DEVELOPMENT OF A STANDARDIZED CHART REVIEW METHOD TO IDENTIFY DRUG-RELATED HOSPITAL ADMISSIONS IN OLDER PEOPLE

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ABSTRACT

Aim: We aimed to develop a standardized chart review method to identify drug-related hospital admissions (DRA) in older people caused by non-preventable adverse drug reactions and preventable medication errors including overuse, underuse and misuse of medications: the DRA adjudication guide.

Methods: The DRA adjudication guide was developed based on design and test iterations with international and multidisciplinary input in 4 subsequent steps: literature review, evaluation of content validity using a Delphi consensus technique, a pilot test and a reliability study.

Results: The DRA adjudication guide provides definitions, examples and step-by-step instructions to measure DRA. A 3-step standardized chart review method was elaborated including 1) data abstraction, 2) explicit screening with a newly developed trigger tool for DRA in older people and 3) consensus adjudication for causality by a pharmacist and a physician using the World Health Organization-Uppsala Monitoring Centre and Hallas criteria. A 15-member international Delphi panel reached consensus agreement on 26 triggers for DRA in older people. The DRA adjudication guide showed good feasibility of use and achieved moderate inter-rater reliability for the evaluation of 16 cases by 4 European adjudication pairs (71% agreement, kappa = 0.41). Disagreements arose mainly for cases with potential underuse.

Conclusions: The DRA adjudication guide is the first standardized chart review method to identify DRA in older persons. Content validity, feasibility of use and inter-rater reliability were found to be satisfactory. The method can be used as an outcome measure for interventions targeted at improving quality and safety of medication use in older people.

What is already known about this subject

- Drug-related hospital admissions represent a growing patient safety threat in older people.
- Identifying drug-related hospital admissions in older people is complex and there is lack of a standardized approach to identify drug-related hospital admissions.

What this study adds

- We developed a standardised chart review method to measure drug-related hospital admissions in older persons.
- Content validity, feasibility of use and inter-rater reliability were found to be satisfactory.
- The method can be used as an outcome measure for interventions targeted at improving quality and safety of medication use in older people.

INTRODUCTION

Adverse drug events (ADEs) are a leading cause of iatrogenic harm globally.[1, 2] A significant proportion of ADEs results in hospitalisation and these so-called drug-related hospital admissions (DRA) have serious clinical and economic consequences.[3-6] DRA can result from non-preventable adverse drug reactions (ADR) or from preventable medication errors.

Older adults have almost a seven-fold increased risk of experiencing a DRA compared to younger persons due to several risk factors such as multi-morbidity and polypharmacy.[7] Around 70% of DRA in older people are caused by potentially preventable ADEs mainly resulting from poor medication adherence and inappropriate prescribing.[8-13] The latter includes the prescription or use of more drugs than are clinically needed (overuse), the incorrect prescription or use of drugs that are needed (misuse) and the failure to prescribe or use drugs that are needed (underuse).[14] Identifying DRA in older people is challenging because ADEs often present as common geriatric problems such as falls, confusion or renal impairment which might be due to the ageing process, underlying diseases or medications.[13, 15]

No standardised and validated method to identify DRA in older people exists in the literature. Yet measuring DRA is potentially an important issue in the light of the World Health Organisation's Global Patient Safety challenge on medication-related harm.[2] Studies have reported DRA prevalence rates ranging from 6% to 50% of all admissions in older adults.[16-20] The wide variance in prevalence rates is associated with the considerable heterogeneity in definitions and methods used to identify DRA, the study population and the setting.[20, 21] DRA identification often relies on a highly subjective and variable process and few attempts have been made to measure DRA resulting from underuse of medications.[12, 19, 22, 23]

We aimed to develop a standardized chart review method to identify DRAs resulting from ADR, overuse, misuse and underuse of medications, specific to older people: the DRA adjudication guide. In this paper we present the developmental pathway of the DRA adjudication guide and the evaluation of its content validity, feasibility of use and reliability, which are defined as desirable attributes of a quality measure by the Agency for Healthcare Research and Quality.[24]

The DRA adjudication guide will be used in 4 European centres to measure the primary outcome DRA in the OPERAM trial (http://operam-2020.eu) that will assess the impact of a pharmacotherapy optimisation intervention in 2000 multi-morbid older people.

METHODS

Design

The DRA adjudication guide was developed in 4 subsequent steps: (I) the first draft of the guide was developed based on literature review; (II) this version was subsequently refined based on evaluation of content validity by a Delphi expert panel; (III) user-feedback in a pilot test and (IV) a reliability study (Figure 1).

Literature review

Two literature searches were performed in PubMed by the first author for articles published between January 1, 1990 and August 1, 2015. Screening of titles and abstracts and data extraction was performed by the first author.

A first exploratory search aimed to review existing structured ADE or DRA identification approaches to inform the development of the overall DRA identification strategy. The search included the following medical subject headings (MeSH): 'Patient admission', 'Drug-related side effects and adverse reactions', 'Quality assurance, Health Care', 'Patient outcome assessment'. Studies published in English, French or Dutch that focused on defining, identifying and/or characterizing ADE or DRA in the adult in-hospital setting were included.

