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Development and validation of an online form for active search for adverse drug reactions

Desenvolvimento e validação de formulário *on-line* para busca ativa de reações adversas a medicamentos

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ABSTRACT

Introduction: Pharmacovigilance is a science related to the early detection and prevention of events associated with the use of drugs, such as adverse drug reactions (ADR). Active surveillance methods are increasingly being used to detect ADRs. Although the use of triggers is recommended, active search tools for suspected ADR are rare in the literature. **Objective:** To develop an active search tool for suspected ADR using triggers. **Method:** This methodological development study was conducted and divided into two stages: i) a literature review to build a list of triggers and the first version of the instrument; ii) content validation using the Delphi technique with the participation of professionals involved in Pharmacovigilance and Patient Safety at the institution. Instrument sessions were considered valid when the Content Validity Index (CVI) ≥ 0.80. **Results:** An online form was developed on the Google Forms platform containing three sections: review of medical records, patient and hospitalization data, and identification of suspected ADR. The final version has 28 questions, including 16 objective and 12 subjective. The material was evaluated by seven experts in two Delphi rounds, and the total CVI was 1. **Conclusions:** The instrument shows evidence of validity in terms of objective, structure, relevance, appearance, and content, representing another pharmacovigilance tool for the hospital. It can be used by healthcare professionals from different backgrounds and is easily adaptable to the reality of other institutions. Future work should be carried out to validate the tool with the target audience.

KEYWORDS: Pharmacovigilance; Drug-Related Side Effects and Adverse Reactions; Patient Safety; Validation Study

RESUMO

Introdução: A farmacovigilância é uma ciência relacionada à detecção precoce e prevenção de eventos associados ao uso de medicamentos, como a reação adversa a medicamentos (RAM). Os métodos de vigilância ativa têm sido cada vez mais utilizados para detecção de RAM. Apesar do uso de rastreadores ser recomendado, instrumentos de busca ativa de suspeita de RAM são escassos na literatura. **Objetivo:** Desenvolver um instrumento de busca ativa de suspeita de RAM com a utilização de rastreadores. **Método:** Foi realizado um estudo de desenvolvimento metodológico, dividido em duas etapas: i) revisão da literatura para a construção da lista de rastreadores e da primeira versão do instrumento; ii) validação de conteúdo por meio da técnica *Delphi* com a participação de profissionais envolvidos com Farmacovigilância e Segurança do Paciente na instituição. As seções do instrumento foram consideradas válidas quando apresentaram um Índice de Validade de Conteúdo (IVC) ≥ 0,80. **Resultados:** Foi desenvolvido um formulário *on-line* na plataforma *Google Forms* contendo três seções: revisão do prontuário, dados do paciente e da internação e identificação da suspeita de RAM. A versão final possui 28 questões, sendo 16 objetivas e 12 subjetivas. O material foi avaliado por sete especialistas em duas rodadas *Delphi* e o IVC total atingiu 1. **Conclusões:** O instrumento apresenta evidências de validade quanto ao objetivo, à estrutura, à relevância, à aparência e ao conteúdo,

representando mais uma ferramenta de farmacovigilância para o hospital. Pode ser utilizado por profissionais de diferentes formações na área da saúde e é facilmente adaptável à realidade de outras instituições. Trabalhos futuros devem ser desenvolvidos para a validação da ferramenta pelo público-alvo.

PALAVRAS-CHAVE: Farmacovigilância; Reações Adversas e Efeitos Colaterais Relacionados a Medicamentos; Segurança do Paciente; Estudo de Validação

INTRODUCTION

Pharmacovigilance plays a crucial role in the early detection and prevention of adverse drug events (ADEs), including adverse drug reactions (ADRs), thus safeguarding patient safety[1,2]. ADRs, defined as harmful and unintentional events caused by drugs at therapeutic doses[3], represent a global health concern due to their significant impacts on clinical outcomes and patients' quality of life.

The occurrence of adverse events, including those related to drugs, is known to increase treatment costs and hospitalization time, and can even lead to death[4].

According to the Global Patient Safety Action Plan 2021-2030[2], in developed countries, one in ten patients is the victim of an adverse event while receiving hospital care. In developing countries, the proportion rises to one in four patients, with an estimated 134 million adverse events per year.

