SHORT COMMUNICATION

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Improving Follow-Up Rates in Spontaneous Adverse Drug Reaction Reporting

Effectiveness of a Targeted Letter Used by a Regional Centre in the UK

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Abstract

Background: Spontaneous reports of suspected adverse drug reactions to regulatory bodies and market authorization holders are important in pharmacovigilance. Follow-up information, which can be difficult to obtain, is often required from reporters; therefore, we developed targeted follow-up letters that we hoped would make replying easier.

Objective: To examine the effects of introducing targeted letters on responses to follow-up requests from a regional pharmacovigilance centre in the UK.

Method: In January 2001 we redesigned our follow-up request letter to include tick-boxes targeted to obtain the appropriate information from reporters. Response rates and the requirement for a second follow-up letter were examined for the 5-year period before introduction of the targeted follow-up letter (1996–2000) and the 5 years after the change to the targeted follow-up system (2001–5). In an 18-month sub-study examining data from 2001–2, time from the production of the first targeted follow-up letter to receipt of a response from reporters was also measured.

Results: The introduction of targeted follow-up letters was associated with an increase in the mean annual response rate for follow-up from 36.4% in the 5 years pre-targeted follow-up to 60.5% in the 5 years post-targeted follow-up ($p < 0.0001$). Fifty percent of all successful follow-up responses were obtained within 70 days.

Conclusion: Targeted follow-up letters were associated with increased follow-up success rates. Results also indicate that closing cases to follow-up information at 70 days would allow collection of 78% of all follow-up that would ever arrive.

Background

The collection of spontaneous case reports by regulatory bodies and market authorization holders (MAHs) of adverse reactions to medicines continues to be an important part of postmarketing surveillance.[1-3] Spontaneous reporting systems depend on the submission of reports of a suspected association between one or more drugs and an adverse event. Reports are submitted by healthcare professionals and, in an increasing number of countries such as the US, Canada, the Netherlands, and the UK, by members of the public.[4] Large databases of aggregated spontaneous reports can be interrogated for potential drug safety signals, for example, by using measures of disproportionality.[5] Evidence from case reports contributes to most drug withdrawals.[6]

Important data are often missing from submitted spontaneous reports because those completing them are under pressure, do not recognize a factor may be of importance, or because the reaction is still ongoing. Reporters are encouraged to report, even if some data are missing. Indeed, the minimum international standard for information for submission of an adverse drug reaction (ADR) comprises four key data fields: the reporter source, the patient's demographic details, a suspect drug and the suspected reaction.[7] As a consequence, regulatory authorities and MAHs often find it necessary to follow up reports to obtain further information for important reactions.

Responses to requests for information in retrospect may require more attention and time than a reporter has available. There is therefore a balance to be struck between the desire for complete information and the wish not to inhibit reports or alienate the reporter.

MAHs have a legal obligation to make appropriate efforts to obtain follow-up information under EU law. The CIOMS Working Group V suggested that "If the first written follow-up attempt on a serious unexpected case or a non-serious unexpected case fails to generate a satisfactory response, a second follow-up letter should be sent no later than four weeks after the first letter. In general, when the reporter does not respond or is incompletely cooperative, the two follow-up letters should reflect sufficient diligence."[7] Site visits are also suggested in some cases. More general advice is given that follow-up should continue until outcome has been established, although follow-up should optimally take place once. The optimal length of time that follow-up information should be sought from reporters before closing a case is uncertain.

