, and questionnaire surveys, comprising a total of eight separate studies.

The objectives of this publication were to evaluate the pharmacovigilance impact of patient reporting of ADRs by analysing reports of suspected ADRs from the UK YCS and comparing reports from patients and HCPs, as well as to elicit the views and experiences of patients and the public about patient reporting of ADRs. Brief summaries of these eight studies and their findings are presented below.

Study 1: literature review on the international experience of consumer reporting schemes

In this study, a range of methods was used to identify countries with patient reporting as part of their national pharmacovigilance activities, including a questionnaire to pharmacovigilance staff in 47 countries, personal communication with key contacts and a literature review. A literature review was performed to identify comparative studies of patient and HCP ADR reports. A search was conducted of MEDLINE (Ovid), EMBASE (Ovid) and Pharm-line databases using both MeSH and text search terms. The search dates were from 1996 to May 2009.

[41] Avery AJ, Anderson C, Bond CM, Fortnum H, Gifford A, Hannaford PC, Hazell L, Krska J, Lee AJ, McLernon DJ, Murphy E, Shakir S, Watson MC. 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 May;15(20):1-234, iii-iv.

Forty-six countries were identified as having consumer reporting schemes. A number of studies of patient reporting of suspected ADRs were identified, including a systematic review published in 2007 by Blenkinsopp et al.[42]. In this systematic review of patient reporting of suspected ADRs seven studies were included, although none involved spontaneous reporting by patients. Where comparisons were available with HCP reports, the quality of reports appeared to be similar. There was some evidence that patients were more likely to report ADRs if they felt that their HCP had not acknowledged their concerns. In addition, in Study 1 two large-scale comparative studies were identified: the one by de Langen et al. presented in this white paper as case study from The Netherlands[43] and another study from Denmark published in 2009 by Aagaard et al.[44]. The Danish study showed that, compared with other sources, patients reported different types of medicines for categories of ADR, but were as likely as physicians to report ADRs that were judged to be serious. No large-scale studies were found investigating the impact of patient reporting on generating potential signals for suspected ADRs.

Study 2: descriptive study of Yellow Card reports

The objectives of this study were to: identify the characteristics of patients reporting to the YCS; identify the types of drug, types of suspected ADR and seriousness of suspected reactions reported by patients; determine whether there are differences in the time lag between ADR occurrence and reporting for patients and health professionals; investigate the factors associated with patient reports compared with those made by health professionals.

Anonymised data was provided by the Medicines and Healthcare Products Regulatory Agency (MHRA) for all patient and HCP reports received by the YCS between 1 October 2005 and 30 September 2007. To compare the two reporter groups, suspected ADR terms were grouped within the hierarchical structure of the industry standard (version 12) and suspect drug names were mapped to the most appropriate code within the ATC drug classification system (2007 version).

For the 2-year study period, 26,129 Yellow Card reports were received from the MHRA [5180 (19.8%) patient reports and 20,949 (80.2%) HCP reports].

[42] 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.

[43] 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(6):515-24.

[44] Aagaard L, Lars Hougaard N, Ebba Holme H. 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.

The data from the YCS reports was cleaned and processed by the same methods as used by the MHRA when processing Yellow Cards and analysed afterwards. Descriptive statistics were calculated for Yellow Card reports from patients and HCPs. Appropriate statistical tests compared the following factors across reporter type: age and gender of patients, reported seriousness of the suspected ADRs (as coded by the MHRA), types and number of suspected ADRs using MedDRA terms, word count used to describe the suspected reaction, number of suspect drugs per report and class of suspected drug using the ATC classification, time lag between suspected ADR and its reporting and reported outcome of the suspected ADR.

