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Review article

Causality assessment of adverse drug reaction: A narrative review to find the most exhaustive and easy-to-use tool in post-authorization settings

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Abstract
Background: The core motive of pharmacovigilance is the detection and prevention of adverse drug reactions (ADRs), to improve the risk-benefit balance of the drug. However, the causality assessment of ADRs remains a major challenge among clinicians, and none of the available tools of causality assessment used for assessing ADRs have been universally accepted.
Objective: To provide an up-to-date overview of the different causality assessment tools.
Methods: We conducted electronic searches in MEDLINE, EMBASE, and the Cochrane database. The eligibility of each tool was screened by three reviewers. Each eligible tool was then scrutinized for its domains (the reported specific set of questions/areas used for calculating the likelihood of cause-and-effect relation of an ADR) to discover the most comprehensive tool. Finally, we subjectively assessed the tool's ease-of-use in a Canadian, Indian, Hungarian, and Brazilian clinical context.
Results: Twenty-one eligible causality assessment tools were retrieved. Naranjo's tool and De Boer's tool appeared the most comprehensive among all the tools, covering 10 domains each. Regarding "ease-of-use" in a clinical setting, we judged that many tools were hard to implement in a clinical context because of their complexity and/or lengthiness. Naranjo's tool, Jones's tool, Danan and Benichou's tool, and Hsu and Stoll's tool appeared to be the easiest to implement into various clinical contexts.
Conclusion: Among the many tools identified, 1981 Naranjo's scale remains the most comprehensive and easy to use for performing causality assessment of ADRs. Upcoming analysis should compare the performance of each ADR tool in clinical settings.

Keywords: Adverse drug reactions; Adverse events; Causality assessment; Healthcare quality; Pharmacovigilance

Highlights:
- All the causality assessment tool published till date were retrieved.
- In this narrative review, we identified the most comprehensive tools.
- How easy the tools were to use in the clinical context was evaluated by reviewers from four different counties.
- We subjectively identified the most easy-to-use tools in different clinical contexts.
- This narrative review identifies the causality assessment tool for ADR assessment, which is both comprehensive and easy-to-use in a clinical context.

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Introduction

According to the World Health Organization (WHO), Health Canada, and the Brazilian Health Regulatory Agency (ANVISA), an adverse drug reaction (ADR) is a noxious and unintended consequence of administering medicine at a dose normally used for treatment (Government of Canada, 2012; Lima et al., 2019; Vogler et al., 2020; WHO, 2022). According to the European Union (EU), an ADR is a noxious and unintended response to a medicine, which occurs as a consequence of using the medicine as indicated, as well as contrary to its defined purpose – such as unintended overdose, drug abuse, off-label use, or medication error (Sienkiewicz et al., 2021). The Hungarian National Institute of Pharmacy and Nutrition (OGYÉI) has compelled the reporting of suspected ADRs by all healthcare professionals and marketing authorization holders (OGYÉI, 2019). Health Canada insists the mandatory reporting of a serious ADR within 30 calendar days from the date of first documentation (Government of Canada, 2019). In Brazil and India, ADR reporting is on a voluntary basis, and the aim is for it to become mandatory in the near future (Amale et al., 2018; Vogler et al., 2020). In developed countries like Canada, there are an estimated 200,000 severe ADRs annually, resulting in the death of up to 22,000 Canadians, and costing the Canadian healthcare system between $13.7 and $17.7 billion (ADR, 2021). Similarly, in developing countries like India, the extrapolated figure would be 400,000 deaths due to ADRs and 720,000 adverse events per annum (Aggarwal, 2023). However, investigating whether a given drug has caused an ADR remains a major challenge and a very subjective process. This is where causality assessment plays a vital role; it remains a valuable approach in pharmacovigilance to detect a causal link between an ADR and a drug treatment (Théophile et al., 2013).

