NCCHTA

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Evaluation of patient reporting to the Yellow Card System

Introduction

The call for an evaluation of patient reporting to the UK Yellow Card System provides a tremendous opportunity to learn more about the role of patients in reporting suspecting adverse reactions.

In this application we present a multifaceted approach from a research team with expertise in pharmacovigilance, and both quantitative and qualitative analysis. We have a strong track record of successful completion of complex studies and of working effectively together.

In this application we present:

- Background literature on the UK Yellow Card System and its use by patients
- Background literature on other patient reporting systems throughout the world
- Our research objectives
- Proposed methods for six studies and a further literature review aimed at addressing our research objectives and the questions raised in the NCCRM call for research
- Scheduling of the studies and responsibilities of co-applicants
- Proposals for the management of the project
- Justification for costings
- References

Background

An adverse drug reaction (ADR) is a reaction to a drug or combination of drugs which is harmful and unintended and which occurs at a dose normally used for prophylaxis, diagnosis or treatment (Metters, 2004). The primary system for reporting suspected ADRs in the UK is the "Yellow Card Scheme" (YCS). As a result of a Health Committee report (House of Commons Health Committee 2004-5), patients (or consumers) in the UK have been able to submit yellow card reports since 2005. The potential benefits of patient reporting were summarised at the First International Conference on Consumer Reports on Medicines in 2000, and included: the promotion of consumer rights and equity; acknowledging that consumers have unique perspectives and experiences; and, that healthcare organisations would benefit from consumer involvement (WHO 2000).

It has been suggested that direct consumer reporting avoids the filtering effect of reporting via health professionals, and that the former could contribute to drug surveillance when reports from the latter are declining (Hammond & Rich 2005), as is the situation in the USA. Consumer reporting of ADRs has also been suggested as a method of hypothesis generation that could be used in addition to health professional reports (Fernandopulle & Weerasuriya 2003).

International experience of consumer reporting systems

Other countries with consumer reporting of ADRs include the USA, Australia, Canada, Denmark, Sweden and the Netherlands. The characteristics of the European schemes are summarised in a report by Health Action International Europe (HAI 2005).The reporting schemes differ in terms of whether they are government-supported or run by consumer groups.

MEDWATCH is the adverse event reporting system in the USA, which is provided by the Food and Drug Agency. The scheme includes reports for adverse events, product problems and errors.

Reports can be submitted by consumers either using mailed or faxed report forms, by telephone, or online (www.fda.gov/medwatch/report.htm). The number of reports from consumers has been increasing since 1993, whilst the number and proportion of reports from health care professionals has been decreasing. In 1996, 41% and 58% of reports originated from consumers and health professionals, respectively (FDA 1997).

In Australia, consumers have access to the "Adverse Medicine Events (AME) Line" to which they can report "suspected AMEs, possible errors or "near misses" with their medicines" (http://www.mater.org.au/ame/HomeAME1.htm). (Consumers can also report to the Adverse Drug Reactions Unit (ADRU) of the Therapeutic Goods Administration (TGA) (Hill & Tan 2006). The AME Line is operated by the Australian Council of Safety and Quality in Health Care. Suspected errors and ADRs are reported using two different forms, therefore, reporting rates for each can be analysed separately. A recent case series of consumer reports to AME relating to the use of zolpidem indicated that that memory disturbances, hallucinations and dependence were more common than was previously thought (Moses et al 2006). An audit of the use of the AME Line showed that 43% of the 3415 calls that were received in a 2-year period were prompted by media publicity (McGuire & Moses 2006). Females and older consumers were more likely to call the Line. One fifth of ADRs reported by callers were previously unrecognised and 8% were related to complementary medicines. In total, 105 serious ADRs and drug-induced hospitalisations that were reported by callers had not been reported by health professionals (McGuire & Moses 2006).

The Canadian Adverse Drug Reaction Monitoring Program (CADRMP) at Health Canada is responsible for the collection and assessment of adverse reaction reports made voluntarily by health professionals and consumers. A public opinion survey on post-marketing surveillance, conducted on behalf of Health Canada, showed that consumers were more likely to believe in the safety of prescribed medicines than non-prescription medicines and natural health products (Health Canada 2003). The authors stated that reported ADRs in general (i.e. not solely ADR reports by consumers to CADRMP) were more likely to be reported by women, older consumers, and by consumers with lower household incomes. Few health professionals who were surveyed had reported an ADR in the past year, and of those who had, they were more likely to be a pharmacist or a nurse compared with other health professionals. In terms of reporting ADRs, the majority of pharmacists (92%) stated that they knew how to make an ADR report, compared with 63% of physicians, 44% of nurses, 19% of naturopaths and 13% of dentists (Health Canada 2003). Over 80% of consumers believed that there should be a legal requirement for health professionals to report ADRs.

In the Netherlands, consumers can report ADRs directly to the Netherlands Pharmacovigilance Centre (Lareb) - a government-run organisation. Of the 6305 reports received in 2005, 819 (13%) were submitted by patients (Lareb 2005). As a result of greater emphasis on patient reporting, the number of reports received from patients in 2005 was 87% higher than the previous year. In addition, there is a consumer-run reporting scheme (DGV, www.meldpuntmedicijnen.nl) which has operated since 2004. Higher numbers of reports are made to DGV compared with Lareb, however, the amount and type of information recorded by the two schemes differs, therefore the data are not entirely comparable. During the first 10 months of the DGV scheme, 49% of reports were related to side-effects (HAI 2005), of which 6% were severe and 30% were not mentioned on the patient information leaflet.

