Development of a Trigger Tool to Identify Adverse Drug Events in Elderly Patients With Multimorbidity

María Dolores Toscano Guzmán, PharmD, Mercedes Galván Banqueri, PhD, PharmD,† María José Otero, PhD, PharmD,‡ Eva Rocío Alfaro Lara, PhD, PharmD,§ Pilar Casajus Lagranja, PharmD,|| and Bernardo Santos Ramos, PharmD¶*

Purpose: Elderly patients with multimorbidity are especially vulnerable to adverse drug events (ADEs) and had high prevalence rates. Identifying ADEs is essential for enabling timely interventions that can mitigate the adverse events detected and for developing targeted strategies to prevent their occurrence as well as to monitor implementation. The aim of this study was to develop a set with appropriate triggers for detecting potential ADEs in elderly patients with multimorbidity.

Methods: A modified Delphi methodology was used to reach consensus. Existing triggers for detecting ADEs in adult patients were identified from a literature search in several databases (EMBASE, MEDLINE, Web of Science, Centre for Reviews and Dissemination, and Cochrane Library) and from Institute for Healthcare Improvement published lists. Twelve experts in patient/medication safety or in chronic diseases scored candidate triggers for appropriateness according to 3 criteria (evidence, usefulness for elderly patients, and feasibility of implementation in clinical practice).

Results: Seventy-two triggers were initially selected to be evaluated. The final set includes a total of 51 triggers for which the panelists who completed the 2 rounds of evaluation reached agreement. These triggers were organized into 5 modules: 11 as care module triggers, 10 as antidotes/treatment, 11 medication concentrations, 18 abnormal laboratory values, and 1 as emergency department trigger.

Conclusions: A set of triggers for detecting ADEs in elderly patients with multimorbidity have been developed, following the consensus of a panel of experts. Subsequent validation in clinical practice is needed to confirm the accuracy and efficiency of these triggers for this population.

Key Words: chronic patient, drug related side effects and adverse reactions/diagnosis, multi morbidity, patient safety

(*J Patient Saf* 2017;00: 00–00)

Adverse drug events (ADEs) continue to be an important and unfortunate cause of morbidity and mortality in all settings of care and among all patient populations.[1] Recent studies have found that ADEs are the most frequent cause of hospital-related complications[2,3] and affect 4.7%[4] or even 14.7%[5] of hospitalized patients, prolonging their hospital stays. Adverse drug events occur fairly frequently as well during transitions of care, accounting for two thirds of all events experienced by discharged patients.[6] In outpatient settings, a summary report on related studies indicates that ADEs cause between 0.3% and 20.2% of visits to emergency departments and between 2.4% and 6.7% of hospital admissions.[7] It should be also noted that according to a meta-analysis,[8] approximately half of ADEs are preventable among both inpatients and outpatients.

Patient-related increased risk factors for experiencing ADEs are number of drugs taken regularly, age, and comorbidities.[9] Hence, older adults with chronic diseases are especially vulnerable to ADEs and have higher ADE prevalence rates compared with other age groups.[1] For example, statistical data from U.S. indicate that older adults (age ≥ 65 years) accounted for 35% of all hospital stays while, at the same time, accounted for 53.1% of hospital ADEs.[4] In the outpatient setting, older adults have a rate of ADEs requiring primary care or emergency department visits 2 to 3 times higher than younger persons[10,11] and are 3 to 7 times more likely to be hospitalized for ADEs.[12,13]

Both detection and characterization of ADEs, and especially of those ADEs classified as preventable, are essential for developing effective and targeted strategies to prevent their occurrence and thus improve patient safety. Various methods for identifying ADEs and medication errors have been proposed, including chart review, voluntary reporting by healthcare professionals, and direct observation, each one with its own characteristics, strengths, and limitations.[14,15] To obtain a comprehensive picture of medication safety within an organization, more than 1 identification method should be applied.[16]

The trigger tool methodology was developed to increase the efficiency of conventional chart review in the identification of ADEs, because this method is considered the criterion standard because of its sensitivity and specificity, but it is time-consuming and expensive.[17,18] A trigger is defined as a flag, occurrence, or prompt that alerts reviewers to initiate further in-depth investigation regarding the patient's record to determine the presence or absence of an adverse event. Triggers commonly used to identify ADEs are abnormal laboratory values or supratherapeutic drug levels, certain medications or antidotes, and changes in clinical status or new signs or symptoms associated with a possible medication-related harm.[19] For example, a trigger is a value of international normalized ratio greater than 6 in a patient with oral anticoagulants, which may alert professionals to perform a more detailed record review for evidence that the patient has an associated bleed. The use of triggers promotes a more focused and selective process for screening the patient's medical record than a full review would do; therefore, it is faster and more cost-effective.[15]

Triggers have often been applied retrospectively, as has been already mentioned, to guide medical record review after clinical episodes have terminated to obtain information about rates of adverse events at institutions and to monitor the impact of interventions. However, they may also be used concurrently, usually integrated

From the *UGC de Farmacia del Complejo Hospitalario Universitario de Huelva, Huelva; †UGC de Farmacia del Área Sur de Sevilla, Sevilla; ‡ISMP-Spain. Complejo Asistencial Universitario de Salamanca, Salamanca; §Agencia de Evaluación de Tecnologías Sanitarias de Andalucía, Sevilla; ||UGC Farmacia. Hospital Universitario Miguel Servet, Zaragoza; and ¶UGC de Farmacia del Área Sur de Sevilla, Sevilla, Spain.

