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REVIEW ARTICLE

User-Driven Development of a Web-Based Tool for Patient Reporting of Drug-Related Harm

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Abstract Commissioned by the Monitoring Medicines project, the Uppsala Monitoring Centre (UMC) led the design and development of a web-based ADR (adverse drug reaction) reporting tool intended for use by patients. The software design was undertaken in close collaboration with representatives of national pharmacovigilance centres (NPCs) and with patient and consumer organizations. The web-based tool was developed by these participants through several telephone conferences, a workshop and site testing. The tool is directly compatible with the UMC's Individual Case Safety Report (ICSR) data management system VigiFlow® and is also compliant with the ICH-E2B(R2) format. The UMC team benefited by working closely with the end-users during the development process. A major challenge was to balance the need for detailed information required by the NPCs to be able to assess reports with the amount of detail patients are able and willing to provide. Needs, ideas and suggestions from the end users were valuable and were taken into account throughout the process of designing the tool.

Key Points

Remote project management, where the project team only meet through telephone conferences, is feasible provided all participants agree on well defined project goals.

Development of a generic web-based reporting tool for patient reporting for potential global implementation and local adaptation is possible.

1 Introduction

Due to well documented under-reporting in systems for spontaneous adverse drug reaction reporting, which in some studies is estimated to amount to 94 % [1], additional sources and channels are needed for national pharmacovigilance centres (NPCs) to obtain vital information on the experiences of patients while they are using medicines. Without the clinical translation of healthcare professionals, new insights are gained to add to the valuable information that the healthcare professionals are providing. Direct patient reporting is not intended to replace any of the existing reporting mechanisms but rather to complement them. Observations and views obtained directly from patients may cover reactions and symptoms that are unpleasant, and affect everyday activities without being fatal or serious, and will increase the likelihood and speed of detecting signals [2].

The Monitoring Medicines project [3], managed by an 11-partner consortium and funded by the EU FP7 (7th Framework Programme for Research and Technological Development) 2009–2013, had as one of its main

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objectives to support and strengthen patient reporting of suspected adverse drug reactions.

As one of the work packages in the Monitoring Medicines project [3], the Uppsala Monitoring Centre (UMC) was commissioned to develop a web-based reporting tool intended for the general public.

It was to be based on, or compatible with, the Individual Case Safety Report (ICSR) management system, VigiFlow®, already used by NPCs, and compliant with the International Conference on Harmonisation ICH-E2B(R2) format. The system would be designed so that entry screens could be understood and operated by patients themselves or by their relatives.

The new EU pharmacovigilance legislation was promulgated in 2010 and due to be implemented in 2012. It was critical for the reporting system to be consistent with requirements of the new legislation. The new legislation was therefore carefully examined to identify any new EU reporting requirements that needed to be taken into account.

Prior to this project some NPCs had already established systems to collect information directly from patients. There had also been encouraging studies on how patient reports contribute to signals [4]. The first work package in the Monitoring Medicines project, preceding this project, was aimed at learning from the experiences of these countries [5].

2 Project Activities and Results

2.1 Recruitment of Partners

Actively involving end users was identified as an important factor early on in the process. The importance of having perspectives from different end users was also identified in the recruitment process [6]. Representatives of patient and consumer organizations who participated in the project were consulted for input during the development and design process of the reporting tool.

A selected number of European patient and consumer organizations were invited to assist in the development process (see Table 1); all those invited agreed to participate. Individual representatives of the organizations took part in one or several of the telephone conferences and the following workshop.

Table 1 Organizations participating in the development process as representatives of end users

European Consumer's Organization
European AIDS Treatment Group
Health Action International
HIV Europe
Swedish Thalidomide Society

2.2 Work Process

Figure 1 shows the timeline of the project, from the initial meeting of the consortium to the start of the pilot stage of the finished system. During the project the recruited partner group participated in four telephone conferences led by the UMC project management team. Prior to each meeting, an agenda and supporting material was distributed, and all participants were expected to have gathered insights to the topics. Participants were prompted to give input to specific questions; for example, regarding report flow and the design of the reporting system. These teleconferences were undertaken using the Go-To-Meeting [7] functionality which allows all meeting participants to view the same computer screen and also referring to the material that was distributed to the group in advance of the scheduled meetings.

2.3 Consortium Meeting

At a consortium meeting held in Uppsala in December 2010, the first discussions took place on how a web-based patient reporting tool might support global pharmacovigilance. The discussions concerned the flow of patient reports and access to the information, among other topics. It was agreed that all information from the general public should be directed to the NPC in the country in which the patient resides before being shared with members of the WHO Programme for International Drug Monitoring via VigiBase®.