No specific completeness indicators were used in this study. Regarding the seriousness, similar proportions of reports contained at least one reaction term that was classified as 'serious' by the MHRA (58.3% for patients vs 58.8% for HCPs; $p = 0.58$). The following were recorded more commonly in HCP reports than in patient reports: 'caused hospitalisation' (18.8% vs 12.9%, respectively); 'life-threatening' (11.1% vs 6.2%, respectively); and 'caused death' (2.6% vs 0.7% respectively) ($p < 0.001$ for each comparison). Other comparisons performed in this study include:

- Age and sex of patients: significantly more Yellow Card reports were made for female patients, whether reported by the patient or via HCPs (both $p < 0.001$); the median age of patients, as reported by either patients or HCPs, was similar ($p = 0.06$)
- Method of reporting: the most frequent method used to report an ADR was the paper Yellow Card form for both reporter groups (79.0% of patients and 87.7% of HCPs); the internet was the next most frequent method (17.6% of patients and 12.3% of HCPs), followed by telephone (3.5% of patients and 0.03% of HCPs)
- Reactions: patient reports contained a significantly higher number of suspected ADRs per report than did HCP reports [median (IQR) of 3 (2 to 5) vs 2 (1 to 3), respectively; $p < 0.001$]; almost one-half (45.2%) of HCP Yellow Card reports contained only one ADR compared with 21.6% of patient Yellow Card reports; only 3.3% of HCPs reported over five reactions per report, compared with 21.8% of patient reports ($p < 0.001$ overall). More patient reports had mention of a nervous system disorder problem (41.5%) than those of another organ system; this was followed by problems categorised as 'general disorders and administration site conditions' (39.8%), problems that were also the second most common organ system affected according to the HCP reports (23.1%). The most common category in the HCP reports was skin and subcutaneous tissue disorders (23.2%). The median (IQR) word count (excluding reports with zero word counts) used to describe the suspected reaction was significantly higher for patient reports than for HCP reports [45.0 (22.0 to 74.0) vs 15.0 (9.0 to 26.0), respectively; $p < 0.001$]

- Suspected drugs: a higher proportion of patient reports than of HCP reports contained more than one suspect drug (16.1% vs 9% respectively; $p < 0.001$); the most frequent category of drug suspected of being linked to an ADR was for the nervous system, for both patient (33.2%) and HCP (26.2%) reports; this was followed by cardiovascular system drugs from patient reports (21.8%) and anti-infectives for systemic use from HCP reports (19.4%). A statistically significant difference in the percentage of type of suspect drug between reporters was shown for drugs of the nervous system; cardiovascular system; systemic hormonal preparations, excluding sex hormones and insulin; antiparasitic products, insecticides and repellents; herbals/complementary medicine (which all had higher proportions in the patient than HCP reports); anti-infectives for systemic use; antineoplastic and immunomodulating agents; blood and blood-forming organs; and, 'various' (all of which had higher proportions in the HCP than the patient reports)
- Time lag between suspect ADR and reporting: patient reporters took a significantly longer median (IQR) time than HCPs to report their reaction to the MHRA [104 (27 to 463) vs 28 (13 to 75) days, respectively; $p < 0.001$]; however, there was a higher percentage of missing data for the variable 'time from reaction to report' among patient reports (61.0% of such reports) than among HCP reports (33.2%)
- Reaction outcome: a significantly higher proportion of HCPs than patient representatives reported fatal outcomes to the reaction (2.6% vs 0.7%; $p < 0.001$); a significantly higher proportion of HCPs than patient representatives reported that the patient was recovering or that the ADR was resolving (28.4% vs 16.8%; $p < 0.001$); more patients than HCPs reported that they had not recovered or that the reaction had not resolved (36.4% vs 22.2%; $p < 0.001$).

In summary, patient reports contained significantly higher number of suspected ADRs per report, a higher proportion of patient reports contained more than one suspect drug and the word count used to describe the suspected reaction was significantly higher for patient reports than for HCP reports.

In this study patients showed different patterns of reporting of drugs and ADRs compared with HCPs. Nevertheless, similar proportions of reports contained at least one reaction term that was classified as 'serious' by the MHRA (58.3% for patients vs 58.8% for HCPs; $p = 0.58$). The following were recorded more commonly in HCP reports than in patient reports: 'caused hospitalisation' (18.8% vs 12.9%, respectively); 'life-threatening' (11.1% vs 6.2%, respectively); and 'caused death' (2.6% vs 0.7% respectively) ($p < 0.001$ for each comparison). Of the patient Yellow Card reports, 44.8% stated that the suspected ADR was bad enough to affect everyday activities. Patient reporters took a significantly longer time to report suspected ADRs than HCPs [median (IQR) of 104 (27 to 463) days vs 28 (13 to 75) days, respectively; $p < 0.001$], although there were missing data on 'time taken to report' for over 60% of patient reports.