A second literature search aimed to review common causes for DRA in older people to inform the development of a trigger tool for DRA in older people for inclusion in the DRA adjudication guide. To improve efficiency and to standardize identification of ADEs, trigger-based chart review has been advocated as the premier ADE identification approach.[25-27] Triggers are defined as 'occurrences, prompts or flags' found upon chart review that 'trigger' further investigation to determine the presence or absence of an adverse event.[28] Trigger tools have been designed for a variety of clinical settings but to our knowledge, no trigger tool for identifying DRA in older people exists. To compile a preliminary trigger tool, the second literature search aimed to identify common causes for DRA in older people and to review

previously developed adverse event triggers tools designed for other settings. PubMed was searched using the following search terms and/or combinations: 'Aged'[MeSH], 'Drug-Related Side Effects and Adverse Reactions'[MeSH], 'Hospitalization'[MeSH], 'Trigger'[All fields], 'Adverse drug events trigger tool'[All fields], 'Pharmaceutical preparations'[MeSH], 'Underuse'[All fields], 'Prescribing omission'[All fields]. Studies on hospitalizations in people aged ≥65 years resulting from preventable ADEs and non-preventable ADRs were included. Studies on the development or evaluation of adverse event trigger tools designed for other settings were also included. Studies on DRA in patients younger than 65 years were excluded. Trigger tool studies focusing on specific patient groups such as surgical patients were also excluded.

A data extraction form was developed to document study characteristics including study aims, population, design, setting, methods used to detect ADE or DRA, causality algorithms used, professionals involved in ADE or DRA assessment, most frequent causes of DRA, most frequent medications involved or omitted in DRA, triggers and their positive predictive value.

Evaluation of content validity

Content validity refers to the relationship between an instrument's content and the construct it is intended to measure.[29] In the absence of a gold standard to measure DRA, content validity of the DRA adjudication guide was assessed by an expert panel.

First, the overall DRA identification method suggested by the guide was agreed on a consensus basis through face-to-face discussions by 3 physicians (BB, JBB, JD) and 2 clinical pharmacists (AS, OD) with expertise in geriatric pharmacotherapy and medication safety.

Secondly, a 2-round online modified Delphi survey using LimeSurvey® software was conducted to validate the triggers derived from the literature review. The Delphi method is a consensus technique that is widely used for questions addressing medication safety in older adults.[30] A modified online 2-round Delphi survey was selected in this study as a way to combine scientific rigor and pragmatism to obtain consensus from a geographically diverse expert panel. Experts were selected based on their recognised academic or clinical expertise on the subject of drug-related morbidity in older patients or were personal contacts. Of the 29 experts invited,

respectively 15 and 14 experts from 8 different countries took part in the first and second Delphi round (Table 1).

The Delphi panel was asked to assess the content validity of the preliminary trigger tool, to develop consensus on the most relevant triggers and to identify additional triggers. Furthermore the panel was asked to assess 2 screening questions for non-triggered, spontaneously detected events. In the first Delphi round participants were asked to rate, for each of the 29 triggers derived from the literature and for the 2 screening questions the 'relevance to screen for a DRA in older people' on a 5-point Likert scale (ranging from 'absolutely irrelevant' to 'absolutely relevant'; relevance was defined as 'the degree to which the item comprehensively includes the full scope of the outcome it intends to measure'). A free-text field was provided for each item, allowing comments to improve the trigger design or to suggest new triggers.

For each item, consensus measurement was based on the median Likert response and the interquartile range. The following cut-off values of consensus were defined before data analysis: consensus that a trigger should be retained if the median score on the 5-point Likert scale was ≥4 and the 25th percentile ≥4 (i.e. ≥75% of the experts considered the trigger as 'relevant'or 'absolutely relevant'); consensus that a trigger should be excluded if the median score was <3 and the 75th percentile <3 (i.e at least 75% of the experts considered the trigger as 'irrelevant' or 'absolutely irrelevant'); no consensus for triggers that failed to meet either of the latter cut-off values.

Triggers that were accepted or rejected unanimously after the first round were not presented in the second round. In the second Delphi round, participants were asked to rate the triggers for which revisions were suggested in the first round. Furthermore, participants were asked to re-evaluate the equivocal triggers on the 5-point Likert scale, taking into account the groups' responses. Participants were provided with a reminder of their own responses from round 1, the median group rating and interquartile range and a summary of the comments made by participants. Equivocal triggers that were rated equivocal again, were not included in the final trigger tool (Supporting Information S1).

Pilot test

A pilot test was performed aimed at ensuring that the newly developed DRA adjudication guide was a workable instrument and to identify points for improvement. For this purpose, the DRA adjudication guide was piloted independently by a geriatrician and a pharmacist from one centre (JBB, ST). For the pilot test, 15 cases from a medical record database of frail older patients admitted to a teaching hospital were randomly selected by using a random number generator. The reviewers' suggestions for improvement were discussed within the OPERAM research team and modifications were subsequently implemented in the DRA adjudication guide.