2.4 First Telephone Conference: Design of the Tool

Prior to the first telephone conference, a questionnaire was distributed to the patient and consumer organizations and to NPCs who had agreed to participate in the work (see Electronic Supplementary Material 1). The questionnaire covered which reporters should be targeted, whether anonymous reports would be accepted, registration requirements, and feedback functions. Feedback from the questionnaire was used as discussion material, and the discussions led to the following decisions being taken at the first meeting:

- Easy to use for patients
  The tool should be designed for use on computers. It should also work on smart phones, but not be optimized for them. Help text would be built into the interface with explanations on how to use each field to assist the patient when reporting. A separate user manual should not be needed.

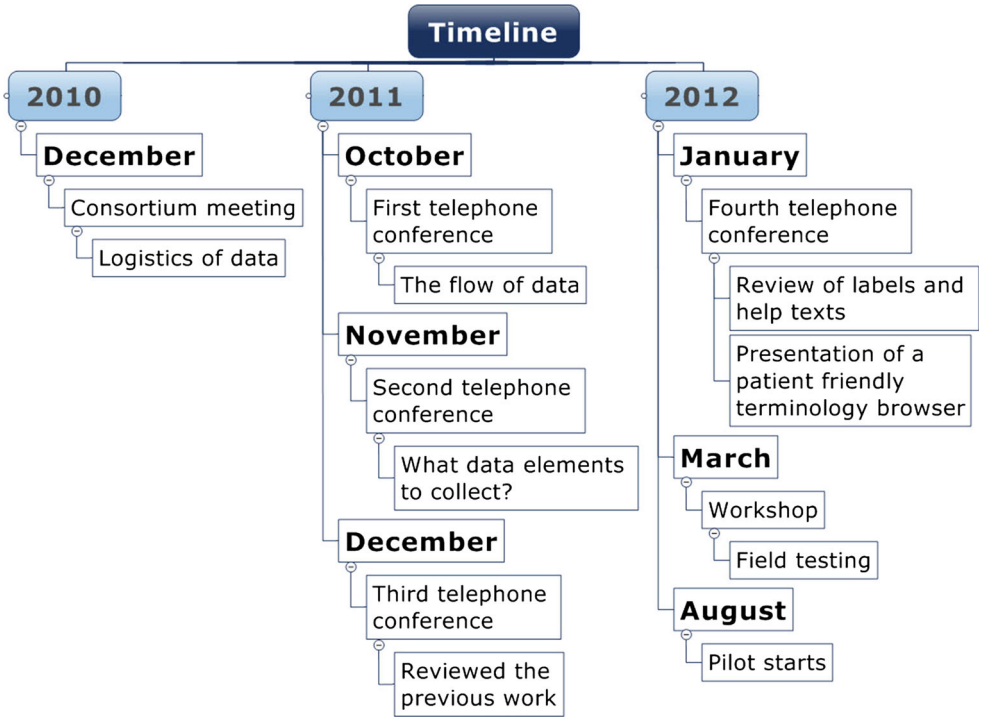

Fig. 1 The timeline of the project

- Identity of patient
  EU legislation requires an identifiable reporter, in this case a patient, in order for a submitted report to be valid. An e-mail address was agreed to be accepted as the unique identifier and would also be used as the means of contact with the patient. If the patient did not want to be identified, an anonymous e-mail address could be created, not including the person's name.
- Login
  Regarding the login process, the partner group decided that there was no need to have a registration process.
- Stopping computer-generated fake reports
  By inclusion of a CAPTCHA [8] in the reporting tool, the risk of receiving fake reports automatically generated by computers would be diminished.
- One page
  The partner group agreed that a one-page system would be preferable, avoiding browsing through several pages with little overview of what will come next.
- Usable around the world
  It was decided to develop the tool with English as the first language. Translations into other languages would need to be easy to implement. The need for the tool to be adjustable to local requirements (e.g., regarding privacy information) was also identified. (The translations are done by exchanging a spreadsheet with the different labels, help text and error messages to translate.) It was decided to use only figures for the CAPTCHA since different languages use different characters in their alphabets.
- International standard
  The tool needed to be ICH-E2B compatible, to harmonize with the international ICSR reporting standards.

2.5 Second Telephone Conference

In the second telephone conference the data elements to be collected by the tool were discussed. Background material based on the E2B information was distributed to the partner group before the meeting. Data elements crucial for causality assessment and regulatory decision-making were contrasted against information that patients have at hand and are likely to be willing to share. It was concluded by the project group that patients are likely to primarily want to tell their own story, not to be forced to pick details from a drop-down menu. Consequently, focusing on narrative became important. However, to prompt the submission of certain critical data elements for case assessment, certain fields needed to be made mandatory. The decision on how many fields were made mandatory was carefully considered, not to make it overwhelming for the reporter to fill in all the information. After the pilot period, two additional fields were made mandatory (see below). It was also agreed to build in a coherency check on dates so as to verify at data entry that the dates are logical; for example, date of birth comes before start of medicine. An overview of all entered information is presented on the screen before the report is submitted to the authority, and a link to the information is sent to the e-mail address of the reporter.

