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PERFORMANCE OF A TRIGGER TOOL FOR DETECTING DRUG-RELATED HOSPITAL ADMISSIONS IN OLDER PEOPLE: ANALYSIS FROM THE OPERAM TRIAL

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Authors' contributions:

Anne Spinewine, Séverine Henrard, and Lorène Zerah had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Ethics approval: The OPERAM trial has received approval from ethics committees at each site. Where needed, approval by a regulatory authority has been obtained before enrolment of the first patient. All participants and their data were handled according to the ethical principles of the Declaration of Helsinki.

Data sharing statement: Data for this study will be made available to others in the scientific community upon request after the publication date. Data will be made available for scientific purposes of researchers whose proposed use of the data has been approved by a publication committee. Data and documentation will be made available via a secure file exchange platform after approval of proposal and a data transfer agreement is signed (which defines obligations that the data requester must adhere to with regard to privacy and data handling). Partially de-identified participant data limited to the data used for this work will be made available, along with a data dictionary and annotated case report forms. For data access, please contact Pr Anne Spinewine: anne.spinewine@uclouvain.be.

Patient and public involvement: Patients were actively involved in the OPERAM trial: trial design, development of the research question, and study intervention. They were not involved again for this sub-study specifically.

ABSTRACT (N = 250)

Background: Identifying drug-related hospital admissions (DRAs) in older people is difficult. A standardized chart review procedure has recently been developed. It includes an adjudication team (physician and pharmacist) screening using 26 triggers and then performing causality assessment to determine whether an adverse drug event (ADE) occurred (secondary to an adverse drug reaction, overuse, misuse, or underuse) and whether the ADE contributed to hospital admission (DRA).

Objective: To assess the performance of those triggers in detecting DRA.

Design: Retrospective study using data from the OPERAM (OPtimising thERapy to prevent Avoidable hospital admissions in Multimorbid older people) trial.

Setting: Four European medical centres.

Subjects: Multimorbid (≥ 3 chronic medical conditions) older (≥ 70 years) inpatients with polypharmacy (≥ 5 chronic medications) were enrolled in the OPERAM trial (N = 2008) and followed for 12 months. We included patients with ≥1 adjudicated hospitalization during the follow-up.

Methods: The positive predictive value (PPV) (number of DRAs identified by trigger/number of triggers) was calculated for each trigger and for the tool as a whole.

Results: Of 1235 hospitalizations adjudicated for 832 patients, 716 (58%) had at least one trigger; an ADE was identified in 673 (54%) and 518 (42%) were adjudicated as DRAs. The overall PPV of the trigger tool for detecting DRAs was 0.66 [0.62 – 0.69].

Conclusions: This tool performs well for identifying DRAs in older people. Based on our results, a revised version of the tool was proposed but will require external validation before it can be incorporated into research and clinical practice.

Key words: trigger tool, hospital admission, drug-related side effects and adverse reaction, elderly

Key points:

- In this cohort of older patients with multimorbidity and polypharmacy, 42% of all hospitalizations at one year after the inclusion were adjudicated as drug-related hospital admissions (DRAs).
- We found that the first trigger tool (including 26 triggers) recently developed to detect DRAs due to adverse drug reactions, overuse, underuse, or misuse of medications in older patients with multimorbidity and polypharmacy performed well: the global positive predictive value (PPV) was 0.66 [0.62 – 0.69].
- The most common reasons for DRAs with a positive trigger were fall/fracture (16%), bleeding (15%) and heart failure exacerbation (13%).
- We propose a user-friendly version of the trigger tool, containing 21 triggers and the drug classes most commonly involved, in order to maximize usability and help clinicians to better identify DRAs.

INTRODUCTION

Patients aged ≥ 70 years are often exposed to polypharmacy (usually defined as the use of ≥ 5 chronic medications) in a multi-morbidity context, increasing the risk of inappropriate prescribing and adverse drug events (ADEs) [1,2]. ADEs can be defined as any incident resulting from the process of the use of medication that causes harm or injury to the patient, encompassing adverse drug reactions and medication errors (related to overuse, misuse, or underuse of prescription and non-prescription medications) [3]. Overuse is defined as the prescription or use of more drugs that are clinically needed, misuse as the incorrect prescription or use of drugs that are needed, and underuse as the failure to prescribe or use drugs that are needed [3].

Drug-related hospital admissions (DRAs) can be defined as hospitalization due to an ADE that is the main reason for or contributed substantially to a patient's hospitalization[3]. In people aged 70 years and older [2,4,5,6,7,8], 5 to 20% of hospital admissions are DRAs, of which 40 to 70% are classified as preventable (i.e. related to medication errors) [2,4,5,8,9]. The wide range in prevalence rates is associated with the considerable heterogeneity in definitions and methods used to identify DRAs, the study population, and the setting [8,10,11].

Identifying DRAs in older people is challenging because ADEs often present themselves as common geriatric problems, which might be due to the ageing process and underlying diseases [3,12,13]. Therefore, a significant proportion of DRAs are not recognized and detected as drug-related by attending physicians. This leads to underestimation of the iatrogenic burden at both individual and population levels and to missed opportunities for preventive measures [14].

The trigger tool methodology is based on a retrospective review of patient records, using triggers to identify potential ADEs associated with patient care [15,16]. Recently, a

standardized chart review method including 26 triggers was developed to identify DRAs in older people using literature review, evaluation of content validity, pilot testing and reliability assessment [3]. The process involves adjudication teams identifying ADEs and then DRAs through screening triggers. For example, the trigger "fall" is positive when the clinical situation (fall) and a potential causative drug (a benzodiazepine, for example) are both present. Then, the adjudication committee performs a causality assessment to consider the event as an ADE (or not) and then to determine if the ADE contributed to the hospitalization (DRA). Non-triggered DRAs (i.e. DRA with no trigger) can also be identified using 2 screening questions [3]. This method was used to adjudicate DRAs, by a pharmacist and physician pair, in the recent multicentre cluster randomized controlled OPERAM (OPtimising thERapy to prevent Avoidable hospital admissions in Multimorbid older people) trial [17].