Various types of tools or assessment methods are available for the causality assessment of ADRs. These are broadly based on three main approaches: (1) expert judgement or global introspection, (2) algorithm-based approaches, and (3) probabilistic or Bayesian approaches (Sassolas et al., 2010). Expert judgement or global introspection is the most-used method for causality assessment of individual ADR (Arimone et al., 2007; Macedo et al., 2005). This is a process where clinical experts execute an individual assessment, employing the expertise based on their knowledge and experience in the field. The global introspection approach has a set of specific questions and each answer has high dependency on individual expertise and judgement (Khan et al., 2016). The algorithm-based method comprises a set of direct queries with defined scores for computing the causal relationship of an ADR. Basically, it comprises the questions in a sequential manner which must be responded to with "Yes/No/Do not know". After this, causality assessment of ADR is decided by computing the score using the total of points. The causal relationship of an ADR is determined from the score (Naranjo et al., 1981). The probabilistic approach is based on Bayesian theorem, which provides results in the form of probability of causation of an adverse event. This is calculated from combining the background information, available knowledge, and the specific findings on a case to determine the probability that a given drug caused the ADR (Behera et al., 2018).

Although these three causality assessment approaches vary in many aspects, they share some common attributes. They all carry a series of questions that elicit pertinent details about a particular case involving a suspected ADR. Different procedures are thereafter adopted to convert answers from these questions to estimate the cause-and-effect relation of an ADR before any decision can be made regarding the suspected drug (Hutchinson and Lane, 1989).

More than 32,000 ADRs are reported annually to Health Canada by the healthcare workers from hospitals and health clinics, but this represents only 5% of the cases experienced by Canadians each year (Hazell and Shakir, 2006; Pearson, 2013). Clinicians suspecting an ADR is enough (Government of Canada, 2019). Clinicians do not need to confirm causality to report an ADR (Government of Canada, 2019), but the major reason behind the underreporting of an ADR might be the non-recognition of ADR due to poor/uneven causality assessment performed in the clinic. Although different approaches and causality assessment tools have been published, no standardized tool permitting the causality assessment of ADRs seems to have been universally accepted.

In this narrative review, our main objective is to fill this gap by providing an up-to-date overview of the different causality assessment tools that have been published so far, and to find a specific causality assessment tool for ADRs that is intuitive, simple, user-friendly, and can be used efficiently by healthcare workers in hospitals and health clinics.

Materials and methods

Study design and search strategy

This is a narrative review of the literature. To identify the different published approaches, tools, and scales for causality assessment of ADRs, electronic literature searches were conducted in MEDLINE (through PubMed), EMBASE, and the Cochrane database from 1976 to 2020. The search procedure employed the following keywords: "causality assessment tool", "adverse event", "adverse drug events", "ADRs", "drug side effect", "causality assessment", "causal", "causal algorithm", and "Bayesian scale". The Medical Subject Heading (MeSH) was also searched using "adverse drug reaction" or "adverse event" and "causality" as terms. A thorough search on Google Scholar was also conducted using the same keywords. While searching the databases, no language restriction was applied. Some relevant publications were also found by manually searching the reference lists of already recovered published articles.

Inclusion and exclusion criteria

All articles included in this review are original research that include tools, scales, and methods for causality assessment of ADRs reported in humans. Articles written in other languages than English, French, and Hindi (the languages understood by the research team members) were excluded (n = 0). We excluded duplicates or highly similar tools, scales, or methods retrieved by the search strategy. The causality assessment tools related to medical procedures like radiography, scanning, or surgery were also excluded. Articles related to studies on adverse events from drug-drug interactions, and accidental or intentional poisoning were also excluded. The eligibility of each causality assessment tool – in relation to an adverse drug reaction in a clinical context – was screened by three reviewers of our research team (R1-JL, R2-ML, R3-PP).

Data extraction and exhaustivity analysis

Each tool deemed eligible was scrutinized by two reviewers for the exhaustivity (R2-ML and R3-PP). Specifically, each tool has a specific set of questions that are used to calculate the causal relationship of an ADR. We investigated each set of questions

to identify each domain covered – as shown in Table 1. The type of causality assessment tool, name of the author, year of publication, title of the article, and all the questions were listed. When a domain was covered by a tool, it was identified and marked with marked with present (P) (Table 1). The percentage of domains covered by each tool was calculated to quantify the most exhaustive and comprehensive tool. Each question was considered to have the same weight for this exercise, as the goal was to assess the exhaustivity of domains and not to be a proper ADR causality assessment.