2.5.1 Mandatory Fields

This telephone conference agreed on the following mandatory fields:

- Identity of the reporter (patient), such as e-mail and initials
- Date of birth/age
- Sex
- Case narrative
- Name of suspected medicine
- The reporter qualification (since a healthcare professional may be reporting on behalf of a patient)
- Date when medicine was started.

2.6 Third Telephone Conference

In the third telephone conference the work so far undertaken was reviewed. A 'walk through' of the flow of the data entry was done.

2.7 Fourth Telephone Conference

The data fields that had been decided upon earlier needed descriptions in layman's language. These descriptions were suggested by patient organization representatives, discussed, and then confirmed. A presentation was made of a draft 'patient-friendly' adverse reaction terminology. However, due to time constraints in the project implementation and the initial decision to prioritize a narrative description from the reporter, this terminology work was not pursued further.

2.8 Workshop

At a workshop that was held in the Netherlands in March 2012 [9], the reporting tool was tested by all the workshop delegates. The delegates represented both NPCs and the end-users group. Feedback from the testers was discussed. A presentation was made of the general structure of the system, which fields to collect, how data is transferred and how it can be adapted for use in a national environment.

Participants were requested to enter some test cases in the system using mobile devices, tablet devices, and computers, and they were also asked to record their views on its functionality and user-friendliness. The need for feedback to be given to the reporter was emphasized in the discussion. As a minimum, the reporter should know what will happen once the report is submitted. A concern was raised that some national centres do not have the capacity to contact all reporters individually. In this case it is important to let the reporter know how (s)he can find out more and where to turn with questions. It is critical to meet expectations from patients and consumers.

2.9 Pilot Users

Two pilot countries, Croatia and Turkey, volunteered to field test the system. They integrated the reporting tool in their respective drug regulatory authority website (see Electronic Supplementary Material 2: screen shots from implementation of patient reporting system). The data collected was automatically forwarded to the national database of the NPC. Since both countries were using VigiFlow®, the data submitted by patients was included in the respective national databases with minimal manual data entry needed. The drug names were reported as free text. They were automatically cross-checked with information in the WHO Drug Dictionary (WHO-DD), which is available within VigiFlow®. If there was an exact match no further mapping of the drug name was needed by the NPC staff, otherwise a new WHO-DD entry might need to be requested from UMC. The reactions were also reported as free text in the narrative. NPC staff always needed to identify relevant adverse drug reaction (ADR) terms and code them according to the terminology used by the NPC, which was either MedDRA (Medical Dictionary for Regulatory Activities) or WHO-ART (The WHO Adverse Reaction Terminology). The causality assessment had to be performed by the staff at the NPC, if it was in the standard procedures of the NPC to do so. Automatic consistency checks on dates were made at data entry in the patient reporting tool. All the data was available for the NPC to scrutinize, add, change or delete information, before a copy was made available to VigiBase®. Since the data was copied from VigiFlow®, which is E2B compatible, no errors in the format should have been present at import to VigiBase®.

During the pilot period, both countries experienced a lack of certain critical information (e.g., start date of reaction). As a consequence, two more fields, 'adverse reaction' and 'start date of reaction', were made mandatory. In the pilot project, the visual layout of the tool was adapted for each country, including colours and logos, to make it similar in style to that of the homepage of the hosting agency.

3 Discussion and Conclusions

The first phase of the Monitoring Medicines project was to make an inventory of existing patient reporting systems in 11 countries, all adapted to their local needs, language, information gathered, and legal requirements [5].

Comparisons were made between them. The challenge then was to design a system that would fit many different countries and allow easy adaptation to local needs regarding language and legal information. None of that was present in any of the existing systems. Output from the patient reporting system needed to use the ICH-E2B(R2) standard for easy transfer of the data into the local ICSR data management system.

In the development phase, the discussion to turn the system into a mobile-phone-based app was considered. However, since most patients hopefully do not experience adverse drug reactions very often, a mobile app, which needs to be downloaded and installed, seemed not to be the answer to the requirements of most patients. The working group decided instead to develop an application that may be reached from an internet homepage, either from a computer or indeed from the browser in the mobile telephone or other mobile devices, but not be optimized for the latter.

In compliance with the pharmacovigilance legislation of the European Union, an identifiable reporter is needed for the submitted case report to be considered a valid ICSR. A reporting tool aimed at individual patients consequently requires that the reporting patient be identified, in this case by an e-mail address. Having access to the e-mail address of the reporter opens up direct feedback possibilities.