Our main objective was to assess the performance of those triggers for detecting DRAs in older patients with multimorbidity and polypharmacy (global performance of the tool and individual performance of each trigger). The secondary objectives were: (1) to assess the performance of the tool for detecting ADEs and preventable DRAs, (2) to produce a revised, improved version of the tool.

METHODS

A retrospective sub-study was carried out, using data from the OPERAM trial [17].

OPERAM trial and DRA adjudication

OPERAM is a recently completed European multicentre, cluster randomized controlled trial that assessed whether a structured medication review compared to usual care reduced DRAs (primary outcome measure) in multimorbid (≥ 3 chronic medical conditions) older (≥ 70 years) patients with polypharmacy (≥ 5 chronic medications) [17]. Two thousand

and eight hospitalized patients were included from December 2016 to October 2018 in four medical centres in Bern (Switzerland), Utrecht (The Netherlands), Brussels (Belgium), and Cork (Ireland) and were followed up 12 months after inclusion. The protocol and intervention have been published previously [3,17,18,19].

In the OPERAM trial, a DRA was defined as the first hospitalization occurring within one year after enrolment that was judged to be drug-related by a blinded adjudication team [17]. For all patient-reported hospitalizations occurring after the initial discharge, detailed documentation was requested from the hospitals involved. Independent and blinded adjudication pairs of experienced pharmacists and physicians at each study site adjudicated DRAs using a three-step standardized chart review procedure [3]. This included **(**see **Appendix 1): (**i) data abstraction, (ii) screening for triggered events using the newly developed trigger tool, screening for non-triggered events using two screening questions, and (iii) adjudication in terms of ADE causality and contribution to hospital admission (DRA) [3]. The 26 triggers included in the tool were classified into three categories **(**see **Appendix 1)** [3]: diagnoses, laboratory values, and 'other' triggers. For each trigger, a list of potentially causative drugs or potential causes for drug underuse was provided. A trigger was positive when the situation and a potential causative drug (or drug lacking in case of underuse) were both present. The whole process followed by the adjudication committee was considered to be the gold standard to define an ADE and a DRA.

The adjudication committee recorded the following data in the Electronic Case Report Forms: presence/absence of (a) each of the 26 triggers, associated ADE for each positive trigger (using WHO causality criteria [20]), medication involved when an ADE was recorded, associated DRA (main reason or contributory reason), and medications involved in each DRA; (b) non-triggered events, associated ADE, associated DRA, and type of event(s) and medication(s) involved. Finally, each hospitalization classified as DRA was also classified by

type: adverse drug reactions, overuse, misuse, or underuse. Each adjudicated hospitalization could have more than one trigger, ADE, or non-triggered event.

Eligibility criteria

All patients enrolled in the OPERAM trial with at least one adjudicated hospitalization during follow-up (hospitalization longer than 24 hours, not due to a diagnostic or elective procedure for a pre-existing condition, with sufficient information for the adjudication) were included in this sub-study. For organizational reasons, hospitalizations were not always adjudicated in chronological order and a patient could have more than one adjudicated hospitalization reported as a DRA. All adjudicated hospitalizations were analysed in this sub-study.

Evaluation of the tool's performance and proposed revised list of triggers

All the triggers that led to a specific DRA were described by type of trigger, number of triggers, and percentage of suspected causative drugs and/or drug underuse. The positive predictive value (PPV) for detecting DRA and ADE was calculated for each trigger, for each category of triggers, and for the tool as a whole. Good performance was defined as PPV $\geq$ 20% [21,22], and poor performance as PPV $\leq$ 5% [23,24]. Because only positive triggers were adjudicated, we could not calculate the tool's sensitivity, specificity and negative predictive value; information was lacking on true and false negatives. Correlation between triggers was also assessed.

For the triggers 'mention of a potential ADE in the medical record' and 'abrupt medication stop within 24 hours of admission', both included in the tool's 'other' category, and for non-triggered events associated with a DRA, the tool contained no list of events or

drugs [3]. We describe these events and the drugs involved as reported by the adjudication committee.

The following principles were a priori defined for potential revision of the list of triggers, in order to improve its performance [23,24]: poorly performing triggers could be considered for removal; merging or dropping triggers could be considered in case of overlap/correlation; recurrent (≥ 5) events and related drugs identified as non-triggered events by the adjudication teams could be considered as new triggers in the revised tool. The results were discussed among research team members with the aim to reach consensus on the revised version of the tool. The team contained at least two members from each participating country, and in each country at least one member of an adjudication committee. It was decided to also propose a more clinically applicable version of the tool, by mentioning, with the triggers, only those drugs most commonly used or underused (≥ 5%) in our cohort and associated with the presence of DRAs.

Statistical analysis:

For descriptive statistics, continuous data were presented using the mean (standard deviation [SD]) for normally distributed data and the median (25%-75% interquartile range [IQR]) for non-Gaussian variables. Categorical variables were presented using numbers and percentages.

We evaluated the global positive predictive value (PPV) (95% confidence interval (CI)) of the tool for detecting DRAs, defined as the number of DRAs identified by triggers ("true positive") divided by the total number of triggers found ("true and false positive") (primary outcome). To define true and false positive, the gold standard was the decision of the adjudication committee. With the same methodology, we evaluated the global PPV (95% CI) of the tool for detecting ADEs and preventable DRAs, and the individual PPVs of each trigger

for detecting associated ADEs and DRAs. This analysis was repeated for each centre (sensitivity analyses).

Based on the description of triggered and non-triggered events adjudicated as DRAs, the PPVs of individual triggers, the correlations found between triggers (Phi coefficient), and the potential identification of additional triggers, a revised version of the tool was devised.

Statistical analyses were performed using R software version 4.0.0. A p-value < 0.05 was considered statistically significant.