It is estimated that approximately 5% of all hospital admissions in Europe are due to ADRs, accounting for around 197,000 deaths annually across the continent[5]. In Brazil, data on morbidity and mortality related to adverse reactions is limited. However, Santos and Boing[6] reported, from 2000 to 2014, that 0.1% of deaths and 0.4% of hospital admissions in Brazil were attributed to poisoning and ADRs.

Traditionally, spontaneous reporting has been the main method of data collection in pharmacovigilance, but it has limitations related to high rates of underreporting[7]. In this sense, active surveillance approaches, such as the Global Trigger Tool (GTT), have stood out. Studies suggest that the GTT can identify up to ten times more ADRs than spontaneous reporting, providing a more comprehensive and accurate view of the risks associated with medicines[8,9].

Despite the advances in active pharmacovigilance, the lack of specific tools for collecting and analyzing data on suspected ADRs is still a gap in clinical practice. After reviewing the literature, it was found that some Brazilian studies used this methodology for the active search for ADRs[10,11,12,13]. However, only Pereira et al.[14] and Lopes e Silva[15] developed instruments for collecting and analyzing data on ADEs. No online form was found specifically aimed at collecting and analyzing data on suspected ADRs using triggers.

Considering this context and the lack of an active pharmacovigilance tool at the institution, this study aimed to develop a data collection and analysis tool based on the active search for suspected ADRs to contribute to patient safety. By filling this gap in the literature, it is hoped that this tool will not only facilitate the early detection of ADRs, but also guide future interventions and risk management strategies, thus promoting safer and more effective patient care.

METHODOLOGY

A methodological development study was carried out in a medium-sized university hospital located in the city of Vitória, Espírito Santo. This study was conducted from January 2022 to February 2023 and divided into two stages: 1) Development of the instrument and 2) Validation of the instrument using the Delphi technique.

1st stage: developing the instrument

Literature review: definition of screeners and drafting of the first version

The purpose of the literature review was to verify the existence of similar instruments and to construct the list of screeners. Scientific articles were searched in the Latin American and Caribbean Center on Health Sciences Information (LILACS), Medical Literature Analysis and Retrieval System Online (MEDLINE), Scientific Electronic Library Online (SciELO), and Google Scholar databases using the following descriptors: "Global trigger tool", "Pharmacovigilance", "Triggers", "Adverse reaction", "Patient safety". National and international publications were selected that worked with the search for adverse events using triggers between 2009 and 2021. The second edition of the Global Trigger Tool for Measuring Adverse Events report produced by the Institute for Healthcare Improvement (IHI) in 2009 was adopted as the guideline.

After the search and selection, the articles were submitted to reflective reading to extract the most recurrent triggers. The research team chose to use the triggers from the Drug Module of the IHI guideline document, which includes some drugs and laboratory tests. In addition to these, others were included according to their occurrence in the articles analyzed. The list was adapted to the local reality, considering the drugs standardized at the hospital and the reference values adopted by the institution's laboratory. It was then submitted for evaluation by the pharmacists of the Clinical Pharmacy and Pharmaceutical Dispensing Unit.

The instrument was drawn up based on the questions and guidelines contained in the documents mentioned below:

- Global Trigger Tool for Measuring Adverse Events (IHI[16]);
- Development of a tool for evaluating reports of suspected adverse drug events (Pereira et al.[14]);
- Pediatric Screening Manual - measuring adverse drug events in a pediatric hospital (Lopes; Silva[15]);
- New form for reporting adverse events related to medicines and vaccines (Anvisa[17]).

It should be noted that although the new Brazilian National Health Surveillance Agency (Anvisa) form is a passive surveillance tool, it was only used in this study to guide the 3rd section, which deals with the identification of adverse reactions.

The researcher evaluated and compiled the relevant questions according to the recommendations in the literature. The online instrument was developed in the Google Forms survey management application and was designed to be used by the institution's healthcare professionals with the aim of actively seeking out ADRs from the review of medical records.

The first version of the instrument was drawn up and then submitted to an expert evaluation using the Delphi technique.

2nd stage: validation of the instrument using the Delphi technique

To validate the content of the instrument, the Delphi technique was used. Its aim is to establish a consensus on a given subject by consulting the opinion of experts on the development of instruments, and it is applied in rounds of questionnaires[18]. At each round, feedback from the participants enables the best development of the instrument being assessed. The number of rounds is defined by building a final consensus based on overcoming disagreements.[19] In this study, the content validity index (CVI) was considered adequate when ≥ 0.80[19,20].