A comparison was made of the reports associated with the use of paroxetine made to the Netherlands Pharmacovigilance Foundation (NPF), with those reported to a telephone medicines information service, which enabled patients to consult a pharmacist regarding the correct use of medicines and problems related to their medicine use (Egberts et al 1996). Proportionally fewer reports were made about paroxetine via the telephone service compared with the NPF (0.5% vs 1.2%, respectively). However, ADRs were reported sooner (mean 229 days (95% CI, 160 to 298))

using the telephone service compared with the NPF. No difference was shown between the two reporting systems in terms of new suspected reactions (i.e. those not included in the patient information leaflet). Nine new ADRs were identified by both systems. Each reaction was first reported using the telephone system for all nine reactions, with a mean time lag of 273 days (95% CI, 89 to 458) between the telephone and NPF system reports. The authors concluded that consumer reporting might assist in the earlier detection of both known and unknown ADRs, but that data from consumers alone was insufficient due to its "crude and incomplete" nature.

Sweden also has a non-government consumer reporting system, known as KILEN (www.kilen.org). This system has been available since 1978. The HAI report (HAI 2005) states that the data collected by KILEN differs from data collected from health professionals. The KILEN system also provides feedback to individuals who submit reports.

Jarernsiripornkul et al 2003, reported that the frequency of consumer reports for ADRs with tramadol were similar to spontaneous reports but higher than prescription event monitoring (PEM) studies. Van den Bemt et al 1999, compared doctor, nurse and patient reporting of ADRs for hospitalised patients. Patients were more likely to report ADRs with new drugs compared with doctors and nurses. Doctors reported more serious reactions. Fromme et al 2004, compared patient reports using a specific instrument, with doctor reports of ADRs associated with chemotherapy. Patients reported more ADRs than doctors. There was little agreement between patient and doctor reporting. A qualitative study by Medawar & Herxheimer, concluded that the quality and interpretation of data provided by health professionals in relation to ADRs associated with paroxetine was poor and might be considered inferior to that provided by consumers (Medawar & Herxheimer 2004).

Summary

The above evidence highlights the differences between ADR reports from patients and health care professionals. These data demonstrate that patient reporting is important and complements ADR reports from health professionals. There is empirical evidence from non-UK studies that highlights the differences between patient and HCP reports, in particular, reports from the former may tend to be reported earlier, and are more likely to include previously unidentified ADRs. The following programme of studies will explore the contribution which patients make to the Yellow Card System in the UK, compared with health professionals, as well as in comparison to existing schemes worldwide.

Objectives

Our objectives are to:

1) Evaluate the pharmacovigilance impact of patient reporting to the Yellow Card System by analysing reports from patients and comparing these with reports from health professionals

2) Report on patient experiences of the Yellow Card System by:

    a) Following up a cohort of patients reporting to the Yellow Card System
    b) Undertaking usability testing with patients of the different methods of reporting to the Yellow Card system

3) Assess public awareness of being able to report to the Yellow Card System by conducting a national survey

4) Offer recommendations for improvements to patient reporting based on our research findings and experience from other countries

Methods

We plan to address our objectives by undertaking:

1) Quantitative analyses of the pharmacovigilance impact of Yellow Card reports [Objective 1]
2) Qualitative analyses of the pharmacovigilance impact of Yellow Card reports [Objective 1]
3) A questionnaire survey of patient experiences of reporting to the Yellow Card System, building on work already done by the MHRA [Objectives 2 & 4]
4) Telephone interviews to explore the experiences of patients who have reported to the Yellow Card System [Objectives 2 & 4]
5) A national survey of public awareness of being able to report to the Yellow Card System [Objective 3]
6) Usability testing and focus groups with patients to help identify recommendations for improvement in the Yellow Card reporting system [Objectives 2 & 4]
7) A further review of the world literature on patient reporting systems to help supplement recommendations for improvement to the Yellow Card System [Objective 4].

Each element of our proposed methods is explained in detail below. Using these methods we will cover all elements of the "research required" that are outlined on page 7 of the NCCRM call for research (RM05/JH30). At the end of this methods section we provide a table illustrating how our research methods will address the specific issues identified in the call for research.

In developing this bid, we have had detailed discussions with the MHRA and believe that our proposals are feasible in terms of the data available and that they will be considered acceptable from an ethical viewpoint. Nevertheless, we recognise that before embarking on any of the studies involving access to Yellow Card reports we will need to gain formal approval from the MHRA Scientific Advisory Committee. In addition we recognise the need to obtain NHS research ethics committee approval for all studies involving patients, including anonymised data from patients.

Study 1: Pharmacovigilance impact of Yellow Card reports - quantitative analyses

This study will:

1) Identify the characteristics of patients reporting to the Yellow Card System
2) Identify the types of drug, types of suspected adverse reaction and seriousness of suspected reactions reported by patients
3) Explore the time-lag between ADR occurrence and reporting for patients and health professionals
4) Investigate the factors associated with patient reports compared with those made by health professionals
5) Explore the relative contribution of patient reporting to signal generation

The MHRA already has over 3000 Yellow Card reports generated by patients (Balall Naeem, personal communication, 2006). Since the start of the national roll-out of the Yellow Card Reporting System for patients there have been 2425 reports (as of 6th June, 2006). The Yellow Card reports from patients have already been entered onto a computer database and we have been

informed that they could be made available in anonymised form as part of our evaluation of the Yellow Card System.