RESULTS

Patient characteristics

A total of 2008 patients were included in the OPERAM trial, of whom 832 had at least one adjudicated hospitalization during the follow-up (41%) **(Figure 1).** The mean (SD) age was 79.4 (6.3) years; 489 patients (59%) were male; the median number of drugs per day (IQR) was at 11 (8 – 14) (**Table 1, Appendices 2)** and 184 (22%) patients died. All baseline characteristics are described in **Table 1.**

Triggers, DRAs, and ADEs

During follow-up of the 832 patients, there were 1235 adjudicated hospitalizations. In total, 716 hospitalizations (58%) had at least one identified trigger and 187 (15%) had at least one identified non-triggered event; 673 (55%) had at least one identified ADE and 518 were adjudicated as DRAs (42%) **(Figure 1).**

The most common reasons for DRAs (found in ≥ 10 % of cases) with a positive trigger were fall/fracture (16%), bleeding (15%), and heart failure exacerbation (13%) (**Table 2)**. The overall PPV value [CI 95%] of the tool for detecting DRAs was 0.66 [0.62 – 0.69], with a PPV value for detecting associated DRAs for all ‘diagnoses’ triggers of 0.61 [0.57 – 0.65], for

all ‘laboratory’ triggers of 0.31 [0.24 – 0.39], and for all ‘others’ triggers of 0.65 [0.58 – 0.72] (**Table 2)**. No trigger had a PPV < 0.05; one had a PPV < 0.20 (hyperglycaemia).

Of the 518 DRAs identified, 219 (42%) could be considered as preventable (due in whole or in part to overuse (N = 55, 11%), underuse (N = 135, 26%), and/or misuse (N = 45, 9%)). The tool’s overall PPV value for detecting preventable DRAs was 0.28 [0.25 – 0.32] (**Table 2, Appendix 3).**

The most common reasons for ADEs with a positive trigger were acute renal impairment (20%), fall/fracture (14%), bleeding (13%), and heart failure exacerbation (11%) (**Table 2)**. The tool’s overall PPV value for detecting ADEs was 0.87 [0.84 – 0.89] (**Table 2)**.

All individual PPV values for each trigger for detecting associated ADEs and (preventable) DRAs are described in **Table 2** and **Appendix 3.** No major differences were found between the centres (**Appendix 4**).

Revised trigger tool

The description of all triggered and non-triggered events responsible for a DRA are in **Appendix 5**.

Predictable overlaps were found between: (1) the triggers ‘INR [International Normalized Ratio] > 5.0’ and ‘bleeding’, (2) the trigger ‘digoxin level > 2 ng/ml’ and the triggers ‘confusion/delirium’, ‘gastrointestinal disorders’, and ‘antidote use’, (3) the trigger ‘hypoglycaemia’ and the triggers ‘fall/fracture’, ‘confusion/delirium’, ‘gastrointestinal disorders’, and ‘antidote use’, (4) the triggers ‘hyperkalaemia’ and ‘acute renal impairment’. Accordingly, we removed four triggers (INR, digoxin, hypoglycaemia, and hyperkalaemia) from the revised version (**Table 3, Appendices 5 and 6**). In addition, correlations and overlaps were found between the triggers ‘WBC [White Blood Cells] < 3000/mm3’, ‘Platelet count < 50000/mm3’, and ‘Neutrophils < 1400/mm3’ **(Appendices 5 and 6)**. We merged

these three into one new trigger in the revised version (**Table 3, Appendices 5 and 6**): 'Pancytopenia or anomaly on one of the three lines: leucopenia, thrombopenia, anaemia'. Because the PPV of hyperglycaemia for detecting DRAs was 0.12 [0.05 – 0.24], i.e. the only PPV < 0.20, we removed this trigger from the revised version.

The description of the others triggers and the non-triggered events (**Appendix 5)**, allowed us to identify four recurrent events with drugs involved: 'infection' (N = 66), 'liver disorders' (N = 15), 'orthostatic hypotension' (N = 9), and 'seizures or movement disorders' (N = 7). In the revised tool, 'orthostatic hypotension' was added to the 'fall/fracture trigger' category, and three new diagnostic triggers were created (**Table 3, Appendices 5 and 6**). The list of potential causative drugs or potential causes for underuse associated with these new triggers was based on the drugs reported by the adjudication committee and in the literature [25,26,27]. To enable automation of the tool, and because this trigger can be identified using the non-trigger question: "could the main or contributory reason for admission be related to a drug or recent change in medications?", we removed 'Abrupt medication stop within 24 hours of admission' from the revised version (**Table 3, Appendices 5 and 6**).

The final revised version (presented in **Table 3**) includes 21 triggers (6 deleted, 3 combined, 3 added), each of which includes a list of potential causative drugs or potential causes for drug underuse (16 'diagnoses triggers', 3 'laboratory values' triggers, and 2 'other' triggers).

A clinically applicable version of this revised tool, with the most commonly used or underused drugs (≥ 5%) in our cohort, is presented in **Table 4.** Hypokalaemia being rare in this cohort (only two events), we have kept the use of diuretics and laxatives as potential causes for this trigger, even though they were not found in this cohort.

DISCUSSION

In a European geriatric cohort of older patients, 42% of hospitalizations were adjudicated as drug-related. Our study shows that the trigger tool recently developed for detecting DRAs in older patients with multimorbidity and polypharmacy performed well, with a global PPV of 0.66 [0.62 – 0.69]. 'Diagnoses' triggers and 'others' triggers performed better than 'laboratory values' triggers.

PPV is highly influenced by prevalence and there are no consensus definitions of good and bad PPVs. After consulting the literature [21,22,23,24], we defined good and bad performance by cut-offs of 20% and 5% respectively. In our study, all PPVs for detecting ADEs and 96% of PPVs for detecting DRAs were equal to or greater than 20%; none were less than 5%. Moreover, the methodology used to assess the tool was gold-standard (adjudication committee)[28]. The international evaluation of the tool in four European centres confirms the external validity of our results.