Reliability study

A reliability study was conducted to assess whether the DRA adjudication guide yields reproducible results when applied by different raters. Raters were OPERAM research team members with clinical and/or research experience in geriatric medicine. Pairs of raters in 3 centres (Brussels, Cork and Utrecht) consisted of a pharmacist and physician (SM, FV, IW, AV, SC, DOM) whereas in 1 centre (Bern) the pair was composed of physicians only (CF, CS). The raters had no prior experience in using the DRA adjudication guide and were provided with a video training tutorial (https://www.youtube.com/watch?v=fadmO-WcCHM).

For the purpose of the reliability study, each centre provided 4 cases of multi-morbid older patients including the discharge and/or admission letter, laboratory values and medication lists. Translation of the cases was performed by OPERAM research team members from their mother tongue (Dutch, French, Swiss-German) to English. No formal back-translation process was undertaken.

Raters were asked to first assess the cases individually and subsequently to come to a consensus result on the case within the pair. The time needed to adjudicate a case was recorded. A dichotomous outcome variable (DRA identified yes/no) was defined and inter-rater reliability was determined by calculating percentage agreement and agreement corrected for chance *between* pairs of raters from 4 European centres (Fleiss' kappa) as well as *within* each pair (Cohen's kappa) for the dichotomous outcome variable. Kappa values were interpreted as slight agreement if <0.20, fair agreement if 0.21–0.40, moderate agreement if 0.41–0.60, substantial agreement if 0.61–0.8 and almost perfect agreement if 0.81–1.00.[31] Next,

adjudication results and discrepancies were shared among all raters, who were asked for feedback. The primary goal was to determine whether discrepancies were due to difficulties in using the adjudication method, missed information or case interpretation.

Ethics approval

The ethics committee from the Cliniques universitaires Saint-Luc (Brussels, Belgium) provided approval for anonymous use of the medical record database (reference number B403201111806).

RESULTS

Literature review and development of the DRA adjudication guide

Development of the overall DRA identification strategy

Twenty-five studies on ADE or DRA identification were reviewed.[3, 7, 12, 26, 27, 32-51] Chart review by 2 or more reviewers has been considered as a gold standard in many patient safety studies because of its high ADE yield and high specificity.[32] To evaluate the relationship between drug treatment and the occurrence of an adverse event, several causality assessment methods have been developed. No causality assessment method is universally accepted but expert judgement is the most widely used.[47] Chart review is however often conducted in an implicit and unstructured way, resulting in low inter-rater reliability.[32] Our method selected to adjudicate DRA therefore involved a structured chart review with the aid of a trigger tool to improve efficiency and standardization in ADE detection.[25] Previous research has demonstrated that by restricting ADE detection to trigger tools only, whole classes of ADE can be missed.[32, 52, 53] Therefore two screening questions for non-triggered, spontaneously detected events were also compiled.

A 3-step approach for DRA identification based on chart review was elaborated (Figure 2). The 3 steps include: 1) abstraction of a standardized list of data from the medical record into an electronic case report form, the main source documents including the admission and discharge letter, laboratory values and medication lists; 2) explicit screening for ADE(s) that are potential DRA with the DRA trigger tool and screening questions for non-triggered events; 3) adjudication: consensus judgement in terms of ADE causality and ADE contribution to hospital

admission with the World Health Organisation-Uppsala Monitoring Centre (WHO-UMC) and Hallas criteria respectively.[36, 54] Steps 2 and 3 are performed by an adjudication pair composed of a pharmacist and a physician given their complementary knowledge and experience.[55, 56] Definitions, step-by-step instructions for use and examples are contained in the DRA adjudication guide (Supporting Information S2).

Development of the trigger tool

Twenty-three studies on common causes of DRA in older people[3, 7-10, 12, 16, 23, 38, 51, 57-69] and 12 trigger tools studies were reviewed.[30, 52, 53, 70-78] Based on the information from the literature and their own clinical expertise, the research team compiled a preliminary list of 29 triggers and 2 screening questions for non-triggered events related to ADR, overuse, underuse or misuse of medications. Key considerations for selecting the triggers were the reported positive predictive value of the triggers, severity (i.e. the trigger should be severe enough to result in hospital admission) and ease of detection. The triggers were divided in 3 categories including diagnoses, abnormal laboratory values and 'other' triggers (e.g. antidote use). Each trigger was elaborated with potential causative drugs or potential causes for drug underuse based on the STOPP/START criteria version 2 and by consulting pharmacology and pharmacotherapy references.[79] Consequently, each trigger consists of a diagnosis or abnormal laboratory value and a corresponding list of potential causative drugs or causes for drug underuse allowing explicit chart screening for DRA.

Evaluation of content validity

None of the 29 triggers or screening questions were removed at the end of the first round by the 15-member Delphi panel. Twenty-five triggers and 2 screening questions for non-triggered events were rated 'relevant' or 'absolutely relevant' to screen for DRA in older people. Of the items on which the group agreed, 10 triggers and 2 screening questions were adopted without alteration in the final tool, whereas 15 triggers were revised according to the participants' suggestions. Revisions included changing cut-off thresholds of laboratory values, adding or removing medications associated with a trigger or adding more detail to the triggers. Four triggers (theophylline level >20 µg/ml, rash, *Clostridium difficile* toxin positive stool, neutrophils <1400/mm^3) were rated equivocal.