If our bid is successful we will ask the MHRA to firstly send our research team any information they have on the initial pilot of the Yellow Card reporting system for patients as this may help to inform our data analysis plan.

We have been informed by the MHRA that 100-200 patient Yellow Card reports are being received per month; at the start date of our proposed evaluation (1st September 2007) the estimated total available for analysis will be between 4000 and 5500. Our main analysis will be conducted on these reports, and we will ask the MHRA to provide us with an anonymised database.

In addition, to allow us to undertake comparisons between patient reports and those from health professionals, we will ask the MHRA for an anonymised database of all reports from health professionals over the same time period (there will be approximately 40,000 of these on the basis of MHRA figures). From this database we will use the following samples of reports for subsequent analyses:

- For the main analysis, a random sample of Yellow Card reports from all health professionals (number to match the numbers of reports from patients)
- For comparison of individual health professional groups with patient reports, sub-samples of reports from the following groups i) doctors; ii) nurses or iii) pharmacists (sub-samples to be taken from the random sample of all health professionals)
- Reports relating to particular classes of drug and for different professional groups for qualitative comparison with patient reports (see Study 2, below)

Our main quantitative analysis will be based on a comparison between patient reports for the period October 2005 to September 2007 and the random sample of reports from all health professionals.

Research questions

With such large datasets it is likely that we will be able to detect a number of differences between the characteristics of patient reports and those from health professionals. We are particularly interested in answering the following research questions:

- What are the characteristics of patients who report ADRs through the Yellow Card System?
- Are patients more or less likely than health professionals to report serious reactions?
- What classes of drug are most commonly reported by patients?
- Are patients more likely than health professionals to report suspected adverse reactions to particular classes of drug?
- What categories of suspected adverse reaction are most commonly reported by patients?
- Are patients more likely than health professionals to report particular categories of suspected adverse reactions?
- Are there important differences in the time taken to report an adverse drug reaction between patients and health care professionals?
- What are the outcomes of suspected side effects and do these differ across reporter groups?

Power calculation

The MHRA has provided us with data to do some illustrative power calculations for the purposes of this bid and we have used differences in the proportions of Yellow Card reports graded as potentially “serious” reactions as an example.

The MHRA has a system for coding Yellow Card reports as "serious" on the basis of the information provided on the reports. These judgements are made in a consistent manner and the same approach is taken to reports from health professionals and patients. Approximately 59% of reports from health professionals are coded as potentially "serious" reactions compared with 68% of reports from patients (Balall Naeem, personal communication, 2006).

To illustrate the sample size of Yellow Card reports needed to identify both a 10% and a 20% difference in the proportion of reports coded as "serious" between patients and health professionals we have provided relevant calculations in the table below fro different levels of power and statistical significance. Note that all calculations assume a two-tailed test.

Table 1: Sample size calculations to detect potential differences between health professionals and patients in the proportion of reports coded as potentially "serious" reactions.

Significance level	Power	Proportion of reports from health professionals coded as potentially "serious" reactions	Proportion of reports from patients coded as potentially "serious" reactions	Number needed in each group
0.05	80%	60%	70%	376
0.05	80%	60%	50%	408
0.01	80%	60%	70%	550
0.01	80%	60%	50%	597
0.05	90%	60%	70%	496
0.05	90%	60%	50%	538
0.01	90%	60%	70%	695
0.01	90%	60%	50%	754

Therefore, with a sample size of over 3000 in each group we will have over 90% power to detect a 10% difference in the proportions of reports coded as potentially "serious" between patient and health professional reports at the 5% significance level.

Data

Having spoken with Balall Naeem from the MHRA we are aware that the Yellow Card System database will contain the following fields based on data extracted from each Yellow Card report:

- Category of reporter (patient, patient's representative, doctor, nurse or pharmacist)
- Age of patients referred to on the Yellow Card
- Sex
- Mode of reporting: electronic, paper or telephone
- For patient reporting, how they obtained the medication (e.g. by prescription or over-the-counter in a pharmacy)
- Numbers of drugs on each form reported as possibly causing side effects
- Name of drugs reported as possibly causing side effects
- Drug class (based on MHRA Licensing Medical Dictionary)
- Classification of suspected side effects (based on MHRA Medical Dictionary of Reaction Types)
- Free text used to describe suspected side effects
- Date drug commenced
- Date that suspected side effect started
- Date that report sent to MHRA
- Reported seriousness of the suspected side effect
- Reported outcome of the suspected side effect

Completeness of data fields will be checked and validation checks on fields will be undertaken to ensure that subsequent analyses are done on clean datasets.

We will create additional data fields for subsequent analyses. In some instances we will be able to automate this process, e.g. converting MHRA drug classes to British National Formulary chapters and subchapters, and calculating the time taken to report suspected adverse events.

In other instances it will be necessary to undertake a detailed review of the information contained in the Yellow Card report, e.g. determining if a suspected side effect is one that has already been recorded in the Summary of Product Characteristics for the drug in question. These detailed reviews will be undertaken by a researcher with experience in pharmacovigilance work. We aim to undertake these reviews on all Yellow Card reports from patients and the similar-sized random sample of reports from health professionals. A one in ten sample of records will be checked for accuracy of interpretation and data entry.