Two studies have reported performance data for two tools designed to identify DRAs. The QUADRAT study (QUick Assessment of Drug-Related Admissions over Time) [29,30] used as its triggers a computerized extraction of pairs of drugs and reasons for hospitalization; these were assessed manually to determine whether they represented DRAs. The cohort was younger (mean age 69.5 years) than ours and the evaluation only examined ADEs due to overuse. Global PPV was lower than ours, at 0.48 [0.47 – 0.49]. The reasons found for DRAs and the associated drugs [30] were either included in our tool or have been added to the revised tool. The AT-HARM10 tool (Assessment Tool for identifying Hospital Admissions Related to Medications) [31] was designed as a questionnaire with ten yes/no answers to detect possible DRAs. Some of the questions are the same as or similar to the screening questions for non-triggered events. Explicit lists with medication-specific triggers or clinical rules were excluded, to make the tool less time-consuming. AT-HARM10 had an overall PPV of 73%, but the population in which it was evaluated was not reported nor were the types of

DRAs identified; this limits the external validity of their results. Moreover, due to its more implicit nature, the AT-HARM10 tool cannot be used in health care databases.

Other trigger tools found in the literature were designed to detect ADEs, usually in an adult population [15,32,33]. Recently, two trigger tools for detecting ADEs among older patients have been proposed and evaluated [23,24,34,35]. The Chinese trigger tool [23] has 20 triggers in five categories (laboratory index, antidotes, clinical symptoms, intervention, and other) and an overall PPV of 28.5%; the Spanish trigger tool [24] has 32 triggers in five categories (care, antidotes/treatments, medication concentrations, abnormal laboratory values, and emergency department) and an overall PPV of 22.1%. Neither included a list of potential causative drugs or potential causes for drug underuse; this may explain the better performance of our tool.

There are limitations to our study that are inherent to the trigger methodology applied. Firstly, adjudications were retrospective, so data were limited to information in medical records. Secondly, although researchers have been trained to apply the three-step chart review method, a degree of subjectivity remains. Thirdly, because only positive triggers were adjudicated, we could not calculate the tool's sensitivity, specificity and negative predictive value. Fourthly, because PPVs are influenced by prevalence, our results are valid in an older multimorbid population with polypharmacy. Fifthly, because a number of DRAs have not been captured (non-triggered DRAs), it should be remembered that this tool is an aid to physicians but cannot replace clinical experience. Finally, PPVs for preventable DRAs were lower because the tool was created to detect all (and not just preventable) DRAs.

Future implications:

There are several perspectives opened up by our study. One is the need for external validation of the revised tool using another cohort of multimorbid older patients [36]:

feasibility and performance of the tool. Another is that, from our revised tool, algorithms could be created to better identify DRAs in older patients using healthcare databases. Better identification of DRAs is important for researchers seeking to accurately assess the iatrogenic burden on healthcare resources and to evaluate the impact of risk minimization measures.

The trigger tool remains time-consuming, so we also developed a user-friendly version that could help clinicians to identify DRAs more effectively.

CONCLUSION :

In this cohort of older patients with multimorbidity and polypharmacy, 42% of hospitalizations were adjudicated as DRAs. We found that the first trigger tool recently developed to detect DRAs due to adverse drug reactions, overuse, underuse, and misuse of medications in older patients performed well. Based on our results, a revised version of the tool was proposed but will require external validation before it can be incorporated into research and clinical practice.

Figure legends:

Figure 1: Flow chart

Table legends:

Table 1: Baseline characteristics of older patients with at least one adjudicated hospitalization during follow-up

Table 2: Global and individual performances of triggers for detecting adverse drug events and drug-related hospital admission during follow-up

Table 3: The proposed revised version of the trigger tool for identifying drug-related hospital admissions in older patients

Table 4: The clinically applicable revised version of the trigger tool for identifying drug-related hospital admissions in older patients

Supplement legends:

Appendix 1: Three-step approach for identifying drug-related hospital admissions in older patients and first version of the trigger tool for identifying drug-related hospital admissions in older patients

Appendix 2: International Classification of Diseases, 10th revision (ICD-10) codes used to identify comorbid conditions during the index hospitalization **and** Anatomical Therapeutical Chemical (ATC) codes used to identify the drugs during the index hospitalization

Appendix 3: Global and individual performances of triggers for detecting drug-related hospital admissions and preventable drug-related hospital admissions during follow-up

Appendix 4: Global and individual performances of triggers for detecting adverse drug events and drug-related hospital admission during follow-up, overall and by OPERAM centre

Appendix 5: Description of triggers and medication involved leading to drug-related hospital admissions and new proposals (in blue or red) for the trigger tool

Appendix 6: First version and revised version of trigger tool

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Table 1: Baseline characteristics of older patients with at least one adjudicated hospitalization during the follow-up

	Total **N = 832** Mean +/- SD or Median [P25; P75] or n (%)
Age (years)	79 +/- 6
Male	489 (59)
Country	
Belgium	132 (16)
Ireland	164 (20)
The Netherlands	192 (23)
Switzerland	344 (41)
BASELINE CHARACTERISTICS	
Medical history	
Dementia	41 (5)
Depression	42 (5)
Stroke	57 (7)
Hypertension	355 (43)
Diabetes	289 (35)
Atrial fibrillation	166 (19)
Coronary artery disease	147 (18)
Heart failure	157 (19)
Chronic renal failure	38 (5)
Chronic hepatic failure	24 (3)
COPD	37 (4)
Cancer	216 (26)
Bleeding	40 (5)
Thromboembolic disease	51 (6)
Charlson comorbidity index	5 [4 – 7]
Hospitalizations during the last year	487 (58)
Medications on index admission*	
Number of drugs per day	11 [8 – 14]
Oral antithrombotics	577 (69)
Antidiabetic drugs	262 (32)
Diuretics	450 (54)
Beta-blocking agents	482 (58)
Agents acting on the renin angiotensin system	474 (57)
Calcium channel blockers	227 (27)
Lipid modifying agents	480 (58)
Analgesics	359 (43)
NSAIDs	49 (6)
Psycholeptics	231 (28)
Antidepressants	209 (25)

Abbreviations: COPD: chronic obstructive pulmonary disease, NSAID: Non-steroidal anti-inflammatory drug
* The medication classes listed are those that are frequently used in older people and frequently listed among the potential causative medications of the trigger tool.