Composition of the panel of experts

The professionals who evaluated the instrument were appointed by the hospital's Quality Management Unit and the invitation was sent by an e-mail. In order to form a heterogeneous panel, ten professionals from different backgrounds involved in pharmacovigilance and patient safety at the institution were invited for convenience.

Development of the evaluation form

To evaluate the instrument, a form was created consisting of ten questions (three related to the appearance and seven to the content of the instrument) and four to characterize the professionals, for a total of 14 questions. Each item was designed with five response options according to the Likert scale (completely disagree, partially disagree, neither agree nor disagree, partially agree, and completely agree). In addition, a blank space was provided so that the professionals could make comments, suggestions and/or criticisms.

The instrument was evaluated based on the following requirements: presentation, semantic clarity, ease of understanding, type and number of screeners, presence of sufficient information to measure what was proposed and appropriateness of the name. The following formulas were used to calculate the CVI: item CVI = number of positive responses/total number of responses and total CVI = number of positive responses/number of judges x number of items[18].

Delphi - first round

To ascertain the experts' opinions on the tool and to reach a consensus, a document was sent by e-mail containing a presentation of the research objectives and access links to Google Forms, in which the active search tool and the evaluation form were implemented.

The panel of experts was instructed to evaluate the instrument independently and anonymously within 15 days. At the end of the first round of Delphi, the responses were analyzed to determine the level of consensus. Total and partial agreement were considered positive responses.

Items that did not reach a CVI greater than or equal to 0.80 were modified or excluded according to the suggestions made by the participants. Moreover, all the items that reached the recommended CVI, but contained some suggestions, were also analyzed and reformulated when necessary. After modifying the items, the second version of the instrument was sent to the professionals for a new Delphi round.

Delphi - second round

A new e-mail was sent to the participants with a document containing all the results obtained in the first round, including all the suggestions made by them and explaining all the changes that were made, where relevant. For the items in which the feedback was rejected, the reasons for not making the changes proposed by the professionals were explained.

At the end of the second round, the panel's responses were analyzed again to determine the level of consensus, and the final version of the instrument was generated.

Ethical aspects

This study was approved by the Ethics and Research Committee of the Cassiano Antônio de Moraes University Hospital (Hucam) of the Federal University of Espírito Santo (UFES) under opinion No. 5.178.824 (CAAE: 54388121.2.0000.5071).

RESULTS

Literature review and definition of triggers

Based on the literature review (Appendix 1), the administration of some medicines and the results of some laboratory tests were selected as triggers, according to the guidelines in the document Global Trigger Tool for Measuring Adverse Events (IHI, 2009).

The first version of the list contained 20 triggers. After the first Delphi round, modifications were made in line with the professionals' suggestions (Chart 1).

Two triggers were removed due to the low incidence of reports in the literature. The detection values of some screeners were modified - creatinine, urea, hemoglobin, and leukocytes - as recommended by some articles and as suggested by "S1" and "S5".

Regarding these suggestions, although they are considered broad and unsuitable for intensive care unit (ICU) patients, they are already well-established in the literature and used in any hospital sector, and adaptations can be made according to the reality of each sector/institution.

The final version of the list has 18 triggers, 11 of which are laboratory-based and seven drug-related (Chart 2).

Chart 1. Reviewers' suggestions on triggers.

	Suggestion	Reviewer	Acceptability
S1	"Some triggers are too broad, because in hospitalized patients, changes in laboratory tests are routine due to the disease and treatment itself. I suggest keeping only those related to drug administration and the others related to changes in blood glucose, kidney function and coagulogram."	RW2	Partially accepted
S2	"It would be feasible to include more of these triggers: application of the Glasgow scale, measurement of blood pressure, measurement of peripheral saturation."	RW4	Not accepted
S3	"I didn't observe a trigger that could infer cognitive problems (Glasgow/Delirium Scale) as well as gastrointestinal problems (vomiting and diarrhea), musculoskeletal problems (myalgia, pain), and cardiovascular problems (heart rate and BP)."	RW7	Not accepted
S4	"In my opinion, the tool assesses adverse reactions in the hematological, renal and partially hepatic systems by evaluating TGO/TGP/TAP and TTPa, but it doesn't look at bilirubin."	RW7	Not accepted
S5	"Regarding blood glucose, hemoglobin, leukocytes, INR > 6, platelets, and creatinine values in the ICU environment (What were the references?)".	RW7	Partially accepted

Source: Prepared by the authors, 2024.
S: Suggestion; RW: Reviewer; BP: Blood Pressure; GOT: Glutamic-Oxalacetic Transaminase; GPT: Glutamic-Pyruvic Transaminase; PTT: Prothrombin Activity Time; APTT: Activated Partial Thromboplastin Time; INR: International Normalized Ratio; ICU: Intensive Care Unit.

