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ORIGINAL RESEARCH



First experiences with a tool to measure the level of clinical information present in adverse drug reaction reports

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ABSTRACT

Background: To make a proper causality assessment of an adverse drug reaction (ADR) report, a certain level of clinical information is necessary. A tool was developed to measure the level of clinical information present in ADR reports. The aim of this study was to test the validity and reliability of the clinical documentation tool (ClinDoc) in an international setting.

Methods: The tool was developed by a panel of pharmacovigilance experts. It includes four domains: ADR, chronology of the ADR, suspected drug and patient characteristics. The final score categorizes reports into: excellent, well, moderately or poorly documented.

In two rounds, eight pharmacovigilance assessors of different countries made a total of 224 assessments using the tool, with the expert panels judgement as a standard. Sensitivity and specificity were calculated.

Results: The tool with four outcome-categories demonstrated low sensitivity. A lack of distinctiveness was demonstrated between the categories moderate and well. Results for the second round were re-analysed using three categories. This demonstrated a better validity.

Conclusion: This is the first tool to give insight in the level of relevant clinical information present in ADR reports. It can be used internationally to compare reports coming from different reporting methods and different types of reporters in pharmacovigilance.

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Pharmacovigilance; adverse drug reaction; ADR; report; clinical information; completeness

1. Introduction

Spontaneous reporting systems primary aim is to timely detect new drug safety signals. These signals include new adverse drug reactions (ADRs) but also new aspects of already known ADRs [1]. In order to assess the causal relationship between exposure to a drug and a reported adverse event in a reliable way, clinical information is needed. Reports in which clinical information is well documented are more likely to contribute to the detection of new drug safety signals since they can provide a more precise statement about the causal relationship. For reports in which clinical documentation is poorly documented, the causality outcome will have a broader range of uncertainty or can be impossible to perform.

However, what clinical information is needed to be able to make a good causality assessment, that is, what information needs to be present to have a well-documented report? To be able to perform a proper causality assessment, all relevant information concerning the ADR, chronology of the ADR, suspected drug(s), and patient characteristics, described in a complete and precisely manner, should be present.


The level of clinical information needed may vary between reports. For some ADRs you might, for example, need extra information to strengthen the diagnosis; for example, laboratory values for a liver disorder reported by a consumer or a

picture for an unspecified reported skin disorder. While for other ADRs, like headache or nausea, which is based on the personal experience of the patient involved, this information may not be necessary. The wide range of different ADRs and the information you need to assess the causality in each of the cases indicates the complexity of how to measure the quality of clinical information reported in ADR reports.

To our knowledge, there are no tools available to describe the level of clinical information reported in ADR reports from a clinical perspective in a standardized way. To give an impression of the quality of information, some previous studies explored the completeness of reported information [2–5]. The *vigiGrade* completeness score was developed to measure the technical completeness of information provided in ADR reports, based on which specific fields are filled [6]. The advantage of this method is that one is able to provide a quick impression of the overall completeness of an ADR report. A restriction however is that it cannot automatically be assumed that the level of completeness reflects the level of clinical information, as required fields may be filled with inadequate, nonspecific, or ambiguous information. Relevant information from a clinical perspective may still be lacking, making it difficult to measure the quality of clinical information and to make a proper causality assessment. On the other hand, even

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with little information, an ADR report can still be properly assessed when it contains all the clinical information that is relevant for that specific situation.

To make sure that the information received in an ADR report contains the right information in order to be useful for signal detection, a dedicated quality assessment, in respect to the available clinical information is necessary. Furthermore, in the context of the Web-Recognizing Adverse Drug Reactions (WEB-RADR) project, there is a need for international uniformity in order to compare reports for clinical quality originating from different methods (way of reporting) or sources (type of reporters). WEB-RADR is a European Union (EU) Innovative Medicines Innovation funded 3-year initiative to recommend policies, frameworks, tools, and methodologies by leveraging new technologies (mobile devices and software applications) to get new insights in drug safety [7].

In the context of case reports assessment, the Netherlands Pharmacovigilance Centre Lareb uses an approach, based on expert judgment, to assess the level of clinical information reported in ADR reports. Recently, this approach has been revised and adapted into a structured clinical documentation tool (ClinDoc) where the completeness and the relevance of information are taken into account. This tool will enable us to compare the quality of information of reports coming from different sources and methods in a more comprehensive way. The aim of this study is to test the validity and reliability of the clinical documentation tool in an international setting.

