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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.

Study concept and design: Zerah, Spinewine, Henrard

Acquisition, analysis, or interpretation of data: All authors

Drafting of the manuscript: Zerah, Spinewine

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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

Background: Identifying drug-related hospital admissions (DRAs) in older people is challenging.

Objective: To assess the performance of the first trigger tool developed to detect DRAs in older people, with the aim of producing a revised version with improved performance.

Design: Retrospective study using data from the OPERAM trial.

Setting: Four European medical centres

Subjects: Patients (≥ 70 years with multimorbidity and polypharmacy) with ≥ 1 adjudicated hospitalization during the one-year follow-up.

Methods: In the OPERAM trial a standardized chart review method was used to adjudicate DRAs due to adverse drug reactions, overuse, misuse, and underuse. The method included screening for adverse drug events (ADEs) and DRAs using a tool with 26 triggers. The positive predictive value (PPV) for detecting ADEs and DRAs was calculated for each trigger and for the tool as a whole. A revised trigger tool was produced based on PPVs, correlations between triggers, and analysis of (non-) triggered events.

Results: Of 1235 hospitalizations adjudicated for 832 patients (mean age 79.4 years), 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 and ADEs were 0.66 [0.62 – 0.69] and 0.87 [0.84-0.89], respectively. The revised version of the tool includes 20 triggers (7 triggers deleted, 3 triggers combined, 3 triggers added).

Conclusions: This tool performs well for identifying DRAs in older people. The revised version will require external validation before it can be incorporated into research and clinical practice.

Key words: trigger tool, drug-related hospital admissions, adverse drug events, older people

Key points:

- In this cohort of older patients with multimorbidity and polypharmacy, 42% of all hospitalizations at one year after the index date 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, and 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].
- We propose a shorter revised version of this trigger tool to improve its performance, containing 20 triggers (7 triggers deleted, 3 triggers combined, 3 triggers added).
- We also propose a user-friendly version of the trigger tool, containing only the 20 triggers related to 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 in a multi-morbidity context; this increases the risk of inappropriate prescribing and adverse drug events (ADEs) [1,2]. Five to 20% of hospital admissions are known to be related to ADEs (drug-related hospital admissions (DRAs)) in people aged 70 years and older [2,3,4,5,6,7], of which 40% to 70% are classified as preventable (related to inappropriate prescribing, administration, monitoring, and/or dispensation) [2,3,4,7,8]. 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 [7,9,10].

Identifying DRAs in older people is challenging because ADEs often present themselves as common geriatric problems such as falls, delirium, or renal impairment, which might be due to the ageing process and underlying diseases [11,12,13]. 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 adverse events associated with patient care [15,16]. Recently, a standardized chart review method including a trigger tool was developed to identify DRAs in older people [11]. The process involves adjudication teams identifying ADEs and DRAs through screening using 26 triggers. Non-triggered DRAs can also be identified [11]. 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 this tool 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 [11,17,18,19].

The following definitions were adopted: (i) ADE: any incident resulting from the process of the use of medication that causes harm or injury to the patient, including adverse drug reactions (ADR) and medication errors (ME, related to overuse, misuse, or underuse of prescription and non-prescription medications); (ii) DRA: hospitalization due to an ADE that was the main reason for or contributed substantially to a patient's hospitalization [11,17, 20]. DRAs attributable, in whole or in part, to ME(s) were considered preventable.

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 [11]. 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) [11]. The 26 triggers included in the tool were classified into three categories (see **Appendix 2**) [11]: 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 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 was classified as DRA or not and, if classified as a DRA, was also classified by type: ADR, overuse, misuse, or underuse. Each adjudicated hospitalization could have more than one trigger, ADE, or non-triggered event.

Eligibility criteria

All patients included 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. Poorly performing triggers could be considered for removal from the revised list and merging triggers could be considered in case of overlap/correlation, to improve the performance of the revised tool and the relevance of the remaining triggers.