Table 1. Pertinent tools for causality assessment of adverse drug reaction (see Suppl. 1)

Author and the type of CA	Previous reports	Temporality	Dechallenge	Rechallenge	Alternative cause	Toxicity in fluid	Reaction to placebo	Dose response	Susceptibility	Objective evidence	Concomitant drug	Pre-existing condition	Therapy given on dechallenge	AE: Irreversible	Suspected drug prescribed	Route of administration	Total (%)
Algorithm																	
Karch and Lasagna (1977)		P	P	P	P			P	P	P				P			50%
Kramer et al. (1979)		P	P	P				P				P		P			38%
Naranjo et al. (1981)	P	P	P	P	P	P	P	P	P	P							63%
Jones (1982)		P	P	P													18%
Begaud et al. (1984)		P	P	P						P				P			31%
Danan and Benichou (1993)	P	P	P	P	P						P			P			44%
Hsu and Stoll (1993)	P	P	P	P						P							31%
Koh et al. (2008)	P		P	P	P		P	P				P					44%
Sassolas et al. (2010)	P	P	P	P													25%
Gallagher et al. (2011)	P		P	P	P			P	P	P				P			50%
Zorzela et al. (2018)		P			P		P				P	P	P	P			44%
Comfort et al. (2018)	P	P	P	P	P			P		P							44%
O'Donovan et al. (2019)	P	P	P	P	P			P	P		P	P					56%
Probabilistic approach																	
Mashford (1984)	P	P		P						P	P	P	P				44%
Lane (1986)	P	P	P	P	P	P		P	P			P					56%
Rodrigues et al. (2018)		P	P	P						P	P					P	38%
Expert judgement																	
Arimone et al. (2006)	P	P	P	P	P					P							38%
Tozzi et al. (2013)	P	P			P		P	P	P	P	P	P					56%
De Boer et al. (2013)	P	P	P	P	P	P		P	P	P					P		63%
Oosterhuis et al. (2019)	P	P	P	P					P	P	P	P					44%
WHO-UMC (2013)	P	P	P	P	P					P							38%

Note: CA, Causality assessment.

Assessment of "ease-of-use" in various clinical contexts

As "ease-of-use" of a given clinical tool may greatly facilitate its implementation in clinical practice, we subjectively assessed this feature for all eligible causality assessment tools. Each tool was analyzed by five reviewers. These included four healthcare workers and one reviewer who had three years of experience working in a pharmacovigilance setup – together they had experience in the Canadian (R1-JL and R2-ML), Indian (R3-PP), Hungarian (R4-SA), and Brazilian (R4-FREG) clinical contexts due to their respective origins. The selection of countries was based on convenience. The reviewers subjectively classified each tool according to its "ease-of-use" and marked them as follows; easy to use (well defined and simple set of questions) – 1; complex (difficult set of questions and not well defined) – 2; time consuming (more than one hour to answer all the questions) – 3; and both complex and time consuming – 4. A subjective assessment was chosen as, to our knowledge, no validated objective standards exist to compare the ease-of-use of such tools among different jurisdictions who all have very different health care systems (*e.g.*, universal vs. private health care systems). Each reviewer identified the easiest tools according to the clinical context of his/her country of origin. The mean value of the score assigned by the reviewers for each tool was calculated and rounded up to the nearest whole number.

Both reviewers from Canada agreed upon a score and this was counted as one single score; no weighted analysis was used to prevent over representativeness of Canada into the final score.

Results

Our search yielded a total of 87 references, out of which 29 ADR causality assessment tools were considered potentially relevant (Fig. 1). After removing the duplicates, only 21 eligible tools met our selection criteria (Fig. 1). The 21 tools fell into three main categories: (i) expert judgement or global introspection (n = 5), (ii) algorithm or standardized assessment method (n = 13), and (iii) probabilistic or Bayesian approaches (n = 3) (Table 1). While some tools (n = 3) were developed for a specific disease (*e.g.*, drug-induced liver injury), others were validated for non-specific therapeutic areas (n = 18) (Fig. 1).