After the second round, all 15 triggers with revisions were rated 'relevant' or 'absolutely relevant'. Three out of 4 equivocal triggers from the first round were rated equivocal again and these were removed from the trigger tool. The trigger 'neutrophils <1400/mm^3' was now rated relevant and was included in the final trigger tool (Supporting Information S1). Following last refinements, the final 26-item trigger tool was created (Table 2).

Pilot test

The two reviewers involved in the pilot considered the trigger tool as a workable instrument for screening for DRA. The same sets of triggers were identified by the two reviewers, however adjudication of DRA was the part where most discrepancies arose. Based on feedback from the reviewers, the following modifications were made after the pilot:

- The Naranjo algorithm and Therapeutic Failure Questionnaire [63, 80], which were proposed as causality algorithms in the DRA adjudication guide v.1, were replaced by the WHO-UMC causality criteria because they reflect clinical practice better. The WHO-UMC criteria were adapted to allow causality assessment due to medication underuse in line with Klopotowska et al.[32]
- Discharge medications were added to the list of data to abstract to aid in the detection of potential underuse.
- The DRA identification strategy and instructions for use were adapted to the process that both reviewers considered as most practical.

Reliability study

Table 3 provides the level of agreement on the presence of a DRA between all centres and within each pair per centre for 16 cases. The DRA adjudication guide achieved a moderate inter-rater reliability score *between* adjudication pairs from 4 European centres (71% agreement, Fleiss' kappa = 0.41). Agreement *within* each pair varied from fair to almost perfect agreement (69%–94% agreement, Cohens' kappa = 0.33-0.86). The mean time needed to assess a case individually was 23±6 minutes and the mean time needed for consensus discussion was 13±5 minutes.

No differences in inter-rater reliability for DRA identification were observed for triggered and non-triggered cases. Detailed analysis of the adjudication results showed that in the majority

of cases the same triggers and potential ADEs were identified but discrepancies arose mainly on the level of assessment of contribution to hospital admission. Discrepancies arose for 8 cases with more subjective assessments including 5 triggered cases with potential underuse, 2 triggered cases with contributory reasons for admission (i.e. an ADE that is not the main reason for admission but plays a substantial role in the admission)[36] and 1 case with a non-triggered DRA (Supporting Information S3).

DISCUSSION

To our knowledge the DRA adjudication guide is the first standardized instrument to identify DRA in older persons caused by ADR, overuse, underuse and misuse of medications. The DRA adjudication guide provides definitions, examples and step-by-step instructions to measure DRA.

DRA identification is based on chart review with the aid of a trigger tool followed by structured consensus judgement, an approach that has been used successfully in previous ADE studies.[25] The novelty of our method lies in the development of a trigger tool for DRA, specific to older people and allowing explicit DRA screening. The DRA adjudication guide calls for a rigorous evaluation of DRA including triggered and non-triggered events as well as non-preventable ADR and preventable medication errors, which is the desired broader focus of studying DRA.[21, 32, 52, 53] Furthermore, an adjudication pair composed of a pharmacist and a physician is a recommended approach for evaluation of ADEs.[55, 56]

To improve safety and quality of care, a valid and practical method to measure and understand a problem is a critical approach to any patient safety threat.[1, 81, 82] It has been acknowledged that patient safety measures are often based on insufficient evidence and finding a balance between scientific soundness and feasibility is a challenge.[81] We addressed these requirements by utilizing a rigorous developmental pathway based on design and test iterations combining evidence from published literature with expert opinion and user-feedback from international and multidisciplinary sources. Content validity, feasibility of use and inter-rater reliability were found to be satisfactory.

Despite the development of a standardised procedure, variability in DRA determination remains. Inter-rater reliability (IRR) *between* adjudication pairs in 4 European centres was moderate, which is the most relevant criterion as it is the consensus judgement between the pharmacist and physician that is of importance. Achieving a good IRR score for ADE identification is a challenge inherent to retrospective chart review studies, with previous adverse event studies reporting kappa scores varying from -0.077 to 0.66.[19, 32, 56, 83-85] The trigger tool allowed to detect the same triggers, yet discrepancies arose mainly on the level of assessment of contribution to hospital admission. Expert judgement using causality criteria is not devoid of individual subjective judgements.[47] Exploring the reasons for discrepancies highlighted the need for further training and standardisation of consensus procedures for more subjective adjudications such as underuse. For example, 2 out of 4 centres in the present study considered omission of a statin in a 90-year old patient admitted for myocardial infarction as a DRA, whereas there is limited evidence of benefit of statins over the age of 80-85.[86]

Our reliability study is the first one evaluating DRA by international adjudication teams, yet rater pairs only came from 4 European countries. The IRR score can be considered as a satisfactory result taking into account the following considerations: (i) participants were at the beginning of their learning curve when IRR was evaluated; (ii) composition of adjudication teams varied with regards to profession, clinical experience and experience in ADE identification. It has been shown that IRR among different professions is lower, which explains the almost perfect agreement score in the team that was composed of only physicians.[56]; (iii) cases were collected in 4 European hospitals and quality of information in source documents such as admission and discharge letters therefore varied. Furthermore, translation of cases into English was needed and was performed by research team members and not by a translation agency, which might have resulted in differences in case quality. Moreover, interpretation of cases and source documents from another country where guidelines and practices might vary, contributes to complexity. However even if the DRA adjudication procedure is applied correctly by all raters, a certain degree of disagreement is to be expected in adjudication of complex multi-morbidity cases.