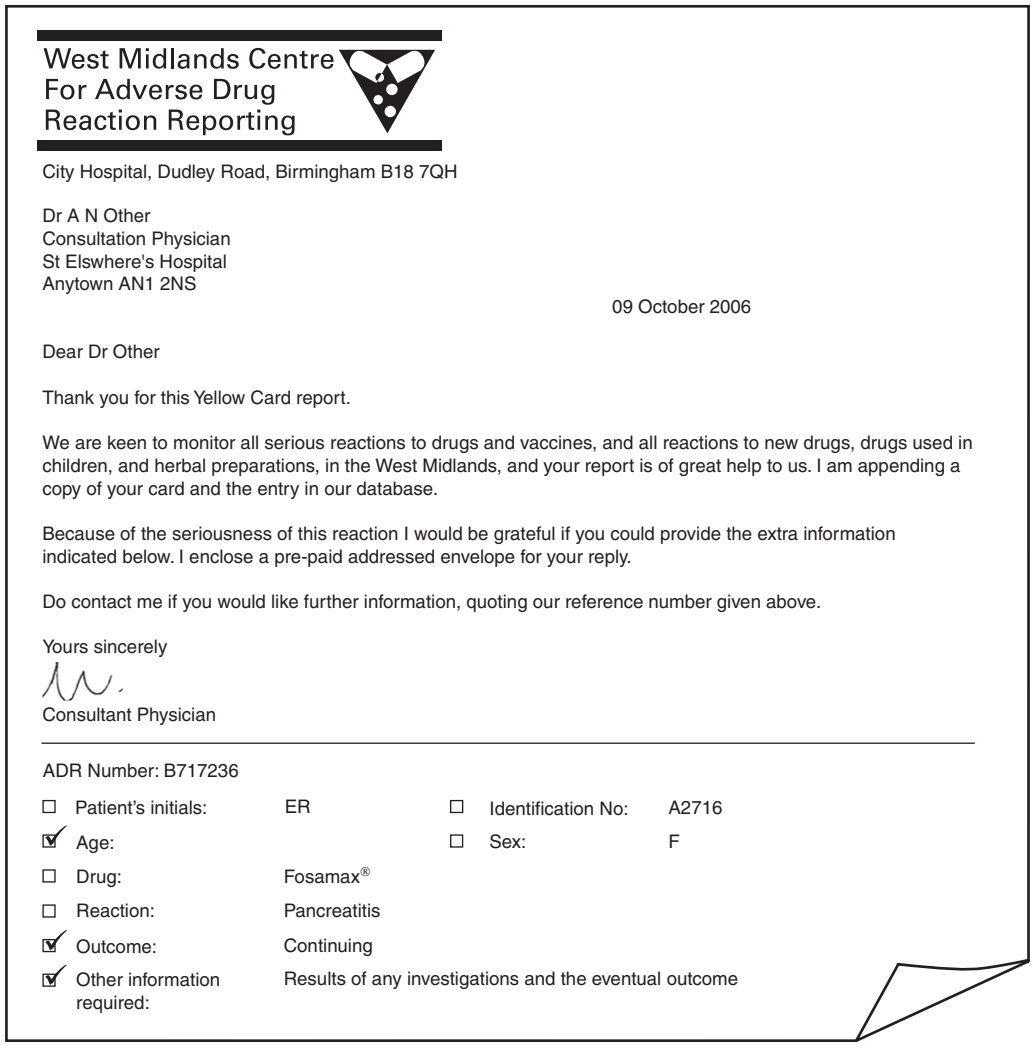
The UK's spontaneous reporting scheme, the Yellow Card scheme, altered its reporting card in the summer of 2000. The changes were designed to improve completeness of submitted reports by reducing the amount of writing required from reporters. The form increased the number of tick boxes to help reporters complete the card. Reporters were asked to indicate if the patient had died, if the reaction was life-threatening, if the report was of a congenital abnormality, if the report involved or prolonged inpatient hospitalization, or if it involved persistent or significant disability or incapacity. In addition, reporters were asked to indicate if a report was serious, or in some other way medically significant. In January 2001 we redesigned our follow-up request letter to include tick-boxes targeted to obtain the appropriate information from reporters. We wondered if the use of such targeted follow-up letters would increase our follow-up success rate and reduce the time taken for such follow-up reports to be obtained.

Objective

The objective of this study was to analyse the effect on follow-up response rates of introducing a targeted follow-up letter, and to measure the time taken to obtain follow-up information from reporters.