Chart 2. Final version of the trigger list.

Trigger	Meaning
Activated partial thromboplastin time (aPTT) greater than 100 seconds	Excessive blood anticoagulation related to heparin use
International Normalized Ratio (INR) greater than six	Excessive blood anticoagulation related to warfarin use
Serum glucose lower than 50 mg/dL	Hypoglycemia associated with the use of insulin or oral hypoglycemic agents
Serum creatinine greater than twice the reference value (RV: 1.30 mg/dL men and 1.10 mg/dL women)	Renal failure associated with the use of medication
Serum urea greater than twice the reference value (RV: 50 mg/dL)	Renal failure associated with the use of medication
Glutamic-Oxalacetic Transaminase (GOT) greater than 38 U/L in men and greater than 32 U/L in women	Drug-induced liver injury
Glutamic-Pyruvic Transaminase (GPT) greater than 41 U/L in men and greater than 31 U/L in women	
Abrupt drop in hemoglobin of more than 25% (RV: 12.8 g/dL)	Bleeding/anemia associated with drug use
Leukocytes under 3,000/mm^3	Medication-induced hematological or bone marrow changes
Platelets less than 50,000/mm^3	Hematological or bone marrow changes induced by medication
Eosinophils greater than 770/mm^3	Hypersensitivity reactions
Administration of vitamin K (phytomenadione)	Used to reverse the action of oral anticoagulants
Administration of protamine	Used to neutralize the anticoagulant action of heparin in cases of severe bleeding following heparin therapy.
Administration of antihistamines (diphenhydramine, hydroxyzine, hydrocortisone, loratadine, methylprednisolone, promethazine)	Used in cases of allergic reactions to medicines
Administration of flumazenil	Used in cases of excessive sedation related to the use of benzodiazepines
Administration of naloxone	Used in cases of excessive sedation related to the use of opiates
Administration of loperamide	Used in cases of diarrhea associated with the use of medication
Drug discontinuation or suspension	Adverse reaction requiring discontinuation of treatment

Source: Prepared by the authors, 2024.

Drafting the first version

After reading and analyzing the guiding document and the articles, the instrument initially called "Alert instrument for reporting suspected adverse drug reactions" was proposed, containing 33 items divided into three sections, in this order: patient data (questions 1 to 13), review of the medical record (questions 14 to 17), and identification of the ADR (questions 18 to 33). The instrument was then submitted for evaluation by professionals in terms of content and appearance.

Delphi - first and second rounds

Ten professionals trained in medicine, nursing, and pharmacy were invited to make up the panel of experts and, of these, seven answered the evaluation questionnaire in both rounds (70% return rate). The characteristics of these professionals are described in Table 1.

The experts had more than ten years of professional training and were engaged in Pharmacovigilance and Patient Safety issues at the institution. The process of evaluating the instrument took place without the need for face-to-face meetings and was facilitated by online forms.

The questions on the instrument's evaluation form and the CVI are shown in Table 2.

Table 1. Characterization of the professionals who took part in both rounds of the Delphi.

Features	Percentage (%)
Gender	
Female	71.40 (n = 5)
Male	28.60 (n = 2)
Training	
Nursing	42.85 (n = 3)
Pharmacy	42.85 (n = 3)
Medicine	14.30 (n = 1)
Higher degree	
Doctorate	14.30 (n = 1)
Specialization	42.85 (n = 3)
Master's Degree	42.85 (n = 3)
Length of professional training	
Up to 10 years	0
11 to 15 years	42.85 (n = 3)
16 to 20 years	57.15 (n = 4)
Length of time at the institution	
Up to 10 years	71.40 (n = 5)
11 to 15 years	14.30 (n = 1)
16 to 20 years	14.30 (n = 1)

Source: Prepared by the authors, 2024.

The main suggestions made by the professionals are shown in Table 3 and involved rewording items/clarifying abbreviations, inserting terms or information, and deleting questions. Initially, the experts proposed changing the names of the sections and reversing the order. They suggested that the "Review of medical records" section should come first, followed by the "Patient and hospitalization data" and "Identification of suspected adverse drug reaction" sections.