Study 3: pharmacovigilance impact of patient reporting: signal generation analysis

The aim of this study was to investigate the relative contribution of patient reports to signal generation. The objectives of this study were quantitative and qualitative, as described below.

The quantitative objectives were:

- To compare the types of SDRs generated by patient reports with those generated by HCP reports, in terms of their importance within the context of pharmacovigilance including:
  - The seriousness of the ADRs involved (using the MHRA's 'dictionary seriousness' classification)
  - The time of marketing of the suspect drugs involved (black triangle drugs)
  - Whether the ADR had been previously been documented on the summary of product characteristics (SPC) for the suspect drug involved
- To investigate how SDRs generated in a spontaneous reporting database of HCP reports may be affected (statistically) by the inclusion of patient reports
- To estimate the extent to which duplicate reporting occurs.

The qualitative objectives were:

- To investigate how the information provided by patient reports may contribute to the assessment of a causal association for selected drug–ADR pairs
- To identify problems incurred when assessing causality from patient reports.

Using the anonymised data provided by the MHRA for all patient and HCP reports received by the YCS between 1 October 2005 and 30 September 2007, signal generation analysis was undertaken on the whole database of patient and HCP reports. There were 5,180 (19.8% of total) reports supplied by patients and 20,949 (80.2%) by HCPs.

The authors identified SDRs, which are 'statistical signals' of the reporting rate for a suspected ADR in association with a particular medicine being disproportionate to that of other products in the database. They then investigated the effects (on SDRs) of including and excluding patient reports from the HCP database. They also did clinical causality assessments on selected drug-ADR pairs from patients and HCPs.

For the signal generation analysis there were 16,566 drug-reaction pairs from patient reports and 28,775 from HCPs, with only 4,340 (10.6%) pairs common to both groups. The HCP data set generated a significantly higher proportion of SDRs from the different drug–reaction pairs reported [1,939 SDRs (6.7%) vs 649 (3.9%) respectively; difference in proportions 2.8%, 95% CI 2.4% to 3.2%]. Also, a higher proportion of HCP SDRs were for reactions classified as 'serious' by the MHRA compared with patient SDRs (48% vs 28.5% respectively; difference in proportions 19.5%, 95% CI 15.4% to 23.6%) or for drugs undergoing intensive surveillance (black triangle drugs) (30.7% vs 10.9% respectively; difference in proportions 19.8%, 95% CI 16.6% to 23.0%). A similar proportion of SDRs in both groups (15%) was assessed as not being listed on the product's SPC and therefore potentially providing new information.

After combining the patient and the HCP data sets, an additional 508 SDRs were generated that were not produced by either data set alone, whereas 186 SDRs generated by the HCP data set alone were no longer present. The combined data set identified 47 SDRs for reactions classified as serious by that MHRA that had not previously recorded on SPCs, whereas eight generated by the HCP data set alone were no longer present. Among the sample of individual reports assessed for causality, most were assessed as having a 'possible' causal association, regardless of reporter group.

Overall, patients appeared to have the potential to make a positive contribution to signal generation by:

- Reporting different drug-ADR pairs and generating different SDRs from HCPs
- Generating SDRs that may be considered important in the context of pharmacovigilance
- Generating additional SDRs when combined with data from HCP reports
- Providing information that may be valuable when assessing the likelihood of a causal association between a particular drug and reaction.

Study 4: qualitative analysis of Yellow Card reports from patients and HCPs

The objective of this study was to explore the richness of patients' descriptions of their suspected ADRs compared with those of health professionals.

The authors undertook a qualitative analysis of reports from patients and HCPs and purposively selected a wide range of different types of report. Focusing on the free-text describing the ADRs, the authors undertook a content analysis to describe the characteristics of 230 patient and 179 HCP reports, followed by a more detailed inductive qualitative analysis of the free-text (which included 40 additional patient reports of drugs purchased OTC and complementary therapies).