Correspondence: María Dolores Toscano Guzmán, UGC Farmacia del Complejo Hospitalario Universitario de Huelva, Ctra. Sevilla-Huelva, s/n, 21080 Huelva, Spain (e-mail: maritogu@hotmail.com).

The authors disclose no conflict of interest.

Project "PI15/01616", funded by Instituto de Salud Carlos III, integrated in the national I+D+i 2013-2016 and co-funded by European Union (ERDF/ESF, "Investing in your future").

Supplemental digital contents are available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.journalpatientsafety.com).

into health information technology, to provide rapid, real-time identification of adverse events and enable timely interventions that can mitigate the adverse events detected.[20]

The usefulness of a trigger tool is dependent on its sensitivity and specificity. Multiple sets of triggers have been developed, from global lists of triggers for hospitals[21] to specific lists that differ according to the specific type of event (e.g., drugs), clinical setting (e.g., mental health settings, nursing homes), or group of patients they focus on (e.g., pediatric),[22–25] each designed to identify the more frequent and severe adverse events in each environment.[20]

Elderly patients with multimorbidity often receive numerous medications and have high rates of ADEs, as mentioned previously. However, as far as we know, the lists of triggers for elderly patients are only available for the primary care setting[26] and for nursing homes,[27,28] and no one has proposed a list that would encompass identifying ADEs across the whole continuum of care. For this reason, we designed this project with the objective of developing a trigger tool using the presumably most appropriate triggers for detecting ADEs in elderly patients with multiple chronic conditions.

METHODS

The study was performed between May 2015 and January 2016, using a modified Delphi methodology.[29] This method combines the synthesis of scientific evidence with the opinions of experts.

Information Search and Development of Scenarios

The first step in this method consists of identifying a list of indications or scenarios, which are subsequently assessed individually and anonymously by an expert panel in 2 successive rounds. In our case, the scenarios consisted of the possible triggers available to be used to identify ADEs in elderly patients with multimorbidity.

To identify existing triggers, a literature review searching for studies that used triggers to detect ADEs in adult patients was conducted in the following databases: EMBASE, MEDLINE (through PubMed), Web of Science, Centre for Reviews and Dissemination, and Cochrane Library. The search included publications from 1990, the year in which the first article on triggers was published, to May 2015. Both free and controlled language was used (see details of the search strategy carried out in MEDLINE and EMBASE in online supplementary appendix A, http://links.lww.com/JPS/A91). A cross-line search from the bibliographic references of the retrieved articles was also performed. Controlled clinical trials, retrospective or prospective observational studies, cohort studies, and case-control studies were included. Articles that did not provide detailed information about the specific triggers used to detect ADEs were not included, nor were those for whom the study population was pediatric patients, or those in which the full text was not in English or Spanish. Collection of the triggers applied in these studies was performed by 2 researchers (M.D.T.C. and M.J.O.). In case of doubt, a third researcher (M.G.B.) was consulted, and discrepancies were resolved by consensus.

In addition, the lists of trigger tools for measuring ADEs[22–24] and the Global Trigger Tool[21] published by the Institute for Healthcare Improvement (IHI) were reviewed, and all triggers that might be used to detect ADEs in elderly patients with multi-morbidity were selected.

After reviewing all of the previous information about existing triggers, the research team eliminated from consideration all triggers that, a priori, would not be useful for the tool we wanted to develop, either because they used medications that were not currently in use in clinical practice or because the triggers overlapped between them. In some cases, laboratory values had to be adapted to the ones used in Spain.

Selecting Members for the Panel of Experts

The criteria considered when selecting the experts were the following: a balanced ratio of men to women and of experts in patient/medication safety and in chronic patients; representation from primary care, hospitals, and healthcare administration; representation from specialists in medicine and pharmacy; and representation from different autonomous regions in Spain and different Latin-American countries. For recruitment, experts were contacted and provided with information on the study objective, possible workload, and schedule. Once they accepted, they were sent a communication agreement. The group of experts consisted of 12 members whose characteristics are shown in Table 1 (see Acknowledgements).

Expert Panel Evaluations

The experts participated in 2 consecutive rounds. In the first round, the panelists were e-mailed a questionnaire with the triggers to be evaluated and instructions for rating them, along with information about trigger methodology and definitions of terms. They were asked to rate the appropriateness of each trigger to be applied for detecting ADEs in chronic patients with multimorbidity according to the following 3 criteria: strength of the evidence supporting the trigger, usefulness in chronic patients with multimorbidity, and feasibility of implementing their use in clinical practice. Following the Delphi-modified methodology appropriateness method, these criteria were rated on a scale of 1 to 9 points, from "completely inappropriate" to "completely appropriate," respectively.