The following recommendations to optimize IRR will be implemented in the OPERAM trial: (i) intensification of training and involvement of experienced clinicians in the adjudication teams, (ii) close monitoring of IRR at different time-points to identify discrepancies and (iii) prompt feedback and sharing of questions and experiences among teams.[84, 87]

The adjudication guide has several limitations. Firstly, data are collected retrospectively and hence are limited to the information available in medical charts. For assessment of underuse in particular, information on patient preferences, life expectancy or adherence are often undocumented in medical charts.[81] To obtain an accurate picture, prospective identification of DRA in combination of with patient, caregiver and healthcare professional interviews would be desirable.[33, 88, 89] Hindsight bias is another limitation of retrospective chart review; knowing the outcome and its severity may influence the adjudication of causation.[90] Furthermore, the response rate of the experts invited to the Delphi survey was limited to 48%, nevertheless the Delphi panel represented various disciplines and countries. Moreover, we did not specify an age cut-off for older people in the Delphi survey, which might have influenced the outcome. However in the literature review on which the preliminary list of triggers was based, we only included studies of patients aged 65 years and older. We therefore believe that our trigger tool is broad enough to trigger DRA in people aged 65 years and older, which corresponds to the World Health Organization's age cut-off to define older people. Finally, we did not compare the adjudication results from the 4 teams with a gold standard such as adjudication by an expert panel.

The DRA adjudication guide is time-consuming for use in clinical practice and is designed for research purposes. The method may be used to study incidence of DRA or drug-related emergency department visits or as outcome measure for the evaluation of interventions to optimize pharmacotherapy in older people.

The performance of the trigger tool for detecting DRA has not yet been evaluated. A future study will determine the predictive validity, sensitivity and specificity of the trigger tool to detect DRA in the OPERAM dataset. An electronic trigger tool with improved specificity consisting of drug-disease combinations could help identify patients at risk of medication-related harm in electronic patient records.[91]

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CONTRIBUTORS

ST conceptualized and designed the study, performed the literature review and pilot test, performed analysis and interpretation of data resulting from the validation, pilot and reliability studies and drafted the DRA adjudication guide. OD and AS conceptualized and designed the study, participated in the development and validation of the DRA adjudication guide and performed analysis and interpretation of data resulting from the validation, pilot and reliability studies. JBB participated in the development and validation of the DRA adjudication guide and

performed the pilot test. BB, JD and NR participated in the development and validation of the DRA adjudication guide. SM, FV, IW, AV, CF, CS, SC and DOM participated in the reliability study. ST drafted the initial manuscript with contributions from OD, AS, JBB, BB, SM, DOM, SC, JD, CF and IW. All authors read and approved the final manuscript.

CONFLICTS OF INTEREST

All authors have no conflicts of interest to declare.

TABLES

Table 1: Characteristics of Delphi panellists

	Experts invited n (%)	Participation Round 1 n (%)	Participation Round 2 n (%)
Total	29 (100)	15 (52)	14 (48)
Profession, area of expertise			
Physician, geriatric medicine	10 (34)	6 (40)	6 (43)
Physician, internal medicine	8 (28)	2 (13)	2 (14)
Physician, primary care	1 (3)	-	-
Pharmacist, geriatric medicine	5 (17)	4 (27)	3 (21)
Pharmacist, medication safety	5 (17)	3 (20)	3 (21)
Country			
Belgium	5 (17)	5 (33)	4 (29)
Canada	1 (3)	1 (7)	1 (7)
Italy	1 (3)	-	-
Ireland	2 (7)	1 (7)	1 (7)
France	2 (7)	1 (7)	1 (7)
Switzerland	4 (14)	2 (13)	2 (14)
The Netherlands	6 (21)	3 (20)	3 (21)
United Kingdom	2 (7)	1 (7)	1 (7)
United States	6 (21)	1 (7)	1 (7)
Sex			
Female	15 (52)	9 (60)	8 (57)
Male	14 (48)	6 (40)	6 (43)