As a result of this processing and analysis of Yellow Card data we will create the following additional data fields:

- British National Formulary chapter of drugs reported (based on MHRA classification)
- British National Formulary sub-chapter of drugs reported (based on MHRA classification)
- Whether the drugs reported are new ("black triangle") drugs
- Whether the drugs are available over-the-counter (OTC)
- Whether the "drugs" reported are complementary therapies, such as herbal preparations
- Time taken to report the suspected adverse event (based on the difference between the date that the suspected adverse event started and the date that it was reported)
- Whether the suspected side effect is one that has already been recorded on the Summary of Product Characteristics for the drug in question

Analyses

Descriptive statistics will be used to provide an overview of reports from patients and health professionals. Categorical data will be described using frequencies and percentages. Continuous data will be explored using frequencies and histograms and described using means and standard deviations if normally distributed and medians and interquartile ranges if non-normally distributed.

A major component of these quantitiative analyses will be a comparison between patient reports and those from health professionals. On the basis of the descriptive analysis we will decide how best to categorise the different classes of drug and different types of suspected adverse reaction experienced by patients. We will use appropriate univariate analyses to identify potential differences between patient reports and those from health professionals in terms of:

- age and sex of patients
- classes of drug
- use of other drugs (number, type)
- time lag between event and reporting of ADR
- types of suspected adverse reaction
- reported seriousness of the suspected adverse reaction (as coded by MHRA)
- reported outcome of the suspected adverse reaction
- number of words used to describe the suspected adverse reaction

On the basis of the univariate analyses, multivariate logistic regression analyses will be undertaken to identify the most important factors associated with patient reports compared with those from those of health professionals.

The main analysis will be undertaken comparing the reports from patients with those from the entire database of health professional reports. We will undertake similar analyses comparing patient reports with those from the different groups of health professionals (doctors, nurses and pharmacists).

Signal Generation Analyses

The MHRA already undertakes Signal Detection Analysis of Yellow Card reports. It does not, however, differentiate between patient and health care professional reports. We plan to undertake disproportionality analysis of the patient reported dataset and compare it with a data set of matched health care professional reports provided from the MHRA. The analysis will be dependent on the number of suspect adverse reactions per drug and the completeness of the information provided.

Study 2: Pharmacovigilance impact of Yellow Card reports - qualitative analyses

This study will:

1) Assess the extent to which patient reports are likely to capture new knowledge about ADRs (in terms of quantity and quality) and contribute to signal generation
2) Explore the richness of patients' descriptions of their suspected adverse reactions compared with health professional

We plan to analyse several different categories of patient report based on information recorded in the database created for the quantitative analysis. We have budgeted to analyse in detail the text on up to 300 reports from health professionals and 300 reports from patients. We will create a sampling frame to ensure that the following categories of report are adequately covered:

- Patient reports by paper, internet and telephone (We will need to over-sample from this last category as telephone reports make up only 2% of patient reports, compared with 65% for paper and 33% for internet) (Balall Naeem, MHRA, personal communication)
- Reports from different groups of health professional (including doctors, nurses and pharmacists)
- New "black triangle" drugs
- Drugs that can be purchased "over-the-counter"
- Complementary therapies (acknowledging that reports may be less common from health professionals)
- A number of specific drugs or drug groups thought to be of interest, based on the initial quantitative analysis, signal generation and discussions with MHRA and members of the study Steering Group.

After stratifying for the mode of reporting, we plan to take a random sample of reports from patients within each category and to match them, where possible, with randomly sampled reports from health professionals for the same drug (stratifying for types of health professional, and mode of reporting). This means that we will be comparing reports for the same drugs, whether patients or health professionals have done the report. The process of matching will be possible using the databases of patient and professional Yellow Card reports mentioned above.

We will undertake two distinct types of qualitative analysis on the reports.

The first will be a detailed clinical assessment of the extent to which patient reports capture potentially new knowledge compared with reports from health professionals. This analysis will be informed by whether the reports capture problems not previously recorded on summaries of products characteristics or patient information leaflet. In addition, we will assess the extent to which useful information from patients might be lost when suspected adverse effects are coded by the MHRA.

The second will be a comparative documentary analysis of the patients' and professionals' reports of suspected medication side effects. We will particularly examine:

- The ways in which patients describe suspected side effects
- The richness of patient reports compared to those of health professionals.

We will seek to identify the features that characterise the reports, then use these to create a coding framework which will be applied to all the data for comparative purposes. Specialist software will be used as an aid to order and categorise the data. Each of three analysts will examine a sub-set of the data and generate tentative codes which will then be discussed in team meetings. Once satisfied with the framework, it will be applied to the whole sample with inter-rater reliability coding checks carried out to ensure the consistency of coding. We will thus ensure that the data are fully explored and interpreted and will identify similarities or differences between patient and health professional reports and the three methods of reporting.

Study 3: A questionnaire survey of patients reporting to the Yellow Card System

This study will obtain feedback from patients reporting to the Yellow Card System in order to address a number of questions raised in the call for research.

Yellow Cards currently submitted by patients usually contain their contact details, including postal address. The MHRA provides a reassurance to patients that their "personal details will not be passed to any person outside the MHRA without [their] permission".

We have spoken with the MHRA and have been informed of their willingness to send a request to patients asking if they would be willing for their contact details to be given to the successful research team. We would then send a postal questionnaire to the consenting patients.