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 [11]. We describe these events and the drugs involved as reported by the adjudication committee. Recurrent (≥ 5) events and related drugs could be considered as new triggers in the revised tool. If events detected by a trigger were also identified by another, dropping one was considered in the revised version, to improve the relevance of the remaining triggers.

The revised version of the tool was approved by all the research team members. 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 ($\geq 5\%$) 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 divided by the total number of triggers found (primary outcome). 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; all patients had multimorbidity, with a median number of drugs per day (IQR) of 11 (8 – 14) (**Table 1, Appendices 3 and 4**). The median number of hospitalizations (IQR) during the follow-up was 1 (1 – 2); 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 $\geq 10\%$ 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 5**).

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, DRAs, and preventable DRAs are described in **Table 2** and **Appendix 5**. Sensitivity analyses describing

all PPVs for each centre are in **Appendix 6**. No major differences were found between the centres.

Revised trigger tool

The description of all triggered and non-triggered events responsible for a DRA (and of the associated drugs) and the correlations found are in **Appendices 7 and 8**.

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’ (**Appendix 7**). Accordingly, we removed four triggers (INR, digoxin, hypoglycaemia, and hyperkalaemia) from the revised version (**Table 3, Appendices 7 and 9**). 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 7 and 8**). We merged these three into one new trigger in the revised version (**Table 3, Appendices 7 and 9**): ‘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 triggers ‘Mention of a (potential) ADE in the medical record’ and ‘Abrupt medication stop within 24 hours of admission’ and the non-triggered events (**Appendix 7**), 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 7 and 9). 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 avoid overlaps and improve the relevance of the remaining triggers, we removed ‘Mention of a (potential) ADE in the medical record’ and ‘Abrupt medication stop within 24 hours of admission’ from the revised version (**Table 3, Appendices 7 and 9).**

The final revised version (presented in **Table 3**) includes 20 triggers (7 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 1 ‘other’ trigger).

A clinically applicable version of this revised tool, with the most commonly used or underused drugs ($\geq 5\%$) 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; only one trigger had a PPV below 20%.

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, and not underuse or misuse. Global PPV was lower than ours, at 0.48 [0.47 – 0.49]. The reasons found for DRAs in this study [30] and the associated drugs 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 PPVs are influenced by prevalence, our results are valid in an older multimorbid population with polypharmacy and may not be extrapolated to other populations. 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].

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. Accurate DRA detection would also help health policy decision-makers plan for safer healthcare in ageing societies. A third is that the revised version could be computerized to offer automated detection of potential DRAs in electronic medical records. This would address the problem of under-detection and under-reporting of DRAs and make possible timely corrective action.

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 ADR, overuse, underuse, and misuse of medications in older patients performed well (global PPV of 0.66 [0.62 – 0.69]). We propose a revised, slightly shorter version. This will require external validation; it could later 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

Appendix 2: First version of the trigger tool for identifying drug-related hospital admissions in older patients

Appendix 3: International Classification of Diseases, 10th revision (ICD-10) codes used to identify comorbid conditions during the index hospitalization

Appendix 4: Anatomical Therapeutic Chemical (ATC) codes used to identify the drugs during the index hospitalization

Appendix 5: Global and individual performances of triggers for detecting drug-related hospital admissions and preventable drug-related hospital admissions during follow-up

Appendix 6: 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 7: Description of triggers and medication involved leading to drug-related hospital admissions and new proposals (in blue or red) for the trigger tool