The results obtained were analyzed statistically. The median and interquartile range were both calculated, as was the level of agreement reached for the criteria for each scenario. Appropriateness

TABLE 1. Characteristics of the Experts on the Panel (n = 12)

Characteristics	Participants n (%)
Sex	
Men	6 (50)
Women	6 (50)
Experience and knowledge profile	
Medication/patient safety	8 (66.7)
Chronic patients	2 (16.7)
Both	2 (16.7)
Profession	
Physician	7 (58.3)
Pharmacist	5 (41.7)
Work setting	
Hospital	8 (66.7)
Primary care	1 (8.3)
Heathcare administration	3 (25)
Geographic setting	
Argentina	1 (8.3)
Brasil	1 (8.3)
Colombia	1 (8.3)
Spain	
Andalucía	2 (16.7)
Asturias	1 (8.3)
Castilla-León	1 (8.3)
Cataluña	2 (16.7)
Extremadura	1 (8.3)
Madrid	2 (16.7)

was classified following the Delphi-modified methodology into the following 3 levels: appropriate, inappropriate, and uncertain. The scenarios in which the 3 criteria were categorized as appropriate were admitted, and scenarios in which 1 of the 3 criteria were considered inappropriate were eliminated.

In the second round, experts were asked to re-evaluate the appropriateness of the scenarios for which consensus had not been achieved in the first round. Each panel member received an individualized evaluation questionnaire with the scenarios that needed to be re-evaluated, which showed the median and range of all the experts' first-round ratings for each criterion, together with his own specific ratings. Also provided were the comments and/or suggestions made anonymously during the first round by all the experts. Thus, each expert had the option of changing his score from the first round or keeping it, bearing in mind the scores from others as well as his own, plus any comments that had been left.

The results obtained from this second round were analyzed and classified using the same methods as with the first round. However, in this case, a trigger was included on the list when the experts judged it appropriate for inclusion according to the 2 criteria of usefulness for elderly patients with multimorbidity and feasibility of implementation into clinical practice even when the criteria of strength of the evidence supporting the trigger made it considered as not appropriate.

RESULTS

Review of Information and Selection of Indications

The literature review includes a total of 261 articles (46 in EMBASE, 42 in MEDLINE, 150 in Web of Science, 5 in Centre for Reviews and Dissemination, 2 in Spanish Medical Index, and 16 in Cochrane Library), of which 54 were initially selected after title and abstract screening. After reviewing the full text of the articles, only 11 were selected. The main reasons for exclusion are summarized in Figure 1, which shows the flow diagram for the selection of articles. Furthermore, 2 additional articles were retrieved by cross references, so that only a total of 13 articles were finally reviewed,[19,26–28,30–38] all of which were observational studies. From the trigger lists published by the IHI, several triggers were selected, most of which coincide.

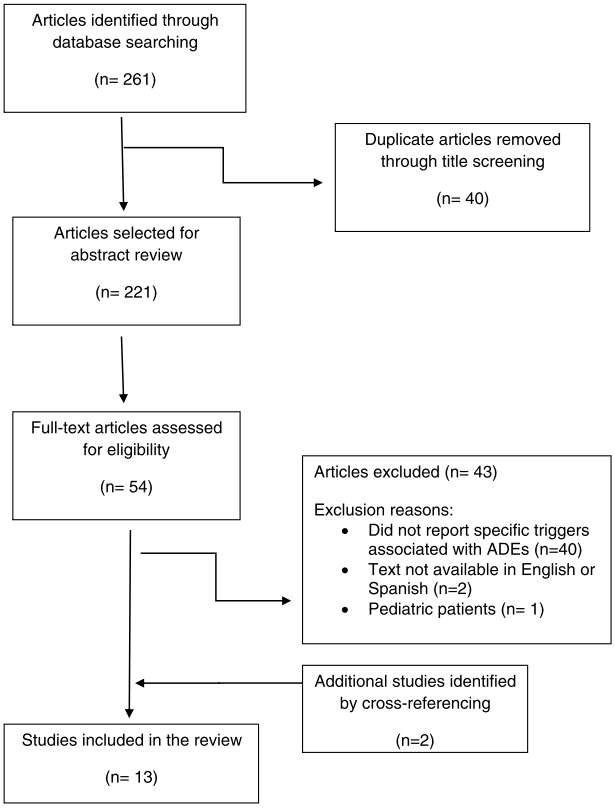

FIGURE 1. Flow diagram of the selection of articles on triggers used to detect ADEs in adult patients.