Table 2: Trigger tool for DRA in older persons

TRIGGER TOOL TO SCREEN FOR DRUG-RELATED HOSPITAL ADMISSIONS IN OLDER PERSONS	
Trigger on admission up to 48h of admission	**Suspected causative drugs or causes for underuse**
Diagnoses	
Fall and/or fracture	**Use** of any of the following drugs? ☐ Benzodiazepines ☐ Non-benzodiazepine hypnotics e.g. zopiclone, zolpidem ☐ Antipsychotics ☐ Antidepressants ☐ Sedating antihistamines ☐ Opioids ☐ Anticholinergic drugs[a] ☐ Other (*Please specify*):
	Use of any drugs causing orthostatic hypotension? ☐ Calcium channel blockers ☐ Diuretics ☐ α1-receptor blockers ☐ Nitrates ☐ β-blockers ☐ ACE-inhibitors ☐ Angiotensin receptor blockers ☐ Direct renin inhibitors (e.g. aliskiren) ☐ Anti-Parkinson drugs ☐ Antidepressants (mainly tricyclic) ☐ Antipsychotics ☐ Gliflozines (SGLT2-inhibitors) ☐ Other (*Please specify*):
	If a fall is caused by hypoglycaemia, look for **use** of drugs contributing to hypoglycaemia (check trigger hypoglycaemia)
	Underuse of any of the following drugs in patients with known osteoporosis and/or history of fragility fracture(s) and/or Bone Mineral Density T-scores of -2.5 or lower in multiple sites? ☐ 800 IU Vitamin D/day (+ 1000-1200 mg calcium/day if dietary intake is <1200-1000mg/day) ☐ Bone anti-resorptive therapy (e.g. bisphosphonates, strontiumranelate,teriparatide, denosumab)
	Underuse of any of the following drugs in patients on corticosteroid therapy ≥ 3 months? ☐ 800 IU Vitamin D/day (+ 1000-1200 mg calcium/day if dietary intake is <1200-1000mg/day) ☐ Bisphosphonates
	Underuse of vitamin D in patients who are housebound and/or experiencing falls or with osteopenia with Bone Mineral Density T-score between -1 and -2.5 in multiple sites?

Confusion/delirium[b]	**Use** of any of the following drugs? ☐ Benzodiazepines ☐ Non-benzodiazepine hypnotics e.g. zopiclone, zolpidem ☐ Antipsychotics ☐ Anti-epileptics ☐ Antihistamines (H1- and H2-receptor blockers) ☐ Antidepressants	☐ Opioids ☐ Dopaminergic agonists ☐ Digoxin ☐ Fluoroquinolones *(dose adjustment in renal impairment required)* ☐ Acetylcholinesterase-inhibitors (new onset confusion in patients with dementia) ☐ Other anticholinergic drugs[a] (*Please specify*):
	Abrupt discontinuation/rapid dose reduction of any of the following drugs? ☐ Benzodiazepines ☐ Non-benzodiazepine hypnotics e.g. zopiclone, zolpidem ☐ Corticosteroids ☐ Dopaminergic agonists ☐ Antidepressants	☐ Opioids ☐ Lithium ☐ Antipsychotics ☐ Other (*Please specify*):
Acute renal impairment[b]	**Use** of any of the following drugs? ☐ Non-steroidal anti-inflammatory drugs ☐ ACE-inhibitors ☐ Angiotensin receptor blockers ☐ Diuretics ☐ Sulphonamides ☐ Cephalosporins ☐ Quinolones (ciprofloxacin) ☐ Aminoglycosides ☐ Vancomycin ☐ Pentamidine	☐ Rifampicin ☐ Acyclovir, valacyclovir, gancyclovir, valgancyclovir, foscarnet, cidofovir ☐ Lithium ☐ Calcineurin Inhibitors (e.g. cyclosporine, tacrolimus) ☐ Cisplatin ☐ Radiology contrast medium ☐ Amphotericin ☐ Bisphosphonates ☐ Other nephrotoxic drugs (*Please specify*):
Dehydration	Use of any of the following drugs? ☐ Diuretics ☐ Gliflozines (SGLT2-inhibitors) ☐ Laxatives	☐ Any drugs causing vomiting ☐ Any drugs causing diarrhoea ☐ Other (*Please specify*):

Bleeding[b]	**Use** of any of the following drugs? ☐ Antiplatelets ☐ Vitamin K antagonists ☐ Direct oral anticoagulants ☐ Unfractionated heparin ☐ Low molecular weight heparins ☐ Selective serotonin reuptake inhibitors ☐ Non-steroidal anti-inflammatory drugs ☐ Other (*Please specify*): ☐ **Underuse** of proton pump inhibitors prophylaxis while - NSAIDs monotherapy (≥ 70 years old) or on concurrent NSAIDs and/or antiplatelets and/or corticosteroids - NSAIDs or antiplatelet or corticosteroids monotherapy with a history of peptic ulcer disease/gastrointestinal bleeding while on these drugs
Stroke	**Underuse** of any of the following drugs in patients with known chronic atrial fibrillation? ☐ Vitamin K antagonists ☐ Direct oral anticoagulants (except valvular atrial fibrillation) **Underuse** of adequate antihypertensive therapy? * *Note*: Adequate antihypertensive therapy is defined according to the recommendations for older patients in the 2013 European ESH/ESC guidelines for the management of arterial hypertension. **Underuse** of any of the following drugs in patients with history of coronary, cerebral or peripheral vascular disease? ☐ Antiplatelets ☐ Statins** (unless end-of-life or > 85 years old) ***Note*: Evidence for statin treatment above the age of 80-85 years is limited and clinical judgement should guide decisions in the very old, taking into account life expectancy, serious adverse events, possible drug interactions. Low to moderate intensity statin regimens are recommended. (**low**: simvastatin 10mg, pravastatin 10-20mg, fluvastatin 20-40 **moderate**: atorvastatin 10-20mg, Rosuvastatin 5-10mg, Simvastatin 20-40mg, pravastatin 40-80 mg, Fluvastatin 80 mg, Fluvastatin 40 mg BID)
Thromboembolic event (DVT or PE)	**Underuse** of adequate anticoagulation? ☐ Unfractionated heparin ☐ Low molecular weight heparins ☐ Direct oral anticoagulants ☐ Vitamin K antagonists
(Recurrent) myocardial infarction or ischaemic disease	**Underuse** of cardiovascular secondary prevention? ☐ Antiplatelets (unless already anticoagulated) ☐ Statins** (unless end-of-life or > 85 years old) ☐ β-blocker/ACE-inhibitor or angiotensin receptor blocker /adequate anti-anginal therapy in case of ischaemic disease **Underuse** of adequate antihypertensive therapy? *