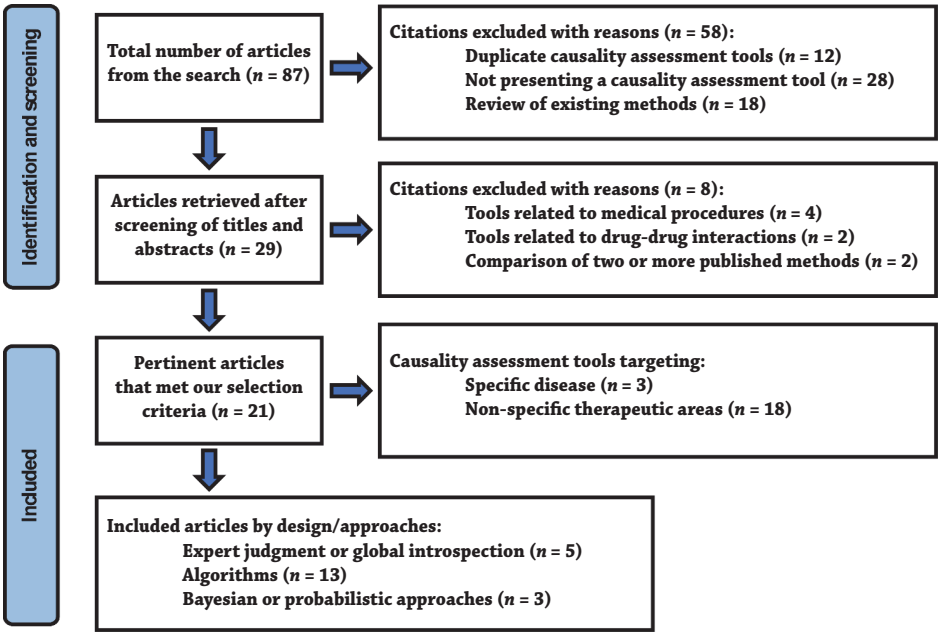

Fig. 1. Flow chart of the search strategy and pertinence study for included and excluded tools

Exhaustivity of domains

The domains covered by each tool varied moderately, as shown in Table 1. The tool covering the fewest domains was Jone's tool (number of domains = 3; representing only 18% of all possible domains considering all tools) (Jones, 1982). The tool from De Boer et al. (2013) and the tool from Naranjo et al. (1981) appeared to be the most exhaustive and comprehensive of all the other tools, (representing 63% of all possible domains). De Boer covers the following domains: [1] previous reports of the adverse event; [2] temporality of the adverse event; [3] dechallenge of the drug; [4] rechallenge of the drug; [5] co-factors other than the drug; [6] toxicity of the drug in fluid; [7] dose-response while increasing or decreasing; [8] susceptibility; [9] objective evidence; [10] suspected drug prescribed. On the other hand, the Naranjo tool covers the following 10 domains: [1] previous reports of the adverse event; [2] temporality of the adverse event; [3] dechallenge of the drug; [4] rechallenge of the drug; [5] co-factors other than the drug; [6] reproducibility of the ADR on placebo; [7] measurement of the toxicity of the drug in blood/fluid; [8] dose-response while increasing or decreasing; [9] susceptibility of the patient; and [10] objectivity of the ADR.

"Ease-of-use" in a clinical context

Ease-of-use in a clinical setting varies according to the individual subjective assessment of the reviewer and the country of origin (Canada, India, Hungary, and Brazil). As seen in Table 2, we uniformly judged that most of the tools were barely implementable in a clinical context because of their complexity and/or lengthiness. Specifically, 17 tools had a mean score >1 (16 with a score of 2 [*i.e.*, complex], and 1 with a score of 4 [complex and time consuming]). We were left with very few tools that could realistically be implemented in clinical practice because they were considered easy to use (score of 1). These were published by Naranjo et al. (1981), Jones (1982), Danan and Benichou (1993), and Hsu and Stoll (1993).

Table 2. Eligible tools for causality assessment of ADRs: "Ease-of-use" in clinical settings (see Suppl. 2)

"Ease-of-use" in clinical context						
Author	Year	R1 and R2* (Canada)	R3** (India)	R4*** (Hungary)	R5**** (Brazil)	Mean value
Karch and Lasagna (1977)	1977	2#	2	2	2	2
Kramer et al. (1979)	1979	3	3	4	4	4
Naranjo et al. (1981)	1981	1	1	1	1	1
Jones (1982)	1982	1	1	1	1	1
Begaud et al. (1984)	1984	1	2	2	2	2
Mashford (1984)	1984	2	2	1	1	2
Lane (1986)	1986	2	2	2	2	2
Danan and Benichou (1993)	1993	1	1	1	1	1
Hsu and Stoll (1993)	1993	1	1	1	1	1
Arimone et al. (2006)	2006	2	2	2	2	2
Koh et al. (2008)	2008	2	2	2	2	2
Sassolas et al. (2010)	2010	1	1	2	2	2
Gallagher et al. (2011)	2011	2	2	2	2	2
Tozzi et al. (2013)	2013	2	2	1	2	2
De Boer et al. (2013)	2013	1	1	2	2	2
Zorzela et al. (2018)	2017	2	2	2	2	2
Comfort et al. (2018)	2018	2	2	2	2	2
Oosterhuis et al. (2019)	2018	2	2	2	2	2
Rodrigues et al. (2018)	2018	2	1	2	2	2
O'Donovan et al. (2019)	2019	2	2	1	3	2
WHO-UMC (2013)	2013	2	2	2	1	2