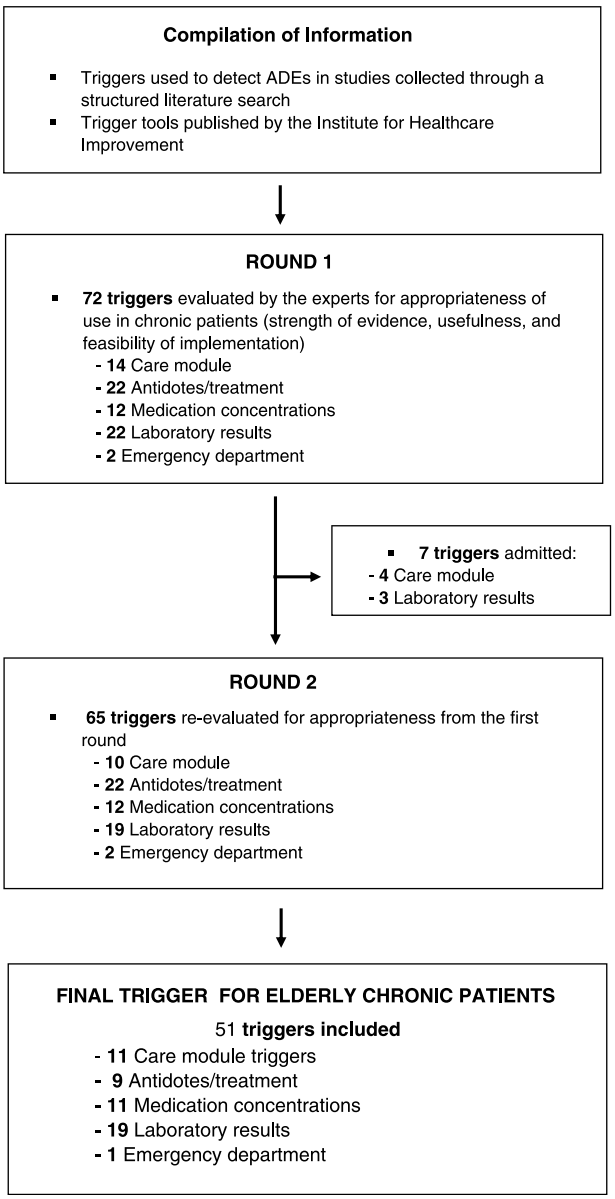

FIGURE 2. Flow diagram for the process used to develop the list triggers for detecting potential ADEs in older patients with multiple chronic conditions.

Using the previous information, a preliminary list with 133 triggers was initially elaborated, of which 72 were selected by the research team to be included in the first Delphi survey. These 72 triggers were organized in the following 5 categories: 14 care triggers, 21 antidotes/treatments, 13 medication abnormal

TABLE 2. Summary of the Results Obtained for the Scenarios Evaluated in the 2 Evaluation Rounds

Scenario	Triggers	Round 1 Result*	Round 2 Result†
Module 1. Care module triggers			
1	Rash	Re-evaluate	Included
2	New allergy	Re-evaluate	Included
3	Oversedation/lethargy	Re-evaluate	Included
4	Hypotension	Re-evaluate	Included
5	Drop in systolic blood pressure	Re-evaluate	Excluded U
6	Falls	Included	—
7	Transfusion or use of blood products	Included	—
8	Diarrhea	Re-evaluate	Excluded UF
9	Constipation	Re-evaluate	Included
10	Vomiting	Re-evaluate	Excluded F
11	Acute dialysis	Re-evaluate	Included
12	Unexpected medical or surgical emergency/sudden death	Re-evaluate	Included
13	Readmission within 30 d	Included	—
14	Adverse reaction recorded	Included	—
Module 2. Antidotes/treatments module triggers			
15	Vitamin K administration	Re-evaluate	Included
16	Antihistamines IV	Re-evaluate	Included
17	Prednisone and hydroxyzine	Re-evaluate	Excluded UF
18	Flumazenil administration	Re-evaluate	Included
19	Naloxone administration	Re-evaluate	Included
20	Methylnaltrexone	Re-evaluate	Excluded UF
21	Antiemetic administration	Re-evaluate	Included
22	Ondansetron administration	Re-evaluate	Excluded U
23	Antidiarrheals	Re-evaluate	Included U
24	Loperamide administration	Re-evaluate	Included UF
25	Enema administration	Re-evaluate	Included UF
26	Digoxin immune fab	Re-evaluate	Included
27	Glucagon	Re-evaluate	Excluded UF
28	50 mL of dextrose 50% and 10 E Actrapid insulin administration	Re-evaluate	Excluded UF
29	Vancomycin oral	Re-evaluate	Excluded U
30	Heparin low molecular weight and CL < 60 mL/h	Re-evaluate	Excluded F
31	Haloperidol administration	Re-evaluate	Included
32	Risperidone administration	Re-evaluate	Included
33	Abrupt cessation of medication	Re-evaluate	Included
34	Abrupt reduction of dose of medication	Re-evaluate	Excluded F
35	Change of habitual medications	Re-evaluate	Excluded F
36	Long-term medications and classifications are at variance	Re-evaluate	Included
Module 3. Medication concentration module triggers			
37	Digoxin level > 2 ng/mL	Re-evaluate	Included
38	Theophylline >20 µg/mL	Re-evaluate	Excluded U
39	Lithium > 1,5 mmol/L	Re-evaluate	Included
40	Carbamazepine > 13 µg/mL	Re-evaluate	Included
41	Phenytoin >20 µg/mL	Re-evaluate	Included
42	Phenobarbital > 45 µg/mL	Re-evaluate	Included
43	Valproic acid >120 µg/mL	Re-evaluate	
44	Gentamicin/Tobramycin levels: peak > 10 µg/mL, trough > 2 µg/mL	Re-evaluate	Included
45	Amikacin levels: peak > 30 µg/mL, trough 10 µg/mL	Re-evaluate	Included
46	Vancomycin level: peak > 40 µg/mL and trough 20 µg/mL	Re-evaluate	Included
47	Cyclosporine > 400 ng/L	Re-evaluate	Included
48	Tacrolimus level >20 ng/mL	Re-evaluate	Included
Module 4. Laboratory results module triggers			
49	*Clostridium difficile*–positive stool	Re-evaluate	Included
50	Serum glucose < 50 mg/dL	Included	—
51	Serum glucose > 110 mg/dL	Re-evaluate	Included
52	Activated Partial Thromboplastin Time > 100 s	Re-evaluate	Excluded U
53	INR >5	Included	—
54	Rising BUN or serum creatinine > 2 times baseline*	Re-evaluate	Included
55	eGFR <35 mL/min/1.73 m^2	Re-evaluate	Included
56	K > 6.0 mEq/L	Re-evaluate	Included
57	K < 2,9 mEq/L	Re-evaluate	Included
58	Na < 130 mEq/L	Re-evaluate	Included
59	Hypercalcemia > 10.5 mg/dL	Re-evaluate	Included
60	ALT > 80 U/L and AST > 84 U/L	Re-evaluate	Included
61	ALP > 350 U/L total bilirubin > 4 mg/dL	Re-evaluate	Included
62	CPK > 269 U/L	Re-evaluate	Included
63	TSH < 0,34 µUI/L or T4 > 12 µg/dL	Re-evaluate	Included
64	TSH > 5,6 µUI/L or T4 < 6 µg/dL	Re-evaluate	Excluded U
65	HA1C > 6% and glucocorticoid	Re-evaluate	Included
66	WBC < 3.000	Re-evaluate	Included
67	Platelet count < 50,000	Re-evaluate	Included
68	Eosinophil > 9%	Re-evaluate	Excluded U
69	Hemoglobin > 12 g/dL	Re-evaluate	Included
70	Decrease in hemoglobin or hematocrit >25%	Included	-
Module 5. Emergency department module triggers			
71	Emergency room visit	Re-evaluate	Excluded F
72	Readmission to ED within 48 h*	Re-evaluate	Included