All questionnaires will be treated confidentially and will be identifiable only by a patient code, to allow follow up of non responders.

If this bid is successful we would also like to explore with the MHRA an option whereby they send the patient a covering letter with a brief explanation of the study, together with a questionnaire. The covering letter can emphasise that the MHRA are not part of the research team, will not see individual completed forms and that the patient is under no obligation to take part in the survey. If the patient is happy to take part in the questionnaire survey they can complete the form and return it directly to the researchers. We feel that this method is likely to result in less attrition than the two-staged approach, and we have used this method successfully in previous patient surveys with patients contacted initially by their GP or other health professionals.

We note that the MHRA already issues an electronic questionnaire to patients that have submitted electronic reports. We will ask the MHRA for reports on the results of these surveys to help inform our own questionnaire design.

To minimise recall bias it is important that we survey patients as soon as possible after they submit Yellow Cards. We propose, therefore, to ask the MHRA to send out requests, on a weekly basis as reports come in. We will ask the MHRA to keep a record of the response rate to these requests.

During the time that we are collecting feedback from patients we believe that it might be best for the MHRA not to send out its electronic questionnaires to patients that have used internet reporting, in order to avoid questionnaire fatigue in patients which could compromise response rates. This is something that we will discuss with the MHRA if our bid is successful.

Questionnaire design

Where possible we will use similar questions to those already used by the MHRA to allow for comparison with their electronic survey. The questionnaire will cover the following issues:

- How patients found out about the Yellow Card System
- How many times they have used the System
- What method of reporting they used for their latest Yellow Card report (electronic, paper or telephone)
- Who did the report (the patient or the patient's representative)?
- How easy they found it to make a report
- Any difficulties encountered in making reports, including whether patients needed additional help in completing the electronic or paper-based forms
- Any suggestions for improvements in the reporting system
- Whether they informed a health professional about the suspected reaction
- Characteristics of respondents (age, gender, ethnicity and educational attainment)

In addition we propose asking patients if they would be willing to participate in a telephone interview to explore in more detail issues around reporting to the Yellow Card System.

Power calculation

As outlined above, the MHRA state that patient Yellow Card reports are coming in at a rate of 100-200 per month at present; approximately 66% of these are paper reports, 33% electronic and 2% reports by telephone.

As a primary outcome measure, we suggest looking for differences between patients making electronic or postal reports in the proportion rating it "easy to make a report" (using a Likert scale). To detect a 10% difference in this measure between the two groups (say 50% in one group and 60% in the other) with a power of 80% and significance level of 5% we would need at least 408 patients in each group (we have suggested similar numbers of patients in each group as the proportion of patients making electronic reports may be similar to the proportion making paper reports by the time of the survey). Therefore, we would aim to obtain a total of 1,200 questionnaire responses, which should be sufficient even if the ratio of paper to electronic reports remains at 2:1.

We propose to send out questionnaires to patients until the sample size is met. To increase the response rate we will send out a reminder to patients that have not replied within 3 weeks.

Given the current rate at which patients are reporting Yellow Cards (100-200 per month) and taking a conservative response rate of 50%, we estimate that it will take up to 18 months to complete the postal questionnaire.

Statistical analysis

Data from the questionnaires will be entered into a Microsoft Access database and a one in ten sample will be checked for accuracy. If any problems are detected, data will be double-entered for the whole sample.

Data will be exported into SPSS for statistical analysis. Categorical data, including many of the questionnaire responses, will be described using frequencies and percentages. Age of respondents

will be described using means and standard deviations if normally distributed and medians and inter-quartile ranges if non-normally distributed.

Appropriate univariate comparisons will be made between the types of Yellow Card report used by patients (electronic, paper and telephone) and their responses to the questionnaire. Multivariate analyses will adjust for potential confounding of factors such as age, gender and educational attainment.

Content analysis will be undertaken on free text comments, such as those relating to potential improvements to the Yellow Card reporting system.

Study 4: Telephone interview follow up of patients reporting to the Yellow Card System

This study will enable us to obtain detailed feedback on current reporting systems and advice on how these could be improved.

Study Design

Semi-structured telephone interviews will be conducted with patients selected from those who have completed questionnaires (Study 3) and given consent to being contacted by the research team. Telephone interviews will begin three months after the start of the questionnaire study to allow the interview guide to be informed by preliminary analysis of the first tranche of questionnaire data (see below). Interviews will be recorded digitally, if patients consent to this, and will be transcribed verbatim.

Sampling

We plan to use maximum variation sampling (Marshall 1996) in order to obtain a wide range of opinions. The factors that we will take into account in the sampling include: age, gender, ethnicity and educational attainment of patients and the mode of reporting. In addition we will take account of issues raised in the questionnaire, such as the perceived ease of reporting.

Issues to be explored in the interviews

The semi-structured telephone interview will be conducted within six weeks of the receipt of the questionnaire, using an interview guide developed by the research team. The development of the guide will be informed by the preliminary analysis of the first tranche of questionnaire data and a number of foreshadowed issues identified by the project team. The latter include:

- Exploration of any 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 making a report
- Patients' willingness to report in future

Analysis

Interview transcripts will be analysed by the qualitative researcher responsible for the data collection in collaboration with two academics with experience in qualitative analysis (one with a pharmacy background, the other with sociology background). The data will be analysed for both anticipated and emergent themes, using the method of constant comparison. Analysis and data collection will proceed simultaneously and continue until 'data saturation' is reached to ensure that the widest possible range of experiences has been included. We anticipate that between 30 and 50 interviews will be required to achieve this.