The content analysis of text describing suspected reactions showed that patient reports were more likely than those from HCPs to include information about symptoms (93% vs 78%) and to stress the extreme nature of these (47% vs 17% of reports). They were also more likely to highlight the impact of the reaction on the patient (47% vs 12%), particularly the emotional impact (34% vs 7%) or social impact (27% vs 7%). Patients commonly reported on temporal associations, with 61% stating that the suspected ADR had followed the administration of the drug; 26% that it had improved on stopping the drug; 22% that it had occurred on withdrawal of the drug, and 7% that it had recurred on restarting the drug.

The in-depth qualitative analysis demonstrated the richness of accounts from patients and provided numerous detailed and elaborate descriptions of suspected reactions. Patient Yellow Card reports also contained information on reasons for drugs being prescribed, reasons for reporting, how patients identified the ADR, and responses from HCPs. Particularly striking were reports of ADRs, often in relation to central nervous system drugs, which were extremely distressing, and sometimes frightening, describing confusion, agitation, panic symptoms, mood swings, suicidal thoughts and electric shock sensations. Patient reports vividly described the effects of suspected ADRs on patients' lives, illustrating impact in terms of serious disruption to social and occupational functioning and marked emotional effects. By contrast, where HCPs did comment on the effects of suspected ADRs on patients' lives, the accounts were usually brief and rarely illustrated the profound impact recorded in patient reports.

Study 5: questionnaire survey of patients reporting to the YCS

The objective of this study was to describe the views and experiences of patients reporting to the YCS.

A questionnaire was developed for distribution by the MHRA to all patients reporting through the YCS between March 2008 and January 2009. The questionnaire elicited information on how patients found out about the YCS, their experiences of, and views on, reporting and their demographic characteristics.

There were 1,362 evaluable responses to the questionnaire sent to 2,008 patient reporters (68%). The most frequent reporting method was postal (59.8%), followed by online (32.8%) and telephone (6.3%). Online reporters were younger (median age in years of reporters: online 50, postal 61, telephone 63; $p < 0.001$) and tended to have a higher education level than those using other reporting methods (e.g. proportion of reporters with a degree: online 48%, postal 28%, telephone 32%; $p < 0.001$). Only 105 (7.7%) respondents had sent in more than one Yellow Card report, and 133 respondents (9.8%) had submitted a Yellow Card report on someone else's behalf.

Almost half of the respondents learned about the YCS from a pharmacy (n = 667; 49.0%), followed by their GP (n = 220; 16.2%). In response to a closed question, most respondents (1,274; 93%) indicated that the report was 'fairly' or 'very' easy to complete, although, in free-text comments, 216 (15.9%) noted difficulties that they had experienced. Suggestions for enhancements were made by 307 (22.5%). One-third (n = 448; 32.9%) expected feedback from the MHRA on their report and 828 (60.8%) would have liked feedback. Almost all respondents (n = 1302; 95.6%) would report again. Respondents indicated a need for increasing health professionals' awareness of patient reporting. Some stressed the importance of having a reporting mechanism that is independent of health professionals so that patients' perspectives can be recognised.

Study 6: telephone interview follow-up of patients reporting to the YCS

The objective of this study was to explore in detail the experiences and views of patients who have made reports to the YCS.

Semi-structured telephone interviews were conducted with a theoretical sample of patients that was purposively selected from those who had completed questionnaires in Study 5 and had indicated a willingness to be approached for a telephone interview. The authors aimed to interview around 30 people in order to gain a wide range of opinions and maximum variation sampling was used to do this in order to obtain a wide range of opinions. Factors that were taken into account in the sampling included: age, gender and educational attainment of patients, and the mode of reporting. In addition, the authors selected some patients based on issues raised in the questionnaire, such as the perceived ease of reporting.

The interviews explored the difficulties in making Yellow Card reports and suggestions for improvement in the reporting system, patients' motivations for making the report and anticipated contribution of their report, patients' expectations about what would happen to their report, patients' satisfaction or dissatisfaction with the process of making a report and patients' willingness to report in future.