According to the suggestions, some questions were excluded, and others reformulated, reducing the number of questions in the instrument from 33 to 28, in line with suggestion "S3".

Suggestions related to problems with abbreviations were accepted and the definitions of ADR and ADE were added to the instrument, to avoid confusion of the terms and make it easier to fill in (suggestions "S2" and S4"). The questions related to dilution and infusion time were reformulated into just two questions, according to suggestions "S5", "S7" and S12". Items 32 and 33 were duplicated and the last item was excluded (suggestions "S9" and "S10").

The wording of the question on drug allergies was changed in line with comments "S8" and "S11", which suggested asking about a previous adverse reaction to medication. In addition, the answer option "Not described in medical records" was included.

Through the suggestion "S6", it was recommended that the patient's ongoing medication be included. The original question asked about the medicines used during hospitalization. However, it is very laborious to fill in and requires a lot of investigator time due to the large number of medicines used during hospitalization by the vast majority of patients and due to the length of hospitalization. For this reason, the question was reformulated to include only medicines used at home.

Most of the items reached the target of 80% agreement among the professionals, however, the considerations made were pertinent and so these items were reformulated. After the second round of the Delphi, all the items in the instrument were re-evaluated and reached CVI 1, indicating total agreement among the experts as to their relevance and suitability, giving rise to the final version of the instrument.

DISCUSSION

The developed instrument has distinctive features, notable for the use of a concise list of triggers and for containing as few questions as possible, but enough to identify suspected ADRs. The design of a short form aimed to optimize data collection and reduce the time needed to complete it, without compromising the quality of the information obtained. In addition, the online nature of the form, together with the ability to generate data in visual formats such as graphs and spreadsheets, facilitates the analysis and interpretation of the results, making the process more dynamic and accessible.

The final version, called "Form for the active search for adverse drug reactions", is made up of 28 questions, 16 of which are

Table 2. Items on the evaluation form and total CVI per item.

Item on the evaluation form	IVC item Round 1	IVC item Round 2
The sequence of the items in the tool is appropriate (current sequence: patient data, review of the medical record, and identification of the adverse drug reaction).	0.875	1
The order of the topics in the tool is appropriate.	1	1
The instrument is written clearly and objectively, with accessible and appropriate language.	1	1
The instrument provides sufficient information to characterize the patient and to understand the context in which they are inserted in the event of an ADR.	0.875	1
The tool as a whole is viable.	1	1
The instrument has no words with double meanings or double interpretations.	0.625	1
The instrument has an adequate number of triggers.	0.875	1
The instrument contains the appropriate types of triggers.	0.875	1
The tool contains relevant information to help identify the ADR.	1	1
The name of the instrument is appropriate and represents what you want to measure.	1	1
Total CVI	**0.9125**	**1**

Source: Prepared by the authors, 2024.
CVI: Content validity index; ADR: Adverse drug reaction.

Table 3. Experts' suggestions on the tool.

	Suggestion	Reviewer	Acceptability
S1	"Change the term pregnant patient to pregnant woman."	RW1	Accepted
S2	"There are acronyms in the instrument that have not been explained before. E.g. ADE."	RW1	Accepted
S3	"I thought it was a bit long."	RW2	Accepted
S4	"Add the description (meaning) of ADR."	RW3	Accepted
S5	"I suggest adding the dilutions of medications, as they can be related to ADRs if done improperly."	RW3	Partially Accepted
S6	"In item 11, patients' medicines for continuous use should be included."	RW4	Accepted
S7	"Insert question in the 'ADR identification' section about diluent and volume used in the preparation of the suspected drug."	RW5	Partially Accepted
S8	"I suggest inserting in item 13, in addition to 'drug allergy', whether an 'adverse drug reaction' that has occurred previously is described in the medical record."	RW6	Accepted
S9	"Item 33 'ADR outcome' is unclear and appears to be a duplicate of item 32 'ADR-related patient evolution'."	RW6	Accepted
S10	"Item 33 is confused with item 32."	RW7	Accepted
S11	"In item 13, the question only reflects drug allergies. I think you could put allergy/ADR previously described in medical records, as it may not be an allergy but just a reaction that the patient has previously presented."	RW7	Accepted
S12	"Item 31 I think the question about infusion time is only appropriate for IV drugs. A writing suggestion: "for IV and/or intrathecal drugs, is the administration time adequate?"	RW7	Accepted

Source: Prepared by the authors, 2024.
S: Suggestion; RW: Reviewer; ADE: Adverse drug events; ADR: Adverse drug reaction; IV: Intravenous.

objective and 12 discursive. Of these, only three require more detailed answers to allow a better understanding of the case and help identify the suspicion. This instrument, which is new to the institution, has the potential to become a valuable tool for health professionals, promoting active search for ADRs and strengthening local pharmacovigilance actions.