Study 5: National survey of public awareness of being able to report to the Yellow Card System

We plan to undertake a representative national survey of adults in England to assess public and patient awareness of being able to report suspected drug side effects using the Yellow Card System.

Survey design

We plan to cover the following issues in the survey:

- Whether respondents use any types of medicines regularly or have taken any types of medicines in the last year
- Whether respondents believe that they have experienced a side effect from a medicine (or complementary therapies) in the past, and if so, whether they told anyone about it
- Whether respondents have heard about the Yellow Card System for patient reporting of suspected side effects to medication
- In rank order, which of the following ways of reporting suspected side effects might be most convenient to respondents:
    - Telephone
    - On line
    - Obtaining a paper form from a pharmacy (chemist) to fill in and post
    - Obtaining a paper form from a general practice to fill in and post
    - Telling a health professional about the problem so that they can decide whether to send in a Yellow Card

In addition we will obtain information on the characteristics of respondents.

Survey administration

It can be extremely time consuming, and prohibitively expensive, to undertake national surveys of patients given current research governance arrangements. Therefore, we propose adding our research questions to a representative national survey of the public. We recognise that there may be some disadvantages to this approach, including low response rate, but believe that these are outweighed by the ease and speed with which the survey can be completed, costs and the ability of national omnibus surveys to collect reasonably representative data.

We have worked successfully with BMRB Omnibus Surveys in the past (www.bmrb.co.uk, Ealing Gateway, 26-30 Uxbridge Road, Ealing, W5 2BP) and suggest using them for the proposed study. This company does national surveys using face-to-face, telephone and on-line methods of collecting data. Following discussions with the company, it is likely that a telephone survey will provide the most representative sample for our study. BMRB national telephone surveys run from Friday to Sunday every weekend and interview a fresh sample of 2,000 nationally representative adults aged 16+ each time. Results can be delivered within a week depending on the complexity and length of the questionnaire and the analysis required. Results are presented in tabulated format in a database programme or spreadsheet, with the responses broken down by sex, age, socio-economic status and geographical region. The organisation is also able to break any question against other demographic details available such as age at leaving education. To give an idea of costings, a "yes/no" question to 2000 people would cost £780 (+ VAT) and a pre-coded question with up to 5 response options would cost £975 (+ VAT). These are relatively low costs for a short national survey and would allow us to put more researcher time into other aspects of the Yellow Card System evaluation.

Statistical analysis

Data from the survey will be exported into SPSS and coded for subsequent analysis. Categorical data, including many of the questionnaire responses, will be described using frequencies and percentages. Age of respondents will be described using means and standard deviations if normally distributed and medians and inter-quartile ranges if non-normally distributed.

Study 6: Usability testing with patients followed by focus groups to help identify recommendations for improvement

We propose to combine two qualitative methods to prospectively examine patient experiences of using yellow cards: usability testing and focus groups. This study will enable us to identify patient views of the user friendliness, effectiveness and usability of different mechanisms of patient reporting, while also identifying potential ways in which the reporting system could be improved.

Recruitment

We shall include patients who believe they may have experienced side effects from medications but who have not previously filled in a Yellow Card report (over 10% of patients on new medications experience side effects (Gandhi et al 2003)). We plan to recruit through advertisements in local media, surgeries and pharmacies in Nottingham. We aim to recruit six groups of eight patients for this study. Each group will be heterogeneous in terms of age, occupational class, gender, educational level and prior experience of using the internet. Each group will take part in a focus group and usability testing in one 2-3 hour session and will be provided with refreshments and an inconvenience payment of £25.

Focus Groups

After a short presentation on adverse drug reactions and the Yellow Card System by the Group Convenor, participants will be encouraged to discuss their readiness or otherwise to use the reporting system, to identify any barriers or facilitators to making use of the system and to identify their initial preferences for using one or other method of reporting. The focus groups will be recorded digitally and fully transcribed.

Usability testing

Usability testing will take place in the pharmacy practice laboratories at the University of Nottingham. These rooms are equipped with computers with access to the Internet, telephone handsets and a stock of paper Yellow Card report forms will be provided.

Each user will be presented with a number of scenarios in which a patient experiences what may be an adverse reaction to taking a drug to treat or prevent a specified condition. These scenarios will be drawn from a 'bank' which relate to the range of drug groupings identified by patients in our analysis of Yellow Card reports. Users will be asked to decide, in relation to each scenario, whether, in their opinion, it would be appropriate to complete a yellow card. Three of the scenarios for which they deem reporting to be appropriate will then be selected and the user will be invited to complete a yellow card, using each of the three methods for one of the scenarios. The order in which they use the three methods will be randomly assigned to avoid learning effects creating bias. As they complete the tasks, the researchers will encourage them to 'talk aloud' about the experience, any difficulties or uncertainties they encounter, any changes to the systems they would find helpful. The discussions will be digitally recorded. The researchers will review the recordings and identify relevant sections for selective transcription.

In order to complete each of these exercises successfully we will need at least eight researchers to observe patients and record their comments. These researchers would be drawn from our study team and we would also use PhD students at the University of Nottingham.