Twenty-seven telephone interviews were carried out; 23 interviewees had originally completed paper reports, two had used the internet and two had used the telephone to make reports. Two reports were completed by parents on behalf of their children. For the majority of people, awareness of the YCS was by chance, either via the pharmacy, GP surgery or on the internet. Therefore, many patients suggested that greater publicity was needed for patient reporting. Most interviewees were clearly able to link the ADR with taking a particular medicine, including making temporal links. Motivations for reporting included:

- Altruism
- A desire to find out if others had experienced similar problems
- A desire to help the pharmacovigilance process.

A number of interviewees had been encouraged to report by their pharmacist. Others said that they made their report because they did not think that they could rely on their GP to make a report on their behalf or could not rely on it being accurate. These interviewees felt that their report would compensate for their GP's lack of commitment to reporting.

Eight interviewees had not expected a response to their report, although were pleased when they received one. Ten interviewees said that they had expected to receive an acknowledgement and or some action. Others showed some understanding of the pharmacovigilance process, but were sceptical as to whether anything would actually change as a result of their report.

There was a general feeling among the interviewees that people ought to be aware of the scheme and not find out about it by chance, as they had. There was also a feeling that people should be encouraged to report, as some people thought that they might not be believed.

The interviewees had a number of ideas as to how the scheme might be better advertised to the public. Interviewees suggested putting information on or in the pharmacy bag or on the medicine label.

The majority of interviewees were very positive about reporting again or encouraging other people to report ADRs, and a number of interviews had already actively promoted the YCS to others. Some saw the importance of reporting for pharmacovigilance.

Several suggestions were made for enhancements to reporting systems, including more space for writing free-text comments on the paper form.

Study 7: focus groups and usability testing with members of the public

The objectives of the study were to:

- Ascertain the views of members of the public on the YCS
- Ascertain the views of members of the public on the user-friendliness, effectiveness and usability of different mechanisms of patient reporting
- Obtain suggestions for potential ways in which the reporting system could be improved.

Members of the public in Nottingham, UK, were invited to seven focus groups at which views on patient reporting of ADRs were explored. Recruitment took place between June and November 2008. At the start of the focus group/usability session there was a 15-minute presentation explaining the YCS and the research project. Recordings of the focus group/usability sessions were transcribed verbatim. The focus group data was analysed thematically, identifying the major predicted and emerging themes and ideas from the data. Usability tests simulated the Yellow Card reporting scheme for online reporting, paper forms and telephone reporting.

Overall 40 participants took part in seven focus groups/usability sessions. Over two-thirds of the participants were female and most (74%) were aged 50 years or over. Despite widely publicising the project, there were few men or younger people. Thirty-seven people completed simulated online reports, 36 people completed paper reports and eight people completed telephone reports (81 reports in total).

The focus groups lasted between 30 and 45 minutes. The main themes identified were awareness of the YCS, its value, direct patient reporting, identifying ADRs, issues regarding reporting and advertising the scheme. After hearing the initial presentation introducing the YCS, all of the participants felt that it was a very worthwhile scheme and they could see the benefit of asking patients to report ADRs directly to the MHRA. Several of the participants also commented that they had reported side effects from medications to their doctor previously and had felt that the doctor was disinterested or dismissive. They believed that direct patient reporting would avoid information being reported to the MHRA through a professional lens. In two of the focus groups there was some discussion relating to the quality of data that would be reported by patients and the possibility that this could be influenced by varying levels of literacy and education.

One issue raised in all of the focus groups was the difficulty of determining whether the symptoms experienced were a side effect of the medicine, due to the patient's illness, or unrelated to their health problems. In addition, several participants discussed the potential complexity of deciding which drug was causing an ADR if the patient was taking multiple drug therapies.

Determining the severity of the ADR was also discussed. There was great concern over what would constitute a side effect worth reporting; whereas some participants felt they would be keen to report any potential side effect, many feared that reports of minor or unimportant side effects would 'waste' the MHRA's time. There was general agreement that participants would only report side effects that were serious enough to be debilitating.