2. Methods

2.1. Content of the clinical documentation tool

A tool to measure the level of clinical information present in an ADR report, ClinDoc, was developed by a panel of pharmacovigilance experts. The tool provides a structured approach to measure the level of relevant clinical data present. It includes four domains, including several subdomains (Table 1):

- (1) **Adverse drug reaction** assesses the description as well as localization or characteristics of the reported ADR. An example is *taste alteration*, which is a nonspecific description of the ADR. A better description would include characteristics of the alteration, for example, *everything tastes salty*. This domain also includes subdomains that strengthen the diagnosis, for example, photos for skin reactions or laboratory values for liver disorders.
- (2) **Chronology** provides insight in time-related aspects, which is important in the assessment to either strengthen or weaken a causal relation between the drug-ADR association. For example, a patient can experience a *nose bleeding* occasionally or, for example, 30 min after every intake of a drug. Information about the course of the ADR would help to understand how the reaction developed and if a relation with the drug is plausible.
- (3) **Drug** is about drug-related characteristics for specific ADR reports, for example, if the specific brand name is present in case of drug substitution.
- (4) **Patient characteristics** give insight in disease as well as lifestyle-related patient characteristics. These aspects

Table 1. Final clinical documentation tool.

		Relevant? yes, no	Present? yes, no
1	Adverse drug reaction (ADR)		
a	Proper description of the ADR	yes ^a	
b	Specification reaction 'localization' and 'characterization' <i>To strengthen the diagnosis (subdomain c or d or e applicable):</i>		
c	Treatment; or		
d	Visual material (photo, video); or		
e	Lab values, test		
2	Chronology		
a	Latency	Yes ^a	
b	Description of the course of the ADR		
c	Action taken on drug	Yes ^a	
d	Outcome of the ADR	Yes ^a	
3	Suspected drug		
a	Brand name in case of drug substitution?		
b	Different forms or route of administration for suspected drug?		
c	Dose-relationship with ADR?		
d	Batch number of relevance?		
4	Patient characteristics		
a	Risk factors/medical history/comorbidity/indication		
b	Concomitant medication	Yes ^a	
c	Age/gender/length/weight		
d	Patient's life style or other risk factors		

Calculation of score

Domain score: Number of present subdomains/number of relevant subdomains * 100%

Final score: Average relevant domain scores

Cut off values: Poorly ($\leq 45\%$), moderately (from 46–74%), and well ($\geq 75\%$)

are of importance to provide a complete picture of the setting of occurrence of the ADR. For example, when *deep venous thrombosis* is reported, background information about smoking and recent airplane flight are valuable to assess possible confounding factors.

2.2. Procedure to use the clinical documentation tool

The information required for a proper clinical assessment varies depending on the type of ADR. Therefore, the tool is not created as a static model, but as a flexible model which takes this diversity into account. The tool should be used on a case-by-case basis. Filling in ClinDoc is a small time investment when used during a case-by-case assessment since all the thinking about the content of the report is already done. The assessor indicates which subdomains are relevant in order to assess the report. Subsequently, it is determined if this relevant information is present or absent in the ADR report. It is important to assess the report in its entirety, even though it might contain more than one ADR and/or suspected drug. In order to simplify the use of the tool, some subdomains were prefilled since these are mostly relevant (e.g. latency and action taken on drug), but these subdomains are not mandatory, and can be set to *not relevant*; for example, for a single dose of a vaccine, action taken on the drug is not relevant.

A score is calculated for each domain by dividing the number of subdomains with information present by the number of subdomains deemed relevant. The final score is the sum of the domain scores of all domains deemed relevant. The final score is arbitrary categorized into one of four categories: excellent (>75%), well (61–75%), moderately (45–60%), or poorly (<45%). For examples of how to use ClinDoc, see Tables 2 and 3, or Appendix 1 (Supplemental data).

2.3. Testing of the clinical documentation tool

For a first evaluation of the tool, eight pharmacovigilance assessors were asked to evaluate the content of the tool. We included two pharmacovigilance assessors of four pharmacovigilance organizations of different countries; the Agency for Medicinal Products and

Medical Devices of Croatia (HALMED), the Uppsala Monitoring Centre; WHO Collaborating Centre for International Drug Monitoring (UMC), the UK Medicines & Healthcare products Regulatory Agency (MHRA), and the Netherlands Pharmacovigilance Centre Lareb. Based on the received comments of the assessors, the content of the tool was adapted. A user instruction was provided to the assessors to provide guidance of how to use the tool, see Appendix 1 (Supplemental data).