*Round 1 result: included; re-evaluated.

†Round 2 result: included; excluded: U, lack of usefulness, F, lack of feasibility.

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CL, clearance; CPK, creatine phosphokinase; ED, emergency department; eGFR, estimated glomerular filtration rate; HA1C, hemoglobin A1c; K, potassium; Na, sodium; T4, thyroxine; TSH, thyroid stimulating hormone; WBC, white blood cell.

concentrations, 22 abnormal laboratory values, and 2 emergency department triggers. All the triggers initially compiled, and the sources of information for each one are shown into the online supplementary appendix B, http://links.lww.com/JPS/A92.

Results of the Evaluation Rounds

Figure 2 shows a scheme of the process used to elaborate the trigger list, and Table 2 summarizes the results obtained for each indication in the 2 evaluation rounds.

TABLE 3. High-Alert Medications for Patients with Chronic Illnesses (HAM List)[43] and Triggers for Detecting Potential ADEs

High-alert Medications for Patients With Chronic Illnesses (HAMC list)	Triggers for Detecting Potential ADEs
Therapeutic classes	
Anticoagulants, oral	INR >5 Vitamin K administration Transfusion or use of blood products Decrease in hemoglobin or hematocrit >25%
Antiepileptics (narrow therapeutic range)	Carbamazepine > 13 μg/mL Phenytoin >20 μg/mL Valproic acid >120 μg/mL
Antiplatelets (including aspirin)	Transfusion or use of blood products Platelet count < 50,000 Decrease in hemoglobin or hematocrit >25%
Antipsychotics	Oversedation/lethargy
β-Adrenergic blockers	Hypotension Falls
Benzodiazepines and analogues	Flumazenil administration Oversedation/lethargy Falls
Corticosteroids long-term use (≥3 months)	HA1C > 6% and glucocorticoid Serum glucose > 110 mg/dL
Cytostatic drugs, oral	Rash ALT > 80 U/L and AST > 84 U/L ALP > 350 U/L and total bilirubin > 4 mg/dL CPK > 269 U/L TSH < 0.34 μUI/L or T4 > 12 μg/dL WBC < 3000 Platelet count < 50,000 Decrease in hemoglobin or hematocrit > 25%
Immunosuppressants	Cyclosporine > 400 ng/L Tacrolimus level > 20 ng/mL eGFR <35 mL/min/1.73 m^2 K > 6.0 mEq/L WBC < 3000 Platelet count < 50,000
Insulins	Serum glucose < 50 mg/dL
Loop diuretics	Hypotension K < 2.9 mEq/L Serum glucose > 110 mg/dL
Nonsteroidal anti-inflammatory drugs	Transfusion or use of blood products Decrease in hemoglobin or hematocrit > 25% Rising BUN or serum urea nitrogen >2 times baseline eGFR <35 mL/min/1.73 m^2
Oral hypoglycemic drugs	Serum glucose < 50 mg/dL
Opioid analgesics	Naloxone administration Oversedation/lethargy Falls Constipation
Specific medication	
Amiodarone/dronedarone	TSH < 0.34 μUI/L or T4 > 12 μg/dL/rising BUN or serum urea nitrogen >2 times baseline*
Digoxin oral	Digoxin level > 2 ng/mL
Methotrexate, oral (nononcologic use)	WBC < 3000
Spironolactone/eplerenone	K > 6.0 mEq/L

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; eGFR, estimated glomerular filtration rate; HA1C, hemoglobin A1c; K, potassium; T4, thyroxine; TSH, thyroid stimulating hormone; WBC, white blood cell.