Note: * R1 and R2: Reviewer 1 and 2 reviewed according to Canadian clinical context. Both Canadian reviewers agreed on 1 single score per tool.
** R3: Reviewer 3 reviewed according to Indian clinical context.
*** R4: Reviewer 4 reviewed according to Hungarian clinical context.
**** R5: Reviewer 5 reviewed according to Brazilian clinical context.
Scoring system: 1 – Easy to use, 2 – Complex, 3 – Time consuming, 4 – Complex and time consuming; Mean score rounded up to the nearest whole number.

Discussion

Major findings

In this narrative literature review, we identified the two most exhaustive/comprehensive ADR causality assessment tools: De Boer et al. (2013) and Naranjo et al. (1981). We also identified four tools that are easy to use in various clinical contexts: Naranjo et al. (1981), Jones (1982), Danan and Benichou (1993), and Hsu and Stoll (1993). In light of these results, one tool stands out as the most exhaustive and easy to use in various clinical contexts: The Naranjo et al. tool (1981).

Covering a total of 10 domains (highest proportion of domains covered in our study) and being considered as "easy to use" in various clinical contexts worldwide (score of 1 in our study), the Naranjo et al. tool (1981) would be an appropriate tool to uniformly implement in clinics (Naranjo et al., 1981). Uniformly implementing the Naranjo tool would have the potential to increase awareness on standardized ADR causality assessment in order to improve ADR reporting to health authorities and, in turn, drug safety worldwide.

Our findings in the current clinical and scientific context

Numerous causality assessment tools for ADRs have been published, but only 5% of ADRs are reported to health authorities worldwide (*i.e.* Health Canada, Food and Drugs Administration, European Medicine Agency, etc.) each year (Hazell and Shakir, 2006; Pearson, 2013). This might be partially explained by the fact that healthcare workers do not know that they can report i.e., lack of awareness, are unsure whether the drug caused the adverse reaction, or they do not know how to assess causality (Adisa and Omitogun, 2019; Herdeiro et al., 2005; Li et al., 2022; Mirbaha et al., 2015; Varallo et al., 2014). Furthermore, although each of them has strengths, most of the ADR causality assessment tools also have limitations. For example, some tools only target a specific disease and cannot be used to assess all the causality of an ADR (Danan and Benichou, 1993; Oosterhuis et al., 2019; Sassolas et al., 2010) (Table 1). The *probabilistic methods* are more sensitive as they have a positive predictive value of 80–84% (Rodrigues et al., 2018; Théophile et al., 2013). In addition, they provide an outcome as constant probabilities, and therefore appear to be more trustworthy for

assessment of ADRs in regular practice or automated evaluation for unknown ADRs (Doherty, 2009; Du et al., 2013). The major drawbacks of the probabilistic method are poor specificity (42%) (Théophile et al., 2013) and their practical complexity: they require specifically calculated information data, such as specific ADR incidence, to reproduce the likelihood distribution (Doherty, 2009; Du et al., 2013). Therefore, it might be concluded that probabilistic methods are unsuitable for use in daily clinical practice.

Other tools using *expert judgements* may also come with major limitations in the identification and rating of potential ADRs (Arimone et al., 2005). Despite their effectiveness, clinical judgement is subject to inter- and intra-rater contradictions, discernible prejudice, ambiguity, and weak reproducibility (Karch and Lasagna, 1977; Kramer et al., 1979). Using algorithm methods for ADR might prevent such limitations.