In order to test the tool we used two different groups: (1) the eight pharmacovigilance assessors who were also included for the first evaluation of the tool and (2) the judgments of the panel of experts who developed the tool. Testing took place in two rounds. In each round, a total of 112 assessments were done by the 8 pharmacovigilance assessors who used the tool to assess the level of clinical information. The reports were selected from the Lareb database in such a way that complex as well as more straightforward reports were included. More straightforward reports, for example, included known drug–ADR associations. More complex reports included reports with multiple suspected drugs and/or ADRs and drug–ADR associations that were more complex to assess. The clinical quality of these reports was also rated based on expert panel's judgement, which was used as a reference. The expert panel first judged the level of clinical information for each report individually. In a next step their judgments were compared. In case of disagreement, the judgments were discussed until agreement was reached. Sensitivity and specificity were explored in order to test the validity of the tool. The mean level of agreement between the pharmacovigilance assessors of the same country was calculated using weighted Cohen's Kappa to test the reliability. The following standards for strength of agreement were used: slight (≤ 0.20), fair (0.21–0.40), moderate (0.41–0.60), substantial (0.61–0.80), and almost perfect (0.81–1.0) [8]. After the first round of testing, assessors were asked for their experiences in using the tool. Based on their comments, the tool and its instruction were adapted. It was then tested if these adaptations resulted in a better performance of the tool in the second round.

3. Results

The first round of testing demonstrated a mean sensitivity of 36% (std. dev. 20%, range 21–55%) and mean specificity of 81% (std.

Table 2. How to use Clindoc considering the item 'proper description of the ADR.'

1	Adverse drug reaction (ADR)	Relevant? yes,no	Present? yes,no	Explanation
a	Proper description of the ADR			
	Gastrointestinal discomfort	yes	no	The kind of gastrointestinal discomfort is not clear By this description you understand what complaints the patient experienced.
	Diarrhea, stomach pain, nausea	yes	yes	

Table 3. How to use Clindoc considering the item 'age/gender/height/weight'.

3	Patient	Relevant? yes,no	Present? yes,no	Explanation
c	Age/gender/length/weight			
	Anaphylaxis in a female, age unknown	no		For this ADR, age and gender are not necessary in order to assess the report properly.
	Osteoporosis in a female, 87 years	yes	yes	For this ADR, age and gender are important since these are also known risk factors. This information is present.

dev. 5%, range 77–86%). Weighted Cohen's Kappa (κ) demonstrated a mean weighted κ of 0.37 (std. dev. 0.20, range 0.20–0.60). Due to comments about difficulties the assessors had when using ClinDoc, some subdomains were made mandatory in order to simplify the use of the tool. The second round of testing demonstrated a mean sensitivity of 48% (std. dev. 25%, range 15–75%) and specificity of 82% (std. dev. 75%, range 87%) and weighted κ of 0.23 (std. dev. 0.22, range 0–0.49).

Because there was a lack of distinctiveness between the middle categories 'moderate' and 'well,' results for the second round were analyzed using three categories instead of four categories: well ($\geq 75\%$), moderately (46–74%), or poorly ($\leq 45\%$). This demonstrated a mean sensitivity of 75% (std. dev. 12%, range 66–83%) and specificity of 83% (std. dev. 6%, range 78–89%). It is interesting to see that the mean sensitivity increases as the level of clinical information present decreases: 57% for well, 68% for moderately, and 97% for poorly documented reports. Reliability testing with three categories demonstrated a mean weighted κ of 0.55 (std. dev. 0.15, range 0.35–0.69). Concerning the validity, it is worth mentioning that for 75 out of 112 assessments (67%) the score of the individual assessors corresponded to the judgment of the expert panel. In case of different scores, the tool scored the level of clinical information of reports slightly higher compared to the judgment of the expert panel. Rarely the expert panel and the tool differed two categories; for four reports (4%), the tool scored well while the expert panel scored poorly. For more information of how ClinDoc was used, see *How ClinDoc was used* or Appendix 1 (Supplemental data).