The response rate for both rounds was 100% of panelists. At the end of the first round, of the 72 triggers that were assessed, only 7 were admitted to the list, because agreement was reached on them by the experts for the 3 criteria evaluated, 4 triggers of the care module, and 3 of the antidotes/treatment module. The rest were categorized as uncertain in at least 1 of the 3 criteria to be evaluated (evidence, usefulness for elderly patients, and feasibility of implementation in clinical practice) and were slated to be re-evaluated in the second round. None of the triggers were rejected because of being considered as inappropriate for any of the 3 criteria.

After the second round, of the 65 triggers that were re-evaluated, 44 were included because the panelists considered them appropriate for at least the 2 criteria of usefulness for elderly patients and feasibility of implementation, even though they were not considered appropriate on the basis of strength of evidence. On the other hand, 21 triggers were excluded, 8 because they were not considered appropriate for usefulness, 5 because they were not considered appropriate for feasibility, and 8 for not being considered appropriate for both criteria.

The final set includes a total of 51 triggers organized into 4 modules: 11 as care module triggers, 9 antidotes/treatments, 11 medication concentrations, 18 abnormal laboratory values, and 1 as emergency department trigger. Thus, 11 (79%) of the 14 care module triggers, 9 (43%) of the 21 antidotes/treatments triggers, 12 (92%) of the 13 medication concentrations, 19 (86%) of the 22 laboratory results, and 1 of the 2 emergency department triggers reached consensus and were admitted.

DISCUSSION

The safe use of medications in patients with multiple chronic conditions is one of the greatest challenges faced by healthcare providers, because these patients often take numerous medications and have a high prevalence of ADEs. Trigger tools have been developed to detect ADEs in elderly patients in ambulatory settings and in nursing homes.[26–28] However, the newer models addressing the care of chronic patients seek integration, coordination, and continuity of care across all healthcare settings.[39,40] Hence, the development of a specific list of triggers to aid in identifying ADEs across the whole continuum of care seems to be more aligned with current strategies for chronicity, although any such list should be customizable according to the objectives and the resources at each specific setting or institution.

The process of developing a list of triggers using a consensus methodology has been used before to create other trigger tools.[25,41,42] From the initial 72 candidate triggers, the experts voted to retain a high percentage (71%) of them. These triggers were categorized into modules, as in other lists of triggers, to facilitate their use when reviewing the medical record. If we analyze each one of the modules separately, in both the analytic parameter module and the plasma concentration module, most of the triggers were considered adequate, perhaps because they are easy to obtain and are useful for detecting adverse events. On the other hand, it was the antidote/treatment module that had the greatest number of triggers rejected. The reason cited for rejecting some of these triggers was that the antidote allowed for detection of an ADE that could also be detected with another trigger from the analytic parameter module (e.g., oral vancomycin versus *Clostridium difficile*–positive stool) or the plasma concentration module (e.g., digoxin immune fab versus digoxin level >2 ng/mL). In other cases, the trigger was excluded because it involved a specific medication and professionals had the option to use a broader trigger instead, which would encompass a complete pharmacologic group (e.g., ondansetron versus antiemetics).

Our list includes triggers that are already included on other IHI lists for identifying adverse events related to drug use but also includes triggers that were retrieved from the Global Trigger Tool because they are associated with signs of ADEs frequently occurring in elderly patients with multimorbidity (e.g., transfusion or use of blood products to identify bleeding caused by aspirin or nonsteriodal anti-inflammatory drugs).

In addition, our new list includes both specific and general triggers, because one of the main limitations of specific triggers is that they only allow for identifying the type of ADEs they are designed to detect and that elderly patients with multimorbidity may present a broad spectrum of adverse events caused by the number of medications they are taking concurrently. For this reason, to make the new list more effective, we decided to select certain general triggers that would allow for identifying a broad variety of iatrogenic adverse events due to medications (e.g., readmission 30 days after a hospital stay) for evaluation by the experts.

We should also point out that another important advantage of this list is that the specific triggers included allows for detecting the most frequent adverse events caused by high-risk medications, which are associated with the greatest likelihood of producing serious harm in chronic patients with multimorbidity. Table 3 shows the drug classes and specific medications classified as high-risk medications for chronic patients in Spain (high-alert medications for patients with chronic illnesses list) and some specific triggers that may identify adverse events caused by these medications.[43] This list should prove to be very useful for minimizing harm associated with the administration of high-risk medicines and for monitoring interventions that prioritize those medications.

There are several limitations in the present study. First, although the Delphi methodology used presents characteristics that are apparently objective, it is really a subjective method, because it basically measures opinions. However, this technique has advantages over other methods also used to reach consensus. It is considered a rigorous method, to be used where a combination of scientific evidence and expert opinion is required, and is recommended as a method for determining the suitability of a procedure or for developing decision-making tools.[44] Second, we did not call the experts in to any face-to-face meetings, which would have allowed individual respondents to share opinions about the triggers. The possibility of having face-to-face meetings was limited precisely by the advantage we sought in having a broad geographic representation on the panel. Third, the tool we developed consisted of a high number of triggers, and so the researchers considered it necessary to carry out a subsequent validation study, applying the list to chronic patients with multimorbidity, to be sure of having achieved a very efficient tool.

In conclusion, we have developed a tool based on triggers described in the literature. Our list comprises the most useful and practicable signs for detecting ADEs in elderly patients with multimorbidity, according to a consensus from a panel of experts. This list will need to be validated through application in clinical practice to confirm that these triggers are indeed the most useful and efficient ones for this population.