Table 2: Global and individual performances of triggers for detecting adverse drug events and drug-related hospital admissions during follow-up

	Number of triggers	Numbers of confirmed ADEs	PPV [CI 95%]	Numbers of confirmed DRAs	PPV [CI 95%]
TRIGGER – DIAGNOSES*					
Fall/fracture	122	95	0.78 [0.69 – 0.85]	82	0.67 [0.58 – 0.75]
Confusion/delirium	63	39	0.62 [0.49 – 0.74]	27	0.43 [0.30 – 0.56]
Acute renal impairment	166	136	0.82 [0.75 – 0.87]	48	0.29 [0.29 – 0.36]
Dehydration	54	44	0.81 [0.69 – 0.91]	29	0.54 [0.40 – 0.67]
Bleeding	90	88	0.98 [0.92 – 1.00]	76	0.84 [0.75 – 0.91]
Stroke	10	7	0.70 [0.35 – 0.93]	7	0.70 [0.35 – 0.93]
Thromboembolic event	3	2	0.67 [0.09 – 0.99]	1	0.33 [0.01 – 0.91]
Myocardial infarction or ischaemic disease	32	28	0.88 [0.71 – 0.96]	18	0.56 [0.38 – 0.74]
Heart failure exacerbation	101	73	0.72 [0.62 – 0.81]	66	0.65 [0.55 – 0.75]
COPD exacerbation	60	40	0.68 [0.53 – 0.78]	37	0.62 [0.48 – 0.74]
Uncontrolled non-neuropathic pain	36	30	0.83 [0.67 – 0.94]	22	0.61 [0.43 – 0.77]
Gastrointestinal disorders	66	44	0.67 [0.54 – 0.78]	27	0.41 [0.29 – 0.54]
Major constipation or faecal impaction	40	34	0.85 [0.70 – 0.94]	14	0.35 [0.21 – 0.52]
At least one 'diagnoses' trigger	**622**	**506**	**0.81 [0.78 – 0.84]**	**381**	**0.61 [0.57 – 0.65]**
TRIGGER – LABORATORY VALUES*					
INR > 5	8	8	1.00 [0.63 – 1.00]	6	0.75 [0.35 – 0.97]
Digoxin level > 2 ng/ml	0	0		0	
Hypoglycaemia	11	8	0.73 [0.39 – 0.94]	4	0.36 [0.11 – 0.69]
Hyperglycaemia	50	34	0.68 [0.53 – 0.80]	6	0.12 [0.05 – 0.24]
Hyperkalaemia	36	29	0.81 [0.64 – 0.92]	11	0.31 [0.16 – 0.48]
Hypokalaemia	10	9	0.90 [0.55 – 1.00]	2	0.20 [0.03 – 0.56]

Continuation of Table 2

	Number of triggers	Numbers of confirmed ADEs	PPV [CI 95%]	Numbers of confirmed DRAs	PPV [CI 95%]
Hyponatraemia	57	45	0.79 [0.66 – 0.89]	18	0.32 [0.20 – 0.45]
WBC < 3000/mm3	12	12	1.00 [0.74 – 1.00]	8	0.67 [0.35 – 0.90]
Platelet count < 50000/mm3	7	7	1.00 [0.59 – 1.00]	5	0.71 [0.29 – 0.96]
Neutrophils < 1400/mm3	9	9	1.00 [0.66 – 1.00]	6	0.67 [0.30 – 0.93]
At least one 'laboratory values' trigger	**169**	**136**	**0.80 [0.74 – 0.86]**	**53**	**0.31 [0.24 – 0.39]**
TRIGGER – OTHERS*					
Antidote use or treatments that suggest a potential ADE	21	19	0.90 [0.70 – 0.99]	16	0.76 [0.53 – 0.92]
Mention of a potential ADE in the medical record	136	128	0.94 [0.89 – 0.97]	96	0.71 [0.62 – 0.78]
Abrupt medication stops within 24 h of admission	119	107	0.90 [0.83 – 0.95]	77	0.65 [0.55 – 0.73]
At least one 'others' trigger	**205**	**191**	**0.93 [0.89 – 0.96]**	**134**	**0.65 [0.58 – 0.72]**
TOTAL					
At least one trigger	**716**	**621*** **	**0.87 [0.84 – 0.89]**	**471*** **	**0.66 [0.62 – 0.69]**
For preventable DRAs, at least one trigger**	**716**			**205*** **	**0.28 [0.25 – 0.32]**

*A trigger is positive when the diagnosis or lab value AND a potential causative drug (or drug lacking in case of underuse) are present.

** Drug-related hospital admission was considered preventable when deemed by the adjudication committee as potentially related to medication errors (drug overuse, underuse or misuse)

*** Number of ADE / DRA identified from triggered events and therefore included in the PPV calculation

Abbreviations: ADE: adverse drug events; DRA: drug-related admission; INR: international normalized ratio; PPV: positive predictive value; WBC: white blood count

Table 3 : The proposed revised version of the trigger tool for identifying drug related hospital admissions in older patients

TRIGGER TOOL FOR SCREENING FOR DRUG-RELATED HOSPITAL ADMISSIONS IN OLDER PERSONS	
Trigger on admission or up to 48 hours of admission	**Suspected causative drugs or causes for underuse**
Diagnoses	
Fall and/or fracture and/or orthostatic hypotension	**Use** of any of the following drugs? □ Benzodiazepines □ Non-benzodiazepine hypnotics e.g. zopiclone, zolpidem □ Antipsychotics □ Antidepressants □ Sedating antihistamines □ Opioids □ Anticholinergics □ Other (*Please specify*):
	Use of any drugs that cause orthostatic hypotension? □ Direct renin inhibitors (e.g. aliskiren) □ Anti-Parkinson drugs □ Antidepressants (mainly tricyclic) □ Antipsychotics □ Calcium channel blockers □ Diuretics □ β blockers □ ACE inhibitors □ Angiotensin receptor blockers □ Nitrates □ Gliflozines (SGLT2-inhibitors) □ α1-receptor blockers □ Other (*Please specify*):
	If a fall is caused by hypoglycaemia, look for **use** of drugs that contribute to 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/d (+ 1000-1200 mg calcium/day if dietary intake is <1200-1000mg/day) □ Bone anti-resorptive therapy (e.g. bisphosphonates, strontium, ranelate, teriparatide, or denosumab)