3.1. General comments of assessors using the tool

Several comments were received from the assessors using the tool. The overall opinion of using the tool was good and the user instruction was found to be clear. Assessors mentioned that they found it difficult to use the tool for complex cases, that is, reports for which medical knowledge is necessary. Also for reports with several ADRs or suspected drugs the tool was more difficult to use. More experience with this tool and the prefilled subdomains made it easier to complete the tool.

4. Discussion

The clinical documentation tool, as presented in this study, is a first step for measuring the level of clinical information present in ADR reports. The tool was developed in such a way that the relevance, completeness, and precision of reported information are taken into account [9]. The assessor first determines which information is relevant. This prevents that reports with irrelevant information concerning clinical documentation get overrated using the tool. Then, the completeness and precision of the information are assessed. Lack of both aspects will result in a poorer level of clinical information, making the report less useful for signal detection. During testing of ClinDoc, the final scores were converted into three categories of clinical documentation. In first instance, the tool had four categories; poor, moderate, well, and excellent clinical documentation. Results however showed that there was a lack of distinctiveness between the middle categories moderate and

well. For this reason, it was decided to choose three categories of clinical documentation: poor, moderate, and well.

Using three outcome-categories, testing demonstrated a sensitivity of 97%, 68%, and 57% for the categories poorly, moderately, and well, respectively. These results indicate that the tool is well capable of categorizing reports in which clinical information is poorly reported. Of all reports in which the clinical information is poorly reported according to the expert panel, the tool categorized 97% as 'poorly.' The tool is less sensitive for reports in which clinical information is moderately or well reported. This might be explained by the individual aspects when the tool is being used. Assessors were not able to discuss the content with others. If, for example, thrombosis is reported you might want information about smoking. If the assessor is not aware of this, a report will earlier be categorized as well. The expert panel consists of several experts who can discuss a report extensively.

4.1. International approach

In order to make the tool usable for an international setting, two assessors from pharmacovigilance organizations of four countries were included for testing of the tool. This made it possible to test the usability of the tool in different countries, which use different approaches to signal detection; MHRA (UK) and UMC (Sweden) primarily statistical signal detection, HALMED (Croatia) and Lareb (the Netherlands) primarily case-by-case review signal detection.

4.2. Study limitations

This tool should be used during a case-by-case assessment. For countries already working with case-by-case reviews, adding the tool to their assessment is a small time investment. For countries not working with case-by-case assessment, using the tool on a routine basis may be time consuming. In these cases, it can be decided to use the tool on a specific sample in order to compare sources (type of reporters), for example, a sample of reports by patients versus health-care professionals. Furthermore, it is dependent on the knowledge and experience of the assessor to deem a subdomain relevant or not.

4.3. Practical implementations

Maintaining quality of incoming information about ADRs is an important aspect of pharmacovigilance. Emerging technologies have introduced new methods for reporting, such as online reporting forms, mobile applications, and transmission of information from medical records to spontaneous reporting systems [7,10]. Furthermore, where in the past only health-care professionals were able to report, nowadays, patients reporting is increasingly accepted [10,11].

The clinical documentation tool gives insight in the level of clinical information present in ADR reports. When certain reporting methods or specific groups of reporters show a poor level of clinical information, efforts can be made to enhance the quality, for example, by training the group of reporters or asking follow-up information for a specific report.

In the Netherlands, Pharmacovigilance Centre Lareb is planning on incorporating ClinDoc into the routine assessment of ADR reports. An example of ClinDoc incorporated in the Lareb system is demonstrated in Appendix 2 (Supplemental data).

This study is a first step into using a tool to explore the level of clinical information present in ADR reports. More research is necessary to explore how its performance can be increased. This may include adaptations to specify the tool, but also more training of the assessors using the tool may help increase its performance. This study, for example, clarified that discussion between assessors within one organization is helpful in order to prevent misinterpretations. For future research, it would be interesting to explore if reports with a high level of clinical information actually favor the detection of new drug safety signals.

5. Conclusion

ClinDoc is the first tool to give insight in the level of relevant clinical information present in ADR reports. This tool was found to be mainly sensitive for reports in which clinical information was poorly reported. The tool is not created as a static model, but as a flexible model which takes the diversity of all types of ADRs and drugs into account. It can be used internationally to compare reports coming from different reporting methods and different types of reporters in pharmacovigilance.

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Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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