Among algorithm methods, Naranjo's tool (1981) provides attractive simplicity while still being exhaustive (Table 1); it could therefore find more application for the assessment of ADRs. Such an algorithm method could potentially reduce inter- and intra-rater dissimilarity, but this needs to be further studied. Likewise, the prevalence of use, and the impact of its use on overall drug safety and population health remains to be investigated. None of the algorithm methods for causality assessment of ADR are universally accepted as a trustworthy tool at this moment, as it has been reported that using different algorithms for the same ADR, yielded significant variations in the results (Arimone et al., 2007).

Finally, some causality assessment tools are too complex to be completed in a particular timeframe, while others present subjective to discrete domains. So, the ease-of-use of a given causality assessment tool is a crucially important process for healthcare workers as they play a salient role in the process of pharmacovigilance in a limited timeframe (Khan et al., 2016).

Is Naranjo's (1981) ADR probability scale the perfect tool?

Our study suggests that the Naranjo tool meets most of the criteria to conquer the above-mentioned limitations. Covering a total of ten criteria and being judged as easy to implement in post-authorization clinical settings, this tool shows a potential to improve and standardize causality assessment of ADRs. Among the many algorithm methods identified, Naranjo's was found to be simple, brief, and conceptually implementable into various post-authorization clinical contexts (Canada, India, Hungary, Brazil). Although it is not the only one, the Naranjo tool improvises the logical feature of causality assessment, and it is frequently employed by various pharmacovigilance centers to spot individual case reports in several nations (Doherty, 2009; Khan et al., 2016).

In contrast to expert judgement and the Bayesian approaches, an algorithms approach such as the Naranjo tool, has good specificity (83–92%) but poor sensitivity (32%) (Naranjo et al., 1981; Théophile et al., 2013). Naranjo et al. (1981) acknowledged that this tool has high reproducibility in ADR assessments but only experience would confirm its utility in clinical practice (Naranjo et al., 1981). Different reports have established the reliability of Naranjo's tool in ADR assessments in adults but not in children (Khan et al., 2016; Weiss et al., 2002). The Naranjo tool was also reported to perform poorly for the causality assessment of hepatic ADRs (n = 32,414, frequency of ADR = 10) (Carrascosa et al., 2009; Lavonas et al., 2010). While addressing different methods of causality assessment, another study suggests that Naranjo's tool does not address the important points that are necessary in causality assessment for potential drug interactions (Agbabiaka et al., 2008). Another important question missing in the Naranjo tool is the "concomitant drug". This question might be included in question 5 if we consider that alternative causes might be concomitant drugs other than the suspected drug. While many might include this evaluation criteria in the Naranjo tool, it is not mentioned explicitly. However, any addition to the Naranjo tool would need to be tested in different diseases and patients of different age groups for its reliability.

Strengths and limitations

To our knowledge, this is the first narrative review illustrating an up-to-date overview of the different ADRs causality assessment tools that have been published. Generalizability of the "ease-of-use" assessment is enhanced due to inclusion of the perspective of clinicians from various healthcare systems worldwide (Canada, India, Hungary, and Brazil). The clinical context of Canada (Martin et al., 2018), Brazil (Machado and Silva, 2019), and Hungary (Gaal et al., 2011) is similar, as these three countries provides universal healthcare. India doesn't provide universal healthcare (Singh, 2013) and hence varies in clinical context when compared to Canada, Brazil, and Hungary. However, we acknowledge that the main limitation of our study is the unavoidable subjective assessment in judgement of the five reviewers, as well as the lack of enough statistical analysis for assessing the ratings from different experts. A residual selection and information bias may also remain as this was not a systematic review of the literature. Nevertheless, we adopted some of the recommendations from the Cochrane Handbook for Systematic Review of Interventions to minimize the bias (Higgins et al., 2019) (*e.g.*, having at least 2 reviewers at article selection and data extraction to assess exhaustivity of the domains). In the current study, a publication bias cannot be excluded but was not measured.

Conclusion

Among the many tools identified, the 1981 Naranjo ADR probability scale remains the most comprehensive and easy to use for performing causality assessment of ADRs. Systematically inserting this tool into medical health records could raise awareness of causality assessment of ADRs. Nevertheless, upcoming analysis should compare the performance of each ADR tool in clinical settings.

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Conflict of interests

The authors have no conflict of interests to declare.

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Ethics approval

As this is a literature review, no ethical review board certificate was needed.

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