	Underuse of any of the following drugs in patients on corticosteroid therapy ≥ 3 months? ☐ 800 IU Vitamin D/d (+ 1000-1200 mg calcium/day if dietary intake is <1200-1000mg/day) ☐ Bisphosphonates **Underuse** of vitamin D in patients who are housebound and/or have experienced falls or with osteopenia with Bone Mineral Density T-score between -1 and -2.5 in multiple sites?
Confusion/delirium	**Use** of any of the following drugs? ☐ Benzodiazepines ☐ Non-benzodiazepine hypnotics e.g. zopiclone, zolpidem ☐ Antipsychotics ☐ Antiepileptics ☐ Antihistamines (H1- and H2-receptor blockers) ☐ Antidepressants ☐ Opioids ☐ Dopaminergic agonists ☐ Acetylcholinesterase-inhibitors (new-onset confusion in patients with dementia) ☐ Digoxin ☐ Fluoroquinolones *(dose adjustment in renal impairment required)* ☐ Other anticholinergics **Abrupt discontinuation/rapid dose reduction** of any of the following drugs? ☐ Benzodiazepines ☐ Non-benzodiazepine hypnotics e.g. zopiclone, zolpidem ☐ Antipsychotics ☐ Dopaminergic agonists ☐ Antidepressants ☐ Lithium ☐ Opioids ☐ Corticosteroids ☐ Other (*Please specify*):
Acute renal impairment	**Use** of any of the following drugs? ☐ Lithium ☐ ACE inhibitors ☐ Angiotensin receptor blockers ☐ Diuretics ☐ Sulphonamides ☐ Cephalosporins ☐ Quinolones (ciprofloxacin) ☐ Aminoglycosides ☐ Vancomycin ☐ Pentamidine ☐ Rifampicin ☐ Acyclovir, valacyclovir, gancyclovir, valgancyclovir, foscarnet, cidofovir ☐ Amphotericin ☐ Calcineurin inhibitors (e.g. cyclosporine, tacrolimus) ☐ Cisplatin ☐ Radiology contrast medium ☐ Bisphosphonates ☐ Non-steroidal anti-inflammatory drugs ☐ 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 (i.e. major bleeding and clinically relevant non-major bleeding)	**Use** of any of the following drugs?	
	☐ Selective serotonin reuptake inhibitors ☐ Antiplatelets ☐ Vitamin K antagonists ☐ Direct oral anticoagulants	☐ Unfractionated heparin Low molecular weight heparins ☐ Non-steroidal anti-inflammatory drugs ☐ Other (*Please specify*):
	☐ **Underuse** of proton pump inhibitors prophylaxis while - On NSAIDs monotherapy (≥ 70 years old) or on concurrent NSAIDs and/or antiplatelets and/or corticosteroids - On NSAIDs or antiplatelet or corticosteroids monotherapy with a history of peptic ulcer disease/gastrointestinal bleeding while on those 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?	
	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)
Thromboembolic event (DVT or PE)	**Underuse** of adequate anticoagulation?	
	☐ Unfractionated heparin ☐ Low molecular weight heparins	☐ Direct oral anticoagulants ☐ Vitamin K antagonists
Heart failure exacerbation	**Use** of any drugs that could precipitate a heart failure exacerbation?	☐ Non-steroidal anti-inflammatory drugs ☐ Corticosteroids ☐ Sodium-containing formulations ☐ Other (*Please specify*):
	☐ Non-dihydropyridine calcium (verapamil, diltiazem) ☐ Thiazolidinediones (glitazones)	
	Underuse of any of the following drugs? ☐ β blockers[¥] ☐ ACE inhibitors[¥] ☐ Diuretics *Note* [¥] β blockers and ACE inhibitors in heart failure due to left ventricular dysfunction	

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?	
COPD exacerbation	**Use** of any drugs that could precipitate a 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 and vomiting)	**Use** of any of the following drugs?	
	☐ Opioids ☐ Selective serotonin reuptake inhibitors ☐ Cholinesterase inhibitors ☐ Digoxin ☐ Antibiotics	☐ Laxatives ☐ Non-steroidal anti-inflammatory drugs ☐ Chemotherapy (*Please specify)*: ☐ Other (*Please specify*):
Major constipation or faecal impaction	**Use** of any of the following drugs?	
	☐ Atypical antipsychotics ☐ Tricyclic antidepressants ☐ Opioids (look for **underuse of laxatives** with regular opioid use) ☐ Calcium antagonists (mainly verapamil) ☐ Chronic (stimulant) laxative use	☐ Calcium ☐ Oral iron ☐ Aluminium antacids ☐ Bladder antimuscarinics ☐ Other anticholinergic drugs ☐ Other (*Please specify*):