For the telephone reporting we will discuss with the MHRA whether we might use their own telephone reporting service for these exercises to help ensure that the experience of reporting is as close as possible to reality. Obviously we would need to identify a way of ensuring that data from these telephone calls were not included in MHRA reports of suspected adverse drug reactions. If it is not possible to use the MHRA system, we would train researchers in the way in which MHRA record data from telephone contacts and use them to take calls from the patients undergoing usability testing.

Analysis of focus groups and usability testing

Data from the focus groups and usability testing will be analysed by a researcher at the University of Nottingham under the guidance of Professors Anderson and Murphy. Data will be analysed for both anticipated and emergent themes, using the method of constant comparison. We are particularly interested in patients' views on:

- the user friendliness, effectiveness and usability of the different mechanisms of patient reporting
- the ways in which the Yellow Card reporting system could be improved for patients.

Study 7: Literature review

The published literature on patient reporting systems in other settings will be reviewed. Search strategies will be based on the findings of the study. For example, if a lack of awareness of the patient reporting system is identified, the search will be focussed on mechanisms used for addressing this problem in other countries. Where possible comparisons will be made with the study findings and recommendations made as necessary to amend the UK system. It is expected that the literature will be wider than traditional academic papers and will include policy documents, web sites and other grey literature.

How our proposed methods will address the questions raised in the call for research

The call for research raised a number of research questions on the themes of patient experience of reporting to the Yellow Card System and pharmacoepidemiological impact. There was a request for researchers to address these themes within a framework that will allow comparisons between the three methods of patient reporting and between reports from patients and different groups of health professionals. We believe that we will be able to address the questions raised in the call for research and we illustrate how we propose to do this below.

Table 2: Research themes highlighted in the call for research and how we plan to address these

Research theme	Methodological approach	Outcomes
Patient Experience		
Patient's awareness of being able to report.	1) National survey to assess public awareness of being able to report (study 5).	1) Knowledge regarding the extent of public awareness of being able to report and on the relative effectiveness of different communication strategies. 2) Knowledge regarding patients' reactions to the reporting system and to the three methods of reporting. 3) A detailed understanding of the benefits of and barriers to using the different methods of reporting and on the usability of the yellow card system. 4) Recommendations for development of the scheme and for future communication strategies.
The relative effectiveness of different communication strategies to encourage patient reporting	1) National survey to assess views of the public on options for reporting (study 5). 2) A questionnaire survey of patients reporting to the Yellow Card Scheme (study 3). 3) Telephone interviews with patients who have reported to the Yellow Card Scheme (study 4). 4) Literature review (study 7)	
Patients' reactions to the reporting system and ability to complete yellow cards without assistance	1) Questionnaire survey of patients reporting to the Yellow Card Scheme (study 3). 2) Telephone interviews with patients who have reported to the Yellow Card Scheme (study 4). 3) Focus groups (study 6). 4) Usability testing (study 6).	
Patient's views on the user friendliness, effectiveness and usability of different mechanisms of reporting	1) Focus groups (study 6) 2) Usability testing (study 6)	
Pharmacovigilance Impact		
A qualitative investigation of the "richness" of patients' descriptions of their symptoms	1) Detailed analysis of the text on up to 300 reports from health professionals and 300 reports from patients (study 2). 2) Detailed clinical assessment of the extent to which patient reports capture potentially new knowledge compared with reports from health professionals. (study 2). 1) A comparative documentary analysis of the patients' and professionals' reports of suspected medication side effects.	1) A detailed evaluation of the extent to which patients' reports are likely to capture new knowledge about ADRs and contribute to signal generation. 2) A detailed exploration of the richness of patients' descriptions of their symptoms compared with those from health professional.
The time lag between ADR occurrence and reporting	1) Quantitative analysis of Yellow Card reports (study 1)	Comparison of time lag for patient reports compared with reports from health professionals.
The relative contribution of patient reporting to signal generation in terms of both quantity and quality	1) Quantitative analyses of yellow card reports (study 1) 2) Qualitative analyses of yellow card reports (study 2))	A detailed evaluation of the relative contribution of patient reporting to signal generation
Framework for the analyses		
Comparisons between the 3 methods of reporting for patients and reports from patients and different groups of health professionals	1) Quantitative analyses of yellow card reports (study 1) 2) Qualitative analyses of yellow card reports (study 2)	1) Knowledge regarding the factors associated with different types of patient reports compared with different types of health professional reports 2) Evaluation of the phamacovigilance impact of different types of these different types of report

Scheduling of the studies and responsibilities of co-applicants

The Gantt chart below indicates the proposed timelines for the seven studies including initial planning and final dissemination. Responsibilities of the different centres involved in the research are highlighted.

ACTIVITIES	**< 0**	**1-2**	**3-4**	**5-6**	**7-8**	**9-10**	**11-12**	**13-14**	**15-16**	**17-18**	**19-20**	**21-22**	**23-24**
Ethics committee and R&D approval	N*	N											
Recruit staff	N	D**		N	A***								
Finalise design	NDA	NDA											
STUDY 1 *Quantitative analyses of YCS*													
Initial			D	D	D	D							
Further						A	A	A	A	A	A		
STUDY 2 *Qualitative analyses of YCS*													
Clinical assessment						D	D	D	D	D	D		
Comparative documentary analyses						N	N	N	N	N	N		
STUDY 3 *Questionnaire survey of patients reporting to YCS*													
MHRA send for permission to patients													
MHRA send details to team													
Questionnaire design		NAL†											
Team sends questionnaires			N	N	N	N	N	N	N	N	N		
Questionnaires returned and entered				N	N	N	N	N	N	N	N		
Analyses									A	A	A	A	
STUDY 4 *Telephone follow-up of patients reporting to YCS*													
Interview design				NAL									
Interviews					N	N	N	N					
Quantitative and qualitative analyses of interviews							N	N	N	N	N	N	
STUDY 5 *National survey of public awareness*													
Question design					NAL								
Omnibus survey													
Analyses								A	A	A			
STUDY 6 *Usability testing in the population*													
Recruitment					N	N	N						
Focus groups and testing						N	N	N					
Analysis						N	N	N	N	N	N		
STUDY 7 *Further literature review*													
Further literature review								A	A	A			
WRITING UP										NDA	NDA	NDA	NDA