Methods

We conducted a sequential trial of targeted follow-up letters containing tick-box fields (see figure 1) in order to make it clear to reporters exactly what additional information was being requested. Prior to 31 January 2001, follow-up letters requested the additional information in the text of the letter. After 31 January 2001, all new



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City Hospital, Dudley Road, Birmingham B18 7QH

Dr A N Other
Consultation Physician
St Elswhere's Hospital
Anytown AN1 2NS

09 October 2006

Dear Dr Other

Thank you for this Yellow Card report.

We are keen to monitor all serious reactions to drugs and vaccines, and all reactions to new drugs, drugs used in children, and herbal preparations, in the West Midlands, and your report is of great help to us. I am appending a copy of your card and the entry in our database.

Because of the seriousness of this reaction I would be grateful if you could provide the extra information indicated below. I enclose a pre-paid addressed envelope for your reply.

Do contact me if you would like further information, quoting our reference number given above.

Yours sincerely

Consultant Physician

ADR Number: B717236

☐	Patient's initials:	ER	☐ Identification No:	A2716
☑	Age:		☐ Sex:	F
☐	Drug:	Fosamax®		
☐	Reaction:	Pancreatitis		
☑	Outcome:	Continuing		
☑	Other information required:	Results of any investigations and the eventual outcome		

Fig. 1. Example of targeted follow-up request.

follow-up requests used the targeted follow-up letter. The rationale for requested material was based on a standard operating procedure used within the regional unit, which did not vary during the duration of the study. Reporters could either use the tick-box fields on the letter they received or attach additional information if necessary. A pre-paid envelope was included for their reply. If no response was received 2 months after the initial follow-up letter, a second targeted follow-up letter was dispatched. Reports were selected for follow-up after review by an experienced clinical pharmacologist. The trial was conducted in the West Midlands region of the UK, which has a population of approximately 5 million.

Time from the production of the first targeted follow-up letter to receipt of a response from reporters was measured for follow-up requests made during 2001–2.

Table I. Follow-up rates and successful response rates

Reports and follow-up requests	Pre-targeted follow-up letter					Post-targeted follow-up letter				
	1996	1997	1998	1998	2000	2001	2002	2003	2004	2005
No. of reports	1127	1236	1305	1307	2654	1317	926	1245	1318	1259
No. of follow-up requests	262	234	234	194	244	170	136	100	105	103
Successful follow-up requests [n (%)]	102 (39)	94 (40)	115 (49)	60 (31)	54 (22)	117 (69)	84 (62)	52 (52)	61 (58)	58 (56)

Results

We requested follow-up information on 15% (n = 1168) of reports (n = 7629) during the period 2001–5, compared with 10% (n = 614) of reports (n = 6065) in the 5 years prior to the introduction of the targeted follow-up (table I).

The mean successful follow-up response rate prior to the introduction of the revised follow-up letters over the period from 1996 to 2000 was 36.4%; the mean rate after the introduction of targeted follow-up (2001–5) rose to 60.5% (Fisher's exact test; $p < 0.0001$) [figure 2].

Before the introduction of the targeted follow-up letter, the proportion of reports requiring a second follow-up letter was 46% (523 of 1146 reports during 1996–2000) and following its introduction the proportion was 21% (54 of 260 reports during 2001–2). This decrease in the proportion requiring secondary follow-up was statistically significant (Fisher's exact test; $p < 0.001$; 95% CI 19, 31).

We analysed the reports for the first 18 months (during 2001–2) after the change in practice and found that 50% of reporters responded to follow up within 70 days (figure 3). Four weeks after the initial follow-up request letter was sent out, only 25% of reporters had responded.

Discussion

Being too busy to report was postulated as one of Inman's seven deadly sins, and has also been reported in other studies.[8,9] This could equally apply to responding to requests for follow-up information. Our forms, which were designed to make it easier for reporters to respond, improved our response rate to follow-up requests when compared with historical data and reduced the proportion of reports requiring a second follow-up letter.

Making follow-up easy for reporters is important since a bad experience of a follow-up request could inhibit future reporting. Reporters can be discouraged by multiple follow-up requests. On the other hand, follow-up contact may provide a reporter with confirmation, and confidence, that their report was worthwhile, and act as a reminder to make further spontaneous reports.