Infection	**Underuse** of any of the following drugs? ☐ Vaccines (haemophilus, pneumococcal, influenza)	**Use** of any of the following drugs? ☐ Immunosuppressants ☐ Chemotherapy ☐ Corticosteroids
Liver disorders	**Use** of any of the following drugs? ☐ Tricyclic antidepressants ☐ Antiepileptics (carbamazepine, phenytoin, valproate) ☐ Methyldopa ☐ Amiodarone ☐ Lipid-lowering agents ☐ Antibiotics (amoxicillin-clavulanate, flucloxacillin, ciprofloxacin, minocycline, nitrofurantoin, sulphonamide, macrolide)	☐ Antituberculosis drugs (isoniazide, rifampicin, pyrazinamide) ☐ Antiretroviral drugs: zidovudine, stavudine ☐ Acetaminophen ☐ NSAIDs ☐ Allopurinol ☐ Chemotherapy ☐ Immunosuppressants
Seizures or movement disorders	**Use** of any of the following drugs? ☐ Antipsychotics ☐ Antidepressants ☐ Antiepileptics (carbamazepine, phenytoin, valproate) ☐ Lithium ☐ Anti-Parkinson's drugs ☐ Amiodarone	**Abrupt discontinuation/rapid dose reduction** of any of the following drugs? ☐ Anti-Parkinson's drugs ☐ Benzodiazepines ☐ Antiepileptics
Laboratory values		
Hypokalaemia (K^+ < 3 mmol/L)	**Use** of any of the following drugs? ☐ Loop diuretics ☐ Thiazides 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? ☐ Selective serotonin reuptake inhibitors ☐ Diuretics ☐ ACE inhibitors ☐ Angiotensin receptor blockers	☐ Tricyclic antidepressants ☐ Carbamazepine and oxcarbazepine ☐ High-dose cyclophosphamide ☐ Other (*Please specify*):
Pancytopenia or anomaly on one of the 3	**Use** of any of the following drugs? ☐ Carbamazepine and oxcarbazepine,	☐ Ganciclovir

lines: leucopenia, thrombopenia, anaemia	☐ Antipsychotics (mainly clozapine) ☐ Mirtazapine (first six weeks of treatment) ☐ Heparin ☐ Thienopyridines (mainly ticlopidine) ☐ Sulfamides ☐ Voriconazole	☐ Immunosuppressants ☐ Chemotherapy (*Please specify):* ☐ Quinine sulphate ☐ Thyreostatics ☐ 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? ☐ Oral metronidazole or vancomycin in a patient who has recently been treated with an antibiotic that may cause *Clostridium difficile*-associated diarrhoea ☐ 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 IV glucoses 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
Mention of a (potential) ADE in the medical record	Assess causality using the WHO-UMC criteria	

Abbreviations: ACE: Angiotensin converting enzyme, NSAID: Non-steroidal anti-inflammatory drug

	Central nervous system drugs
	Cardiovascular drugs
	Anti-infective drugs
	Others

Table 4: The revised clinical version of the trigger tool for identifying drug related hospital admissions in older patients

Trigger on admission or up to 48 hours of admission	Suspected causative drugs or causes for underuse	
TRIGGERS – 'OTHERS'		
Antidote use or treatments that suggest a potential ADE	Use of any of the following drugs on the day of admission: metronidazole/vancomycin naloxone	vitamin K protamine sulphate sodium polystyrene Adrenaline Antihistamines Corticosteroids
Mention of a (potential) ADE in the medical record	Assess causality using the WHO-UMC criteria	

The list of suspected causative drugs or causes for underuse is not exhaustive. This list is based on the most commonly used or underused drugs (≥ 5%) found in the OPERAM cohort and/or in the literature for liver disorders and seizures/movement disorders* (January 2021).

A trigger is positive when both the category AND a potential causative drug (or drug lacking in case of underuse) are present.

Abbreviations: ACE: angiotensin converting enzyme; COPD: chronic obstructive pulmonary disease; NSAID: Non-steroidal anti-inflammatory drugs; SSRI: Selective serotonin reuptake inhibitors

	Central nervous system drugs
	Cardiovascular drugs
	Anti-infective drugs
	Others

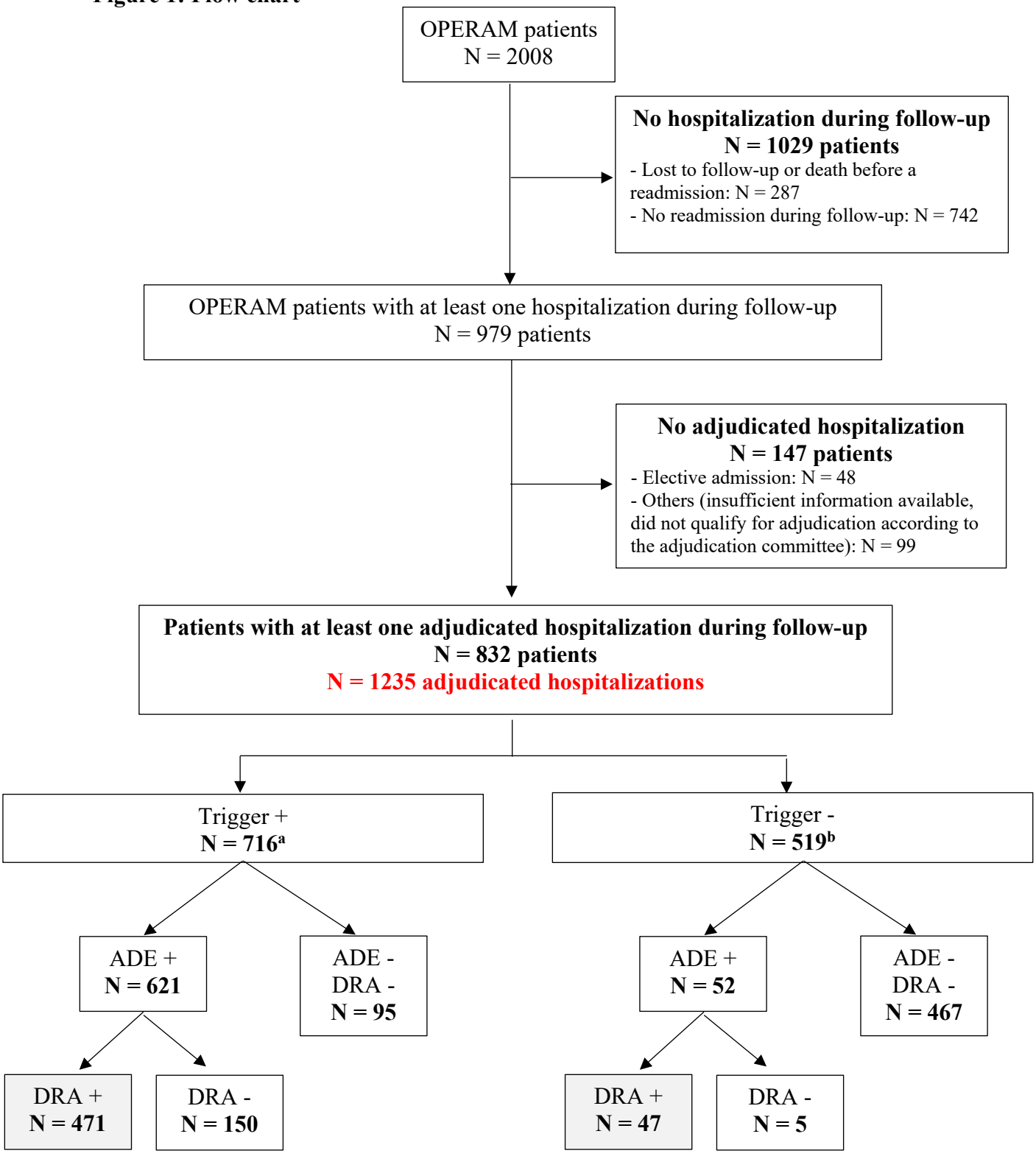
THE REVISED CLINICAL VERSION OF THE TRIGGER TOOL FOR IDENTIFYING DRUG RELATED HOSPITAL ADMISSIONS IN OLDER PATIENTS