Feedback to the patient/reporter was discussed both initially and at the workshop, where all parties felt that it was of utmost importance. However, a fear was also expressed that the resources of the NPCs would be insufficient to manage a customization of feedback to all reporters. The project management team decided to postpone the development of a direct feedback functionality to reporters until further experience had been gained from live use of the tool. In the current version, all submitted reports trigger an automated 'thank you' note when the data has reached the NPCs. This function may be expanded in a future version to provide more customized feedback to reporters.

A formal registration procedure for reporters was initially considered because of the perceived fear of submission of false adverse drug reaction reports and the desire to be able to follow-up on the report if considered necessary. The counter argument was that reporting should be easy, with minimum thresholds. It was also considered that if a registration from a public computer was made the personal e-mail programme might not be available from it to confirm the authenticity of the reporter. There would also need to be many steps before the actual reporting could take place. It was argued that patients might not be willing to disclose a personal e-mail address. The group concluded that if this was indeed a concern it is possible to create an anonymous e-mail account, not including one's name. A registration procedure will not stop fake reports being submitted, but the inclusion of CAPTHCA will block computerized reports submitted through the system.

The partner group agreed that having all information on one page would give a good overview of the data entry process for the patient.

The need to develop a patient-friendly adverse reaction terminology was considered. A prototype was constructed and was well received. The partner group decided, however, to focus more on the story that the patient has to tell. Supplementing the tool with a patient-friendly terminology is an idea for a possible future enhancement.

Mechanisms allowing individual feedback on each report were also discussed. The view of the project group, supported by opinions expressed at the workshop, was also to put this on hold until further experiences had been gathered. One reason for the decision was the fear that the NPC would not have enough time to give individual personalized feedback if numerous ICSRs were received.

Although the product was intended to be a reporting tool for patients, some healthcare professionals also found the link on the homepage of the NPCs and used it for their ADR reporting.

The data collected during the pilot phase were assessed, and in the process of making causality assessment of the reports, the lack of start date of the reaction was identified as a frequently missing item. This resulted in the introduction of two more mandatory fields, a reaction (in free text) and a start date of the reaction.

How this reporting tool is contributing to the detection of new signals is too early to say. The two pilot countries have now (January 2015) gathered around 1000 ICSRs via the web-based patient-reporting tool.

Another area of future interest is to automatically link ICSRs that refer to the same incident and patient, so as not to replace any of them but to gain different perspectives on the same event [2]. As the number of ICSRs is increasing and are contributed from multiple sources, reports might be submitted on the same incident more than once, making it attractive to automatically link such duplicates or triplicates, combining more than one perspective on the same event [10].

The joint effort by the stakeholders involved contributed to a successful delivery of the Monitoring Medicines project. The use of remote meetings worked thanks to a strong commitment from all the participants, a clear goal that all believed in, and well prepared meetings from all participants.

The resulting tool is fully compatible with UMC's ICSR data management system VigiFlow®. To benefit the WHO Programme for International Drug Monitoring, UMC has decided to make the tool available as an optional add-on module, free of charge, to the national pharmacovigilance

centres which are users of VigiFlow®. Based on the output from the pilot period, the system was available in English, Turkish, and Croatian, but now additional languages such as Spanish are available, and Arabic is due for release; these have been added because Venezuela and Egypt is about to start using the patient reporting tool. These NPCs are in the process of being configured by IT staff at UMC. New countries, where the above languages are not spoken, will need to translate labels and help texts in the interface. A caveat for the patient also needs to be written by each NPC, based on a draft provided by UMC, including privacy information that is applicable in Sweden, due to the location of the servers. For patients to be able to find the reporting tool, the link to the system needs to be placed in an easy-to-find position on the homepage of each agency.

The UMC product management team benefited from working closely with the potential end users in the development process. UMC collaborated with designated representatives of patient organizations. At all steps in the development process, the representatives were able to consult with their members in order to properly represent their views. Their needs, ideas, and suggestions were invaluable and were taken into account in the design of the final product. They gave concrete and very useful feedback.

The results from this work have now been made available to members of the WHO Programme for International Drug Monitoring using VigiFlow® as their data management system. More than 60 NPCs have VigiFlow® and are therefore potential users of the system. The two pilot countries, Croatia and Turkey, have continued to use the system, and there are an additional three NPCs intending to start using it soon (January 2015). The name of the reporting module is eReporting. eReporting has been promoted at events such as the annual WHO meetings of NPCs in Brazil (2012), Rome (2013) and Tianjin (2014), at a seminar at World Health Assembly (2013), presented at UMC pharmacovigilance courses, and through a presentation at DIA Europe (2013). Information is also available on the UMC website [11].

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