N* = Nottingham: Administrator, months 1-24 (24 months) 0.5 wte; Qualitative researcher months 7 to 24 (18 months) 0.8 wte: D** = DSRU: Researcher, months 3 to 20 (18 months) 0.6 wte: A*** = Aberdeen: RA/statistician, months 9 to 24 (16 months) 0.6 wte: L† = Liverpool John Moores:

Project Management

Professor Avery will have overall responsibility for the successful management of the whole project. Areas of lead responsibility of other applicants are as follows:

University of Nottingham

Dr Fortnum	Liaison with the MHRA and coordination of the studies between the different sites.
Professors Anderson and Murphy	Qualitative work led by the University of Nottingham

Drug Safety Research Unit

Professor Shakir	Overall responsibility for analyses undertaken by the DSRU
Dr Marshall	Supervision of work of researcher at DSRU

University of Aberdeen

Professor Hannaford	Overall responsibility for quantitative analyses undertaken by the University of Aberdeen
Dr Lee	Finalisation of statistical analysis plans and supervision of quantitative analyses undertaken in Aberdeen
Dr Watson	Supervising the literature review
Professor Bond	Questionnaire design for studies 3 and 5 (with Professor Krska)

Liverpool John Moores University

Professor Krska	Questionnaire design for studies 3 and 5 (with Professor Bond)

Project Management Group

Our project management group will include all the applicants in this bid with the leads from each institution being required to ensure that a representative is available for all relevant meetings. Through previous collaborative projects we have experience of working effectively together using regular teleconferences and we would envisage having these every fortnight at the start of the project and then once a month for the duration of the studies. We would plan to have face-to-face meetings at the beginning, middle and end of the project and to use the final meeting to evaluate our findings and agree on recommendations for any improvements in the Yellow Card Reporting System for patients.

Project Advisory Group

A project advisory group will be convened to provide additional feedback into the detailed study design and contribute to making recommendations for improvements in the Yellow Card Reporting System for patients. The group will include representatives of the MHRA, the main professional groupings making reports, and patient representatives from both Patient Support Groups and Patient Advocacy groups.

Justification for costings

In order to address the research questions raised by the NCCRD and to take maximum advantage of the wealth of information available we have proposed an ambitious, but achievable, set of seven studies. We have costed these carefully and the total comes close to the upper limit of £250,000 that applicants were invited to bid for. We believe that our bid represents good value given the range of outputs that we will be able to deliver.

We are requesting funding to employ four people to work solely on this project.

- A research fellow with clinical skills in pharmacovigilance (0.6 wte) will be required at the Drug Safety Research Unit for 18 months in the middle of the project to undertake initial analyses for study 1 and clinical assessment for study 2 under the supervision of Dr Marshall.
- A research assistant with quantitative skills (0.6 wte) will be required in Aberdeen for the final 16 months of the project to undertake the quantitative analyses for studies 1, 3 and 5 under the supervision of Dr Lee.
- A research assistant with qualitative skills (0.8 wte) will be required in Nottingham for the final 18 months of the project to undertake analyses for studies 2 and 4 under the supervision of Professors Murphy and Anderson.
- An administrator (0.5 wte) will be required in Nottingham for the duration of the project to provide general administrative support to the whole project but specifically to co-ordinate the questionnaire mailing and data entry in study 3, and patient recruitment and interview transcription from studies 4 and 6 under the supervision of Dr Fortnum.

In addition the time of an IT specialist (20 days) will be required at the DSRU in Southampton to ensure data quality.

Management of the project will be facilitated by regular team meetings. We propose to meet together face to face as a whole team on three occasions, at the beginning, middle and towards the end of the project. We request funds for travel to Nottingham and for an overnight stay of the final meeting. In addition we propose to maintain management of the project via teleconferences, fortnightly for the first six months and monthly thereafter (N=30).

Study 3 will involve the printing and mailing of up to 2000 questionnaires for which we are requesting £2000.

The Omnibus survey for Study 5 will be costed per question and we estimate we shall include 5 yes/no questions and 2 choice questions at a cost of £6875.

Study 6 will involve recruitment of 48 people to focus groups and we propose to pay them an inconvenience allowance of £25 each. We shall also recruit local PhD students to supervise the sessions and have requested £885 to cover these costs for 8 sessions.

The time of the co-applicants in Nottingham, Aberdeen and Liverpool is included at 6 days per person over the 2-year course of the project in accordance with full economic costing as applied at each university. In addition an equivalent allowance has been requested for Professor Shakir and Dr Marshall at the DSRU.

Estates charges and indirect costs have been calculated on the basis of TRAC methodology for each of the higher education institutions.

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