Appendix 8: Correlations found between triggers and non-triggered events

Appendix 9: First version and revised version of trigger tool

REFERENCES

1. Leendertse AJ, Egberts ACG, Stoker LJ, van den Bemt PMLA, HARM Study Group. Frequency of and risk factors for preventable medication-related hospital admissions in the Netherlands. *Arch Intern Med* 2008; 168: 1890–1896.
2. Parameswaran Nair N, Chalmers L, Peterson GM, Bereznicki BJ, Castelino RL, Bereznicki LR. Hospitalization in older patients due to adverse drug reactions -the need for a prediction tool. *Clin Interv Aging* 2016; 11: 497–505.
3. Gurwitz JH, Field TS, Harrold LR *et al.* Incidence and preventability of adverse drug events among older persons in the ambulatory setting. *JAMA* 2003; 289: 1107–1116.
4. Pirmohamed M, James S, Meakin S *et al.* Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. *BMJ* 2004; 329: 15–19.
5. Shehab N, Lovegrove MC, Geller AI, Rose KO, Weidle NJ, Budnitz DS. US emergency department visits for outpatient adverse drug events, 2013-2014. *JAMA* 2016; 316: 2115–2125.
6. Budnitz DS, Lovegrove MC, Shehab N, Richards CL. Emergency hospitalizations for adverse drug events in older Americans. *N Engl J Med* 2011; 365: 2002–2012.
7. El Morabet N, Uitvlugt EB, van den Bemt BJF, van den Bemt PMLA, Janssen MJA, Karapinar-Çarkit F. Prevalence and Preventability of Drug-Related Hospital Readmissions: A Systematic Review. *J Am Geriatr Soc* 2018; 66: 602–608.
8. Assiri GA, Shebl NA, Mahmoud MA *et al.* What is the epidemiology of medication errors, error-related adverse events and risk factors for errors in adults managed in community care contexts? A systematic review of the international literature. *BMJ Open* 2018; 8: e019101.
9. Leendertse AJ, Visser D, Egberts ACG, van den Bemt PMLA. The relationship between study characteristics and the prevalence of medication-related hospitalizations: a

literature review and novel analysis. *Drug Saf* 2010; 33: 233–244.

10. Linkens AEMJH, Milosevic V, van der Kuy PHM, Damen-Hendriks VH, Mestres Gonzalvo C, Hurkens KPGM. Medication-related hospital admissions and readmissions in older patients: an overview of literature. *Int J Clin Pharm* 2020; 42: 1243–1251.
11. Thevelin S, Spinewine A, Beuscart J-B *et al.* Development of a standardized chart review method to identify drug-related hospital admissions in older people. *Br J Clin Pharmacol* 2018; 84: 2600–2614.
12. Davies EA, O’Mahony MS. Adverse drug reactions in special populations - the elderly. *Br J Clin Pharmacol* 2015; 80: 796–807.
13. Lavan AH, Gallagher P. Predicting risk of adverse drug reactions in older adults. *Ther Adv Drug Saf* 2016; 7: 11–22.
14. Hohl CM, Zed PJ, Brubacher JR, Abu-Laban RB, Loewen PS, Pursell RA. Do emergency physicians attribute drug-related emergency department visits to medication-related problems? *Ann Emerg Med* 2010; 55: 493-502.e4.
15. Hibbert PD, Molloy CJ, Hooper TD *et al.* The application of the Global Trigger Tool: a systematic review. *Int J Qual Health Care* 2016; 28: 640–649.
16. Griffin F, Resear R. IHI Global Trigger Tool for Measuring Adverse Events (Second Edition). IHI Innovation Series white paper. Cambridge, MA: Institute for Healthcare Improvement. 2009 Available on www.IHI.org.
17. Adam L, Moutzouri E, Baumgartner C *et al.* Rationale and design of OPTimising thERapy to prevent Avoidable hospital admissions in Multimorbid older people (OPERAM): a cluster randomised controlled trial. *BMJ Open* 2019; 9: e026769.
18. Crowley EK, Sallevelt BTGM, Huibers CJA *et al.* Intervention protocol: OPTimising thERapy to prevent avoidable hospital Admission in the Multi-morbid elderly (OPERAM): a structured medication review with support of a computerised decision support system. *BMC*