Heart failure exacerbation	**Use** of any drugs that could precipitate heart failure exacerbation? ☐ Non-steroidal anti-inflammatory drugs ☐ Corticosteroids ☐ Thiazolidinediones (glitazones) ☐ Non-dihydropyridine calcium channel blockers (verapamil, diltiazem) ☐ Sodium-containing formulations (effervescent, dispersible and soluble medications) ☐ Other (*Please specify*):
	Underuse of any of the following drugs? ☐ β-blockers[¥] ☐ ACE-inhibitors[¥] ☐ Diuretics *Note*: [¥] β-blocker and ACE-inhibitors in heart failure due to left ventricular dysfunction
COPD exacerbation	**Use** of any drugs that could precipitate COPD exacerbation? ☐ Benzodiazepines with acute or chronic respiratory failure ☐ Opioids ☐ Other (*Please specify*):
	Underuse of any of the following drugs? ☐ Single or dual inhaled bronchodilator therapy i.e. a β2 agonist and/or anticholinergic bronchodilator according to the GOLD (Global Initiative for Chronic Obstructive Lung Disease) grade
Uncontrolled (non-neuropathic) pain	**Underuse** of adequate pain treatment (according to the WHO analgesic ladder)? ☐ A strong opioid in moderate to severe pain if paracetamol, NSAIDs or weak opioids are not appropriate (e.g. because of insufficient pain relief) ☐ Short-acting opioids for break-through pain during treatment with long acting opioids ☐ Other (*Please specify*):
Gastrointestinal disorders (severe diarrhoea, vomiting)	**Use** of any of the following drugs? ☐ Antibiotics ☐ Laxatives ☐ Selective serotonin reuptake inhibitors ☐ Digoxin ☐ Cholinesterase-inhibitors ☐ Opioids ☐ Non-steroidal anti-inflammatory drugs ☐ Chemotherapy (*Please specify)*: ☐ Other (*Please specify*):

Major constipation or faecal impaction	**Use** of any of the following drugs? ☐ Chronic (stimulant) laxative use ☐ Opioids (look for **underuse of laxatives** with regular opioid use) ☐ Calcium antagonists (Mainly verapamil) ☐ Calcium ☐ Oral iron ☐ Aluminium antacids ☐ Atypical antipsychotics ☐ Tricyclic antidepressants ☐ Bladder antimuscarinics ☐ Other anticholinergic drugs[a] ☐ Other (*Please specify*):
Laboratory values	
INR > 5	Look for evidence of bleeding (see trigger) to determine if an adverse drug event (ADE) has occurred. A raised INR in itself is not an ADE.
Digoxin level > 2ng/ml	Look for signs or symptoms of digoxin toxicity (bradycardia, nausea, diarrhoea, confusion) to determine if a potential ADE has occurred. Not all levels above normal will result in an ADE.
Hypoglycaemia (blood glucose < 4 mmol/L or 72 mg/dl)	Look for symptoms such as lethargy, tremor, confusion, faintness or administration of intravenous or oral glucose. **Use** of any of the following drugs? ☐ Insulin ☐ Oral hypoglycaemic agents (except metformin in monotherapy) ☐ MAO – inhibitors ☐ β-blockers (masking symptoms of hypoglycaemia)
Hyperglycaemia (blood glucose > 11 mmol/L or 198 mg/dl)	**Use** of any drugs that may cause or worsen hyperglycaemia? ☐ Corticosteroids ☐ Atypical antipsychotics (mainly olanzapine & clozapine) ☐ Thiazide diuretics *less frequent* ☐ β-blockers (except carvedilol and nebivolol) *less frequent* ☐ Protease-inhibitors ☐ Calcineurin Inhibitors (cyclosporine, sirolimus, tacrolimus) ☐ Other (*Please specify*): In case hyperglycaemia is part of diabetic ketoacidosis or hyperosmolar hyperglycaemic state in a patient, review for **underuse** of insulin or oral hypoglycaemic agents.
Hyperkalaemia (K^+ > 5.5 mmol/L)	**Use** of any the following drugs? ☐ Intravenous or oral potassium ☐ Potassium-sparing diuretics ☐ ACE-inhibitors ☐ Angiotensin receptor blockers ☐ Direct renin inhibitors (e.g. aliskiren) ☐ Non-steroidal anti-inflammatory drugs ☐ Heparins (seldom, mainly when treated > 7days and concomitant other risk factors) ☐ Trimethoprim-sulfamethoxazole ☐ Cyclosporine ☐ Tacrolimus ☐ Other (*Please specify*):