After an extensive review of the literature, only two Brazilian studies were identified that had developed instruments for collecting and analyzing data on ADEs. When compared to the 63 items of the Pereira et al. form[14] and the 26 items of the simplified Lopes and Silva form[15], it is believed that the instrument proposed in this study has greater potential for use, mainly because it is digital and composed mostly of objective questions.

Furthermore, two other studies of great relevance to clinical practice were found. However, both were developed for specific audiences, which limits their applicability. Leopoldino[21] created a tool to predict ADRs in neonates admitted to the ICU. The study conducted by Albino[22] developed a tool to monitor serious adverse reactions in patients undergoing chemotherapy for colon and rectal cancer at different stages of the disease.

Despite being based on a retrospective analysis method that reviews a random sample of medical records of patients who have died, or have already been discharged or been transferred to another service, this tool was developed for real-time monitoring of hospitalized patients. In addition, by using the same reasoning as the GTT tool, the form also aims to measure the occurrence of adverse reactions over time from the data obtained, thus enabling opportunities to be identified for improving care processes and monitoring the impact of these changes on patient safety[16].

It is also noteworthy that the validation of the instrument by a multi-professional team provided a diverse evaluation, valuing different views on the same subject, incorporating the opinion of professionals from other areas of training, in addition to pharmacy[23]. By using judges from different backgrounds, the aim was to create a practical and meaningful instrument[24]. However, the limited number of specialists involved in the initial validation may affect the generalizability of the results. Although the multi-professional panel ensured a diversity of perspectives, a validation phase with professionals from the target population is recommended to confirm the applicability and effectiveness of the instrument in diverse contexts. This additional step is crucial to ensure that the instrument meets the needs of different hospital institutions.

Some reviewers suggested including other triggers, such as changes in clinical signs and symptoms. However, these suggestions were discussed with the institution's pharmacists, who considered these screeners to be unspecific and outside the guidelines of the Drug Module of the IHI guideline document and, for this reason, they were not included in this work. Although some suggestions were not accepted, the experts validated the instrument. After the second round of Delphi, the level of agreement reached was similar to that described in the literature[18,19,25], reinforcing the robustness of the process, despite the relatively small number of experts involved.

There is a consensus that assessing the occurrence of an adverse reaction is a complex process, which requires study and judgment on the part of investigators, and several factors must be considered. The use of polypharmacotherapy and symptoms that may or may not be related to the underlying disease make it difficult to identify the cause of the ADR. Definitions of causality based on clinical judgment generally show a high degree of intra- and inter-evaluater agreement[26]. Furthermore, in order not to discourage completion and generate incomplete data, it was decided not to work with the analysis of ADR causality. This instrument was designed to be filled in by any health professional in the institution, and it is up to the pharmacovigilance committee to determine causality once the suspicion has been identified and recorded.

Therefore, some of the questions in the "ADR identification" section have been reworded to make it easier to fill in, since many adverse reactions are not identified due to lack of knowledge or fear of the culture of punishment and are not reported in medical records for various reasons.

The impact of the tool on clinical practice and pharmacovigilance could be significant, as it facilitates the identification and recording of ADRs. By simplifying the data collection process and reducing the time needed to fill in the form, the tool encourages greater participation by health professionals in detecting and documenting adverse reactions. Finally, this work also aimed to raise awareness among healthcare professionals of the importance of identifying and recording ADRs to prevent future events, helping to mitigate underreporting, promote a culture of safety and provide safer and more effective care.

CONCLUSIONS

The tool developed is new to the institution and has shown evidence of validity in terms of its objective, structure, presentation, relevance, appearance, and content, representing yet another pharmacovigilance tool for the hospital.

It is recommended that future work be carried out to validate the tool with the target audience. It is hoped that the tool will be incorporated into the institution's routine to contribute to a better understanding of the dynamics of care and to improving work processes, thus making a unique contribution to patient safety.