ACKNOWLEDGMENT

The authors thank the following experts who participated on the panel: Pedro Amariles Muñoz, PhD, PharmD, Profesor de la Universidad de Antioquia, Medellin, Colombia; Tania Azevedo Anacleto, PharmD, Vicepresidenta del Instituto de Prácticas Seguras en el Uso de Medicamentos, Belo Horizonte, Brasil; Laura Bugna, PharmD, Farmacéutica en el Programa Provincial del Farmacovigilancia, Santa Fe, Argentina; Consuelo Climent Bolta, PhD, PharmD, Servicio de Farmacia del Hospital Clinic de Barcelona, España; Marta del Nozal Nalda, PhD, PharmD,

Subdirectora Médica del Área de Gestión Sanitaria Sur de Sevilla, Sevilla, España; Judit García Aparicio, MD, PhD, Servicio de Medicina Interna del Complejo Asistencial Universitario de Salamanca, Salamanca, España; Enrique Gavilán Moral, MD, PhD, Médico de Familia del Centro de Salud de Montehermoso, Cáceres, España; Susana Lorenzo Martínez, MD, PhD, Jefe de Unidad de Calidad Asitencial de la Fundación Hospital de Alcorcón, Madrid, España; María Queralt Gorjas Torner, PhD, PharmD, Jefa de Servicio de Farmacia del Hospital Universitario Parc Taulí Sabadell, Barcelona, España; Manuel Alfonso Rincón Gómez, MD, PhD, Servicio de Medicina Interna del Hospital Universitario Virgen del Rocio, Sevilla, España; Pedro Ruiz López, MD, PhD, Coordinador de Calidad del Hospital 12 de Octubre, Madrid, España; and Fernando Vázquez Valdés, MD, PhD, Catedrático de la Facultad de Medicina de la Universidad de Oviedo, Oviedo, España.