Hypokalaemia (K^+ < 3 mmol/L)	**Use** of any of the following drugs? ☐ Loop diuretics ☐ Thiazide and thiazide-like diuretics ☐ Corticosteroids	☐ Laxatives ☐ Salbutamol (IV or aerosol) ☐ Theophylline ☐ Other (*Please specify*):
Hyponatraemia (Na^+ < 130 mmol/L)	**Use** of any of the following drugs? ☐ Diuretics ☐ Selective serotonin reuptake inhibitors ☐ Tricyclic antidepressants ☐ ACE-inhibitors	☐ Angiotensin receptor blockers ☐ Carbamazepine & oxcarbazepine ☐ High dose cyclophosphamide ☐ Other (*Please specify*):
White blood cells < 3000 /mm^3 or < 3 x 10^3/µL	**Use** of any of the following drugs? ☐ Carbamazepine & oxcarbazepine ☐ Antipsychotics (mainly clozapine) ☐ Thyreostatics ☐ Ganciclovir ☐ Immunosuppressants	☐ Chemotherapy (*Please specify):* ☐ Mirtazapine (first 6 weeks of treatment) ☐ Voriconazole ☐ Other (*Please specify*):
Platelet count < 50000 /mm^3 or < 50 x 10^3/µL	**Use** of any of the following drugs? ☐ Carbamazepine & oxcarbazepine ☐ Ganciclovir ☐ Unfractionated heparin ☐ Low molecular weight heparins ☐ Immunosuppressants ☐ Thienopyridines (mainly ticlopidine)	☐ Quinine sulfate ☐ Sulfamides *Less frequent* ☐ Chemotherapy (*Please specify):* ☐ Other (*Please specify*):
Neutrophils < 1400/mm^3 or < 1.4 x 10^3/µL	**Use** of any of the following drugs? ☐ Ganciclovir ☐ Antipsychotics (mainly clozapine) ☐ Thyreostatics ☐ Thienopyridines (mainly ticlopidine)	☐ Chemotherapy (*Please specify):* ☐ Other (*Please specify*):

Other	
Antidote use or treatments that suggest a potential ADE	**Use** of any of the following drugs on the day of admission? ☐ Flumazenil in a patient on benzodiazepines ☐ Naloxone in a patient on opioids ☐ Phytonadione (vitamin K) in a patient on VKA ☐ Protamine sulphate in a patient on heparins ☐ Oral or intravenous glucose or glucagon in a patient taking hypoglycaemic drugs ☐ Potassium supplements in case of hypokalaemia ☐ Sodium polystyrene (Kayexalate) in case of hyperkalaemia ☐ Adrenaline, antihistamines and corticosteroids (general drug allergy) ☐ Acetylcysteine (paracetamol overdose) ☐ Digoxin antibodies in a patient with supratherapeutic digoxin levels ☐ Oral metronidazole or vancomycin in a patient who has recently been treated with an antibiotic that may cause *Clostridium difficile* associated diarrhoea
Mention of a (potential) ADE in the medical record	Assess causality using the WHO-UMC criteria
Abrupt medication stop within 24h of admission	When medications are stopped or withheld as compared to medications taken at home, look for reasons why this was done. Abruptly stopping medications is a trigger requiring further investigation for cause. A sudden change in patient condition requiring adjustment of medications is often related to an ADE.

ADE, adverse drug event; ADR, adverse drug reaction; COPD, chronic obstructive pulmonary disease; DVT, deep vein thrombosis; FEV_1, forced expiratory volume in 1 second; ESH/ESC, European Society of Hypertension/European Society of Cardiology; INR, international normalised ratio, NSAIDS, non-steroidal anti-inflammatory drugs; PE, pulmonary embolism; VKA, Vitamin K antagonists
[a]A list of medications with clinically relevant anticholinergic properties is available in the DRA adjudication guide; [b]Detailed definition of trigger available in the DRA adjudication guide

SCREENING QUESTIONS FOR NON-TRIGGERED, SPONTANEOUSLY DETECTED EVENTS

1. Could the main or contributory reason for admission be related to a drug or recent change in medications?

☐ Adverse drug reaction (non-preventable side effect, first allergic reaction)
☐ Overuse of medication(s) (drug without an indication, too long duration of therapy, therapeutic duplication)
☐ Inappropriate discontinuation (removal or dosage decrease) leading to physiological withdrawal signs/symptoms or return of the underlying disease signs/symptoms
☐ Wrong drug
☐ Wrong dose (supratherapeutic or subtherapeutic)
☐ Clinically significant drug-drug or drug-food interactions
☐ Inappropriate monitoring
☐ Other (e.g. drug not correctly dispensed/prepared/administered)

2. Could the main or contributory reason for admission be related to underuse?

☐ Omission of an indicated drug
☐ Too short duration of medication therapy
☐ Suspected adherence concerns

Table 3: Inter-rater reliability for DRA presence between 4 adjudication pairs and per centre for the evaluation of 16 cases. *Respectively Fleiss' and Cohen's kappa were calculated to determine the level of agreement between the 4 adjudication pairs and within each centre.

Raters	% Agreement	Kappa*
4 adjudication pairs	71%	0.41
Centre 1 (2 physicians)	94%	0.86
Centre 2 (physician + pharmacist)	75%	0.42
Centre 3 (physician + pharmacist)	69%	0.33
Centre 4 (physician + pharmacist)	88%	0.74

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