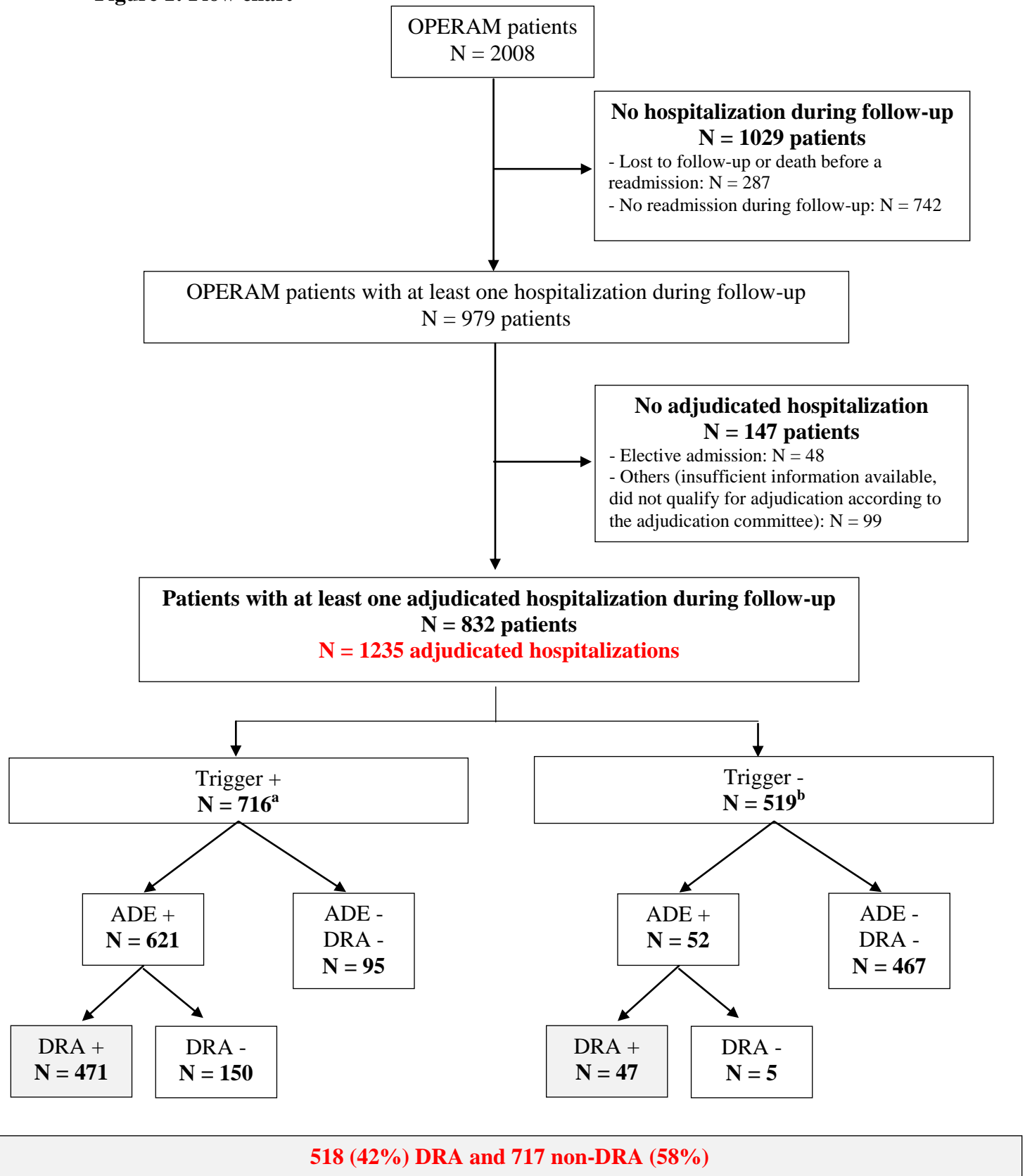
Health Serv Res 2020; 20: 220.

19. Drenth-van Maanen AC, Leendertse AJ, Jansen PAF *et al.* The Systematic Tool to Reduce Inappropriate Prescribing (STRIP): Combining implicit and explicit prescribing tools to improve appropriate prescribing. *J Eval