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Authors' contributions

Marton ACG, Primo CC, Gonçalves RCR - Conception, planning (study design), data acquisition, analysis, interpretation. Araújo DCSA, Marton ACG - Writing the paper. All the authors approved the final version of the paper.

Conflict of Interest

The authors declare that there is no potential conflict of interest with peers and institutions, political or financial, in this study.

APPENDIX 1 - MANUALS AND ARTICLES USED TO BUILD THE LIST OF TRIGGERS

Author	Title	Country	Year	Data source
Agrizzi et al.	*Metodologia de busca ativa para detecção de reações adversas a medicamentos em pacientes oncológicos*	BRA	2013	*Revista Brasileira de Farmácia Hospitalar e Serviços de Saúde*
Almeida et al.	Use of a trigger tool to detect adverse drug reactions in an emergency department	BRA	2017	BMC Pharmacology and Toxicology
Araújo et al.	*Avaliação dos resultados da metodologia de medicamentos gatilho para busca de reações adversa*	BRA	2018	*Jornal de Ciências da Saúde do HU da Universidade Federal do Piauí*
Bretas et al.	*Avaliação da implantação de busca ativa de reações adversas a medicamentos com auxílio de ferramentas informatizadas*	BRA	2017	*Infarma Ciências Farmacêuticas*
Fabretti et al.	*Rastreadores para a busca ativa de eventos adversos a medicamentos em recém-nascidos*	BRA	2018	*Cadernos de Saúde Pública*
Fortenberry et al.	Development of an electronic trigger tool at a children's hospital within an academic medical center	EUA	2019	American Journal of Health-System Pharmacy
Griffin and Resar	IHI Global Trigger Tool for Measuring Adverse Events	EUA	2009	Institute for Healthcare Improvement
Hu et al.	Validating the Chinese geriatric trigger tool and analyzing adverse drug event associated risk factors in elderly Chinese patients: A retrospective review	CHI	2020	PlosOne
Lopes e Silva	*Manual de Rastreadores em Pediatria Medindo eventos adversos a medicamentos em hospital pediátrico*	BRA	2017	*Livro Editora UFG*
Menat et al.	An evaluation of trigger tool method for adverse drug reaction monitoring at a tertiary care teaching hospital	IND	2021	Perspectives in Clinical Research
Musy et al.	Trigger Tool-Based Automated Adverse Event Detection in Electronic Health Records: Systematic Review	SUI	2018	Journal of Medical Internet Research
Nagai et al.	*Uso de rastreadores para busca de reações adversas a medicamentos como motivo de admissão de idosos em pronto-socorro*	BRA	2018	*Ciência & Saúde Coletiva*
Nogueira et al.	*Eventos adversos a medicamentos: descrição de um processo de busca ativa em um hospital de ensino da Rede Sentinela*	BRA	2021	*Revista Brasileira de Farmácia Hospitalar e Serviços de Saúde*
Pandya et al.	Global Trigger Tool: Proficient Adverse Drug Reaction Autodetection Method in Critical Care Patient Units	IND	2020	Indian Journal of Critical Care Medicine
Ramirez et al.	Incidence of Suspected Serious Adverse Drug Reactions in Corona Virus Disease-19 Patients Detected by a Pharmacovigilance Program by Laboratory Signals in a Tertiary Hospital in Spain: Cautionary Data	ESP	2020	Frontiers in Pharmacology
Rozenfeld et al.	*Eventos adversos a medicamentos em hospital terciário: estudo piloto com rastreadores*	BRA	2013	*Revista de Saúde Pública*
Sousa et al.	*Acurácia de gatilhos na identificação de eventos adversos a medicamento em idosos hospitalizados*	BRA	2020	Research, Society and Development
Zimlichman et al.	Adverse Drug Event Rate in Israeli Hospitals: Validation of an International Trigger Tool and an International Comparison Study	ISR	2018	The Israel Medical Association Journal

APPENDIX 2 - FINAL VERSION OF THE TOOL

Active search form for adverse drug reactions

REVIEW OF MEDICAL RECORDS

1. Mark the triggers present in the medical record review

( ) Activated partial thromboplastin time (aPTT) greater than 100 seconds

( ) International Normalized Ratio (INR) greater than six

( ) Serum glucose less than 50 mg/dL

( ) Serum creatinine greater than twice the reference value
RV: 1.30 men and 1.10 women