REFERENCES

1. U.S. Department of Health and Human Services, Office of Disease Prevention and Health Promotion. National Action Plan for Adverse Drug Event Prevention. Washington, DC: Author; 2014.
2. Levinson DR. *Adverse events in hospitals: national incidence among Medicare beneficiaries*. Washington, DC: Department of Health and Human Services. Office of Inspector General; 2010.
3. Classen DC, Resar R, Griffin F, et al. "Global trigger tool" shows that adverse events in hospitals may be ten times greater than previously measured. *Health Aff (Millwood)*. 2011;30:581–589.
4. Lucado J, Paez K, Elixhauser A. Medication-related adverse outcomes in U.S. hospitals and emergency departments, 2008. In: *HCUP Statistical Brief #109*. Rockville, MD: Agency for Healthcare Research and Quality; 2011.
5. Davies EC, Green CF, Taylor S, et al. Adverse drug reactions in hospital in-patients: a prospective analysis of 3695 patient-episodes. *PLoS One*. 2009;4:e4439.
6. Foster AJ, Clark HD, Menard A, et al. Adverse events among medical patients after discharge from hospital. *CMAJ*. 2004;170:345–349.
7. Expert Group on Safe Medication Practices. Creation of a Better Medication Safety Culture in Europe: Building up Safe Medication Practices. Strasbourg: Council of Europe; 2006.
8. Hakkarainen KM, Hedna K, Petzold M, et al. Percentage of patients with preventable adverse drug reactions and preventability of adverse drug reactions—a meta-analysis. *PLoS One*. 2012;7:e33236.
9. Saedder EA, Lisby M, Nielsen LP, et al. Number of drugs most frequently found to be independent risk factors for serious adverse reactions: a systematic literature review. *Br J Clin Pharmacol*. 2015;80: 808–817.
10. Budnitz DS, Pollock DA, Weidenbach KN, et al. National surveillance of emergency department visits for outpatient adverse drug events. *JAMA*. 2006;296:1858–1866.
11. Sarkar U, López A, Maselli JH, et al. Adverse drug events in U.S. adult ambulatory medical care. *Health Serv Res*. 2011;46:1517–1533.
12. Taché SV, Sönnichsen A, Ashcroft DM. Prevalence of adverse drug events in ambulatory care: a systematic review. *Ann Pharmacother*. 2011;45: 977–989.
13. Salvi F, Marchetti A, D'Angelo F, et al. Adverse drug events as a cause of hospitalization in older adults. *Drug Saf*. 2012;35(Suppl 1):29–45.
14. Schneider PJ. Workshop summaries. *Am J Health Syst Pharm*. 2002;59: 2333–2336.
15. Meyer-Masseti C, Cheng CM, Schwappach DL, et al. Systematic review of medication safety assessment methods. *Am J Health-Syst Pharm*. 2011;68:227–240.
16. Shojania KG. The elephant of patient safety: what you see depends on how you look. *Jt Comm J Qual Patient Saf*. 2010;36:399–401.
17. Resar RK, Rozich JD, Classen D. Methodology and rationale for the measurement of harm with trigger tools. *Qual Saf Health Care*. 2003;12 (Suppl II):ii39–ii45.
18. Classen DC, Lloyd RC, Provost L, et al. Development and evaluation of the Institute for Healthcare Improvement Global Trigger Tool. *J Patient Saf*. 2008;4:169–177.
19. Rozich JD, Haraden CR, Resar RK. Adverse drug event trigger tool: a practical methodology for measuring medication related harm. *Qual Saf Health Care*. 2003;12:194–200.
20. Agency for Healthcare Research and Quality. Triggers and Targeted Injury Detection Systems (TIDS) Expert Panel Meeting: Conference Summary. Rockville, MD. AHRQ. Pub. No. 090003; 2009.
21. Griffin FA, Resar RK. *IHI Global Trigger Tool for Measuring Adverse Events*. 2nd ed. Cambridge, MA: Institute for Healthcare Improvement; 2009.
22. Institute for Healthcare Improvement. Trigger Tool for Measuring Adverse Drug Events. Cambridge, MA: Institute for Healthcare Improvement; 2003.
23. Institute for Healthcare Improvement. Trigger Tool for Measuring Adverse Drug Events in a Mental Health Setting. *Version 2*. Cambridge, MA: Institute for Healthcare Improvement; 2008.
24. Institute for Healthcare Improvement. Trigger Tool for Measuring Adverse Drug Events in the Nursing Home. Cambridge, MA: Institute for Healthcare Improvement; 2009.
25. Unbeck M, Lindemalm S, Nydert P, et al. Validation of triggers and development of a pediatric trigger tool to identify adverse events. *BMC Health Serv Res*. 2014;14:655.
26. Singh R, McLean-Plunckett EA, Kee R, et al. Experience with a trigger tool for identifying adverse drug events among older adults in ambulatory primary care. *Qual Saf Health Care*. 2009;18:199–204.
27. Handler SM, Hanlon JT, Perera S, et al. Assessing the performance characteristics of signals used by a clinical event monitor to detect adverse drug reactions in the nursing home. *AMIA Annu Symp Proc*. 2008:278–82.
28. Marcum ZA, Arbogast KL, Behrens MC, et al. Utility of an adverse drug event trigger tool in Veterans Affairs nursing facilities. *Consult Pharm*. 2013;28:99–109.
29. Fitch K, Bernstein SJ, Aguilar MD, et al *The RAND/UCLA Appropriateness Method User's Manual*. Santa Monica, CA: RAND Corporation; 2001.
30. Franklin BD, Birch S, Schachter M, et al. Testing a trigger tool as a method of detecting harm from medication errors in a UK hospital: a pilot study. *Int J Pharm Pract*. 2010;18:305–311.
31. Seynaeve S, Verbrugghe W, Claes B, et al. Adverse drug events in intensive care units: a cross-sectional study of prevalence and risk factors. *Am J Crit Care*. 2011;20:e131–e140.
32. Brenner S, Detz A, López A, et al. Signal and noise: applying a laboratory trigger tool to identify adverse drug events among primary care patients. *BMJ Qual Saf*. 2012;21:670–675.
33. Carnevali L, Krug B, Amant F, et al. Performance of the adverse drug event trigger tool and the global trigger tool for identifying adverse drug events: experience in a Belgian hospital. *Ann Pharmacother*. 2013;47: 1414–1419.
34. Nwulu U, Nirantharakumar K, Odesanya R, et al. Improvement in the detection of adverse drug events by the use of electronic health and prescription records: an evaluation of two trigger tools. *Eur J Clin Pharmacol*. 2013;69:255–259.
35. O'Leary KJ, Devisetty VK, Patel AR, et al. Comparison of traditional trigger tool to data warehouse based screening for identifying hospital adverse events. *BMJ Qual Saf*. 2013;22:130–138.

36. Seddon ME, Jackson A, Cameron C, et al. The Adverse Drug Event Collaborative: a joint venture to measure medication-related patient harm. *N Z Med J*. 2013;126:9–20.

37. Eggleton KS, Dovey SM. Using triggers in primary care patient records to flag increased adverse event risk and measure patient safety at clinic level. *N Z Med J*. 2014;127:45–52.

38. Hébert G, Netzer F, Ferrua M, et al. Evaluating iatrogenic prescribing: development of an oncology-focused trigger tool. *Eur J Cancer*. 2015;51: 427–435.

39. World Health Organization. Preventing Chronic Diseases: A Vital Investment. Geneva: World Health Organization; 2005. Available at: http://www.who.int/chp/chronic_disease_report/en/. Accessed July 21, 2016.

40. Institute of Medicine. Living Well With Chronic Illness: A Call for Public Health Action. Washington, DC: The National Academies Press; 2012. Available at: http://www.nap.edu/catalog.php?record_id=13272. Accessed July 21, 2016.

41. Handler SM, Hanlon JT, Perera S, et al. Consensus list of signals to detect potential adverse drug reactions in nursing homes. *J Am Geriatr Soc*. 2008;56:808–815.

42. Griffey RT, Schneider RM, Adler LM, et al. Development of an emergency department trigger tool using a systematic search and modified Delphi process. *J Patient Saf*. 2016; Jun 16. [Epub ahead of print].

43. Otero MJ, Moreno-Gómez AM, Santos-Ramos B, et al. Developing a list of high-alert medications for patients with chronic diseases. *Eur J Intern Med*. 2014;25:900–908.

44. Nair N, Aggarwal R, Khanna D. Methods of formal consensus in classification/diagnostic criteria and guideline development. *Semin Arthritis Rheum*. 2011;41:95–105.