Participants were informed that they would only receive an acknowledgement of their report from the MHRA. Concern was raised about this. Several participants felt that the lack of detailed feedback would potentially discourage them from completing a report. The majority of the participants felt that there ought to be more feedback provided to the reporter than a simple acknowledgement. The participants felt that reporters would want to know how their experience of a side effect related to that of other people reporting side effects from the same drug. It was felt important that the reporting forms and information provided about the YCS made clear that feedback on an individual's specific case and medical condition would not be possible. This would avoid disappointment or anger when reporters did not receive a more detailed response.

None of the participants had seen a poster or leaflet relating to the YCS, despite some of those involved in the focus groups being individuals who regularly attended both GP and outpatient clinics and received regular prescriptions from their local pharmacy. A high level of concern was expressed by participants about this apparent lack of promotion of the scheme. Several suggestions were made on how to improve awareness of the scheme among those most likely to suffer from ADRs. Simple measures, such as ensuring that posters are displayed in all pharmacies, general practice surgeries and hospital outpatient departments were seen to be a good method for raising general awareness.

Regarding the usability testing findings, the telephone reporting system was popular with all of those who used it. The interactive nature of the conversation with the person staffing the telephone was highlighted as a factor that made the process much easier for the reporter. Participants expressed concern that such a convenient method of reporting was only available for a limited number of hours, thereby limiting access. Specific suggestions for enhancing online and paper reports were identified.

Study 8: omnibus survey

The objectives of this study were:

- To estimate the percentage of members of the general public in Great Britain who had heard of the YCS for patient reporting of ADRs
- To determine whether those respondents, who believe that they have experienced an ADR and who were aware of the YCS, have made a report using the YCS
- To assess the views of members of the public on the convenience of the three different ways of reporting (online, telephone, obtaining a paper form from a GP/pharmacy to fill in and post).

Eight questions were added to a national omnibus survey that was carried out by telephone over two weekends in January 2009, using a database of residential telephone numbers in Great Britain. Questions were developed to assess public knowledge of the YCS, previous experiences of side effects from medications, previous reporting of ADRs and preferred methods for reporting ADRs.

Over the two weekends, 62,018 telephone calls were made, resulting in 31,390 contacts (50.6%) and 2,028 responses (6.5% of contacts). The analysis was based on the 2,028 subjects who responded to the survey. Compared with the general population in 2008, respondents were more likely to be female, of older age, living in London/south-east/south-west, of lower-middle class, and economically inactive. It should be noted, however, that although all differences reached statistical significance, which was partly owing to the general population sample size; overall percentage differences were fairly small.

A total of 477 (23.5%) people said that they had suffered a side effect from a medicine, the majority of whom (408, 85.5%) had reported it to their GP or another HCP. The main reasons why respondents did not report it to a HCP were the side effect not being serious enough or respondents expecting or knowing about the side effect. Only 172 respondents (8.5%) had heard about the YCS and, of these, only three had self-reported to the YCS the last time they had a side effect (two reported it online and one by post). Nearly 60% (n = 1295) of the sample had used the internet within the last month.

There was no significant association between awareness of the YCS and gender, age group, geographical region, working status and ethnicity (all $p > 0.05$). However, significantly more people who were aware of the YCS came from the upper or middle social grades compared with the skilled working and working class ($p = 0.006$). In addition, awareness of the YCS was associated with respondents having completed post-secondary or university education ($p < 0.001$).

Multiple logistic regression with awareness of the YCS as the dependent variable and social grade or highest level of education as independent variables confirmed that people of upper and lower middle social grades were more likely to be aware of the YCS than those in the skilled working and working grades (overall p-value = 0.009).

The perceived levels of convenience for online or telephone reporting of side effects were higher than those of a form from the local pharmacy or GP. Participants felt that online reporting was either very inconvenient or very convenient. Telephoning was noted to be very convenient by the majority of subjects, whereas using a paper form from the pharmacy or GP was less favoured by some. The respondents who thought that it would be convenient to report online were more likely to be male, younger, living in the Midlands/south, of middle social grade, have some form of further education and be working full time. In contrast, those who thought that the telephone would be a convenient method of reporting were more likely to be female and of lower social grade. Finally, people who thought that reporting via a paper form from their GP or pharmacy would be a convenient method tended to be female, older, of a lower social grade, have a lower level of completed education and be retired.