Trigger on admission or up to 48 hours of admission	Suspected causative drugs or causes for underuse	
TRIGGERS – 'DIAGNOSES'		
Fall/fracture/orthostatic hypotension	Use of any of the following drugs: Benzodiazepines and analogues Antipsychotics Antidepressants Anti-Parkinson's drugs Opioid analgesics Calcium channel blockers Diuretics Beta blockers ACE inhibitors Angiotensin receptor blockers	ACE inhibitors Angiotensin receptor blockers Anticholinergic Alpha1 receptor blockers Underuse of any of the following drugs: Vitamin D Bone-antiresorptive therapy
Confusion/delirium	Use or stopping of any of the following drugs: Benzodiazepines and analogues Antipsychotics	Antiepileptics Antidepressants Dopaminergic agents Opioids
Acute renal impairment	Use of any of the following drugs: ACE inhibitors Angiotensin receptor blockers	Diuretics Sulphonamides
Dehydration	Use of any of the following drugs: Diuretics Laxatives	Any drugs causing vomiting Any drugs causing diarrhoea
Bleeding	Use of any of the following drugs: Antiplatelets Anticoagulants	

Trigger on admission or up to 48 hours of admission	Suspected causative drugs or causes for underuse	
TRIGGERS – 'DIAGNOSES'		
Stroke	Underuse of: Oral anticoagulants in patients with known chronic atrial fibrillation	Underuse of: Antiplatelets or statins in patients with history of coronary, cerebral, or peripheral vascular disease
Thromboembolic event	Underuse of adequate anticoagulation	
(Recurrent) myocardial infarction or ischaemic disease	Underuse of cardiovascular secondary prevention Antiplatelets Statins	Beta blockers / ACE inhibitors or angiotensin receptor blocker / adequate anti-anginal therapy in case of ischaemic disease
Heart failure exacerbation	Underuse of any of the following drugs Beta blockers ACE inhibitors Diuretics	Use of any of the following drugs: NSAIDs Corticosteroids
Gastrointestinal disorders (diarrhoea, vomiting)	Use of any of the following drugs: Opioids Antibiotics	Chemotherapy Laxatives
Major constipation	Use of any of the following drugs: Opioids	Oral iron Laxatives Underuse of laxatives
COPD exacerbation	Use of any of the following drugs: Benzodiazepines Opioids	Underuse of any of the following drugs: Single or dual inhaled bronchodilatator therapy
Infection	Underuse of any of the following drugs Vaccines (haemophilus, pneumococcal, influenza)	Use of any of the following drugs: Immunosuppressants Chemotherapy Corticosteroids

Trigger on admission or up to 48 hours of admission	Suspected causative drugs or causes for underuse	
TRIGGERS – 'DIAGNOSES'		
Uncontrolled (non-neuropathic) pain	Underuse of any of the following drugs: Opioids	
Liver disorders*	Use of any of the following drugs: Tricyclic antidepressants Antiepileptics (carbamazepine, phenytoin, valproate) Methyldopa Amiodarone Lipid-lowering agents Antibiotics (amoxicillin/clavulanate, ciprofloxacin, minocyclic, nitrofurantoin, sulfonamide, and macrolide)	Antituberculosis drugs (isoniazid, rifampicin, pyrazinamide) Antiretroviral drugs (zidovudine, stavudine) Acetaminophen Immunosuppressants Chemotherapy NSAIDs Allopurinol
Seizures and movement disorders*	Use of any of the following drugs: Antipsychotics Antiepileptics Antidepressants Anti-Parkinson's drugs	Abrupt withdrawal from: Anti-Parkinson's drugs Antiepileptics Benzodiazepines Use of any of the following drugs: Lithium Amiodarone
TRIGGERS – 'ABNORMAL LABORATORY VALUES'		
Hypokalaemia	Use of any of the following drugs:	Diuretics Laxatives
Hyponatraemia	Use of any of the following drugs: SSRI	ACE inhibitors and angiotensin receptor blockers Diuretics
Pancytopenia or anomaly on one of the 3 lines	Use of any of the following drugs:	Immunosuppressants Chemotherapy

Figure 1: Flow chart



Abbreviations: ADE: adverse drug event, DRA: drug-related hospital admission; Trigger: one of the 26 triggers of the trigger tool; +: at least one; - : none

[a]: For 129 hospitalizations, a non-triggered event was also identified.

[b]: For 58 hospitalizations, a non-triggered event was also identified.