( ) Serum urea greater than twice the reference value
RV: 50 mg/dL

( ) Glutamic-Oxalacetic Transaminase (GOT) greater than 38 U/L in men and greater than 32 U/L in women

( ) Glutamic-Pyruvic Transaminase (GPT) greater than 41 U/L in men and greater than 31 U/L in women

( ) Abrupt drop in hemoglobin of more than 25%
RV: 12.8 g/dL

( ) Leukocytes less than 3,000/mm^3

( ) Platelets less than 50,000/mm^3

( ) Eosinophils greater than 770/mm^3

( ) Administration of vitamin K or phytomenadione

( ) Administration of protamine

( ) Administration of antihistamines (diphenhydramine, hydrocortisone, hydroxyzine, loratadine, methylprednisolone, promethazine)

( ) Administration of flumazenil

( ) Administration of naloxone

( ) Administration of loperamide

( ) Discontinuation or suspension of medication

2. If the trigger is a laboratory test, was this test(s) already altered on admission?

( ) Yes ( ) No ( ) Not applicable

For the next question, consider the following concepts:

ADVERSE DRUG EVENT (ADE): unfavorable occurrences such as any damage or injury caused to the patient by the intervention related to medicines, caused by the use or lack of use when necessary. ADEs can be preventable or non-preventable.
Preventable ADEs are those damages caused by an error in the use of certain drug. Non-preventable ADEs are damages induced by the drug, after its appropriate use. These are adverse drug reactions.

ADVERSE DRUG REACTION (ADR): is any harmful and unintentional event caused by medicines at doses usually used for treatment, prophylaxis, diagnosis or to modify physiological functions.

3. Is there an ADE associated with the trigger(s)?

( ) Yes ( ) No

4. Which trigger(s) are you associated with?

5. Categorize the ADE

( ) Preventable (drug error) ( ) Non-preventable (adverse drug reaction) ***Skip to question 6***

PATIENT AND HOSPITALIZATION DATA

6. Medical records

7. Date of birth

8. Age

( ) 18 to 30 years old
( ) 30 to 40 years old
( ) 40 to 50 years old
( ) 50 to 60 years old
( ) 60 to 70 years old
( ) 70 to 80 years old
( ) Over 80 years old

9. Sex

( ) Female
( ) Male
Skip to question 12

10. Pregnant patient?

( ) Yes
( ) No
Skip to question 12

11. Gestational age at admission (in weeks)

12. Date of admission

13. Nature of admission

( ) Eletiva
( ) Urgência/Emergência

14. ICD on admission

15. Comorbidities

( ) Hypertension
( ) Diabetes
( ) Dyslipidemia
( ) Heart disease
( ) Hepatopathy
( ) Other:
( ) Nephropathy
( ) Alcoholism
( ) Smoking
( ) Overweight/Obesity
( ) Unknown

16. Home use drugs

17. Drug allergy or previous adverse reaction?

( ) Yes
( ) No
Skip to question 19
( ) Not described in medical records
Skip to question 19

18. Which drug(s)?

IDENTIFYING SUSPECTED ADVERSE DRUG REACTIONS

19. Manifestation of suspected ADR

Brief reaction report with relevant laboratory data

20. Rapporteur's professional category

( ) Nurse
( ) Nursing technician
( ) Pharmacist
( ) Not described in medical records
( ) Doctor

21. Date symptoms first appeared

22. Final date of symptom onset

23. Suspected drug(s)

Describe the daily dose, route of administration, start and end date, and reason for use of each suspected drug.

24. For parenteral drugs, was the prescribed dilution adequate??

( ) Yes
( ) No
( ) Not applicable

25. For parenteral drugs, was the prescribed infusion time adequate?

( ) Yes
( ) No
( ) Not applicable

26. Conduct adopted in relation to suspected ADRs

( ) Dose reduction — ***Skip to question 27***
( ) Suspension of the drug — ***Skip to question 27***
( ) Batch or brand replacement — ***Skip to question 28***
( ) Drug treatment of ADR — ***Skip to question 28***
( ) None — ***Skip to question 28***

27. Did the reaction stop after discontinuing use or reducing the dose?

( ) Yes
( ) No
( ) Not described in medical records

28. Patient evolution related to suspected ADR

( ) Recovered
( ) Death
( ) Recovered with sequelae
( ) Ignored/Unknown
( ) Not recovered
( ) In recovery
( ) Not described in medical records