Our initial success at improving the follow-up response rate was attenuated in later years. This may be explained by the widening of the reporter base in the UK since different professions, such as community pharmacists, may have more difficulty in obtaining follow-up data. Alternatively, it may have been due to differences in the nature of the reports that required follow-up.

This study included only historical controls. Differences in the reporter profiles, the drugs being reported or the ADRs being detected may have affected follow-up request rates and response rates. Notably, bupropion (under intense surveillance during 2000) and meningitis C vaccine (under intense surveillance during 1999–2000) both contributed a relatively high proportion of reports during 1999–2000, which may have adversely affected follow-up response rates. Many of these reports may have been of less serious reactions not requiring follow-up. The meningitis C vaccine campaign was also the first experience of the Yellow Card scheme for nurses, which could have influenced follow-up response rates.

	Successful	Unsuccessful
Before intervention	425	743
After intervention	372	242

Fig. 2. Comparison of successful follow-up rate pre- and post-intervention. Fisher's exact test (two-tailed $p < 0.0001$).

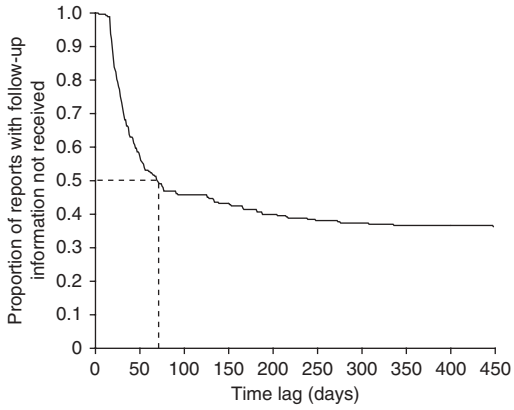

Fig. 3. Kaplan-Meier survival curve showing response to follow-up for 2001–2.

Another possible confounder to this study could be changes in the type of follow-up information requested. The regional centre requested follow-ups to a standard operating procedure, which did not vary throughout either study period. However, changes in the demographics of reporters (such as age, sex and professional group) may have also influenced follow-up rates. Unfortunately, we are unable to provide details of such changes as our local database was deleted following the decision to centrally manage all ADR reports. We are therefore also unable to provide information on the demographics of follow-up reports, such as the seriousness of reports, or black triangle status of the reported drug. In the UK, newly licensed drugs with provisional safety records are indicated by the black triangle symbol (▼). Reporters are encouraged to report any ADR potentially associated with a black triangle drug, no matter how trivial, to the Yellow Card scheme. No set duration for black triangle status exists, but the status is usually re-assessed at 2 years. There is evidence that reporters are more likely to report suspected ADRs to black triangle drugs, with a selective bias for ADRs of greater clinical concern.[10]

Analysis of response time showed that regulators and MAHs might be hasty in closing cases when no follow-up information has been forthcoming after a letter sent at 4 weeks. Follow-up reports continue to arrive for several months following the sending of a follow-up request. Closing cases to follow-up information at 70 days, when the response to follow-up requests is at 50%, would allow collection of 78% of all the follow-up information that would ever arrive. Some follow-up information is easily obtained, whereas other may depend on the results of further tests or investigations, or the time taken for the final outcome of the reaction to be known. Consequently, the type of follow-up may vary with the length of time from the initial report.

Other ways of improving follow-up success rates could be the provision of individual feedback of use to the prescriber. An investigation by the Dutch regulator showed information provision to reporters and individual feedback were highly valued by reporters.[11] Such feedback may further improve follow-up success rates by increasing the awareness to the reporter of the importance of their report.

Conclusions

We found that the use of targeted follow-up letters increased the ease of providing follow-up information, decreased the proportion of reports requiring a second follow-up letter, and was associated with an increase in our follow-up success rates. Our results also suggest closing cases to follow-up information at 70 days would allow the collection of the bulk of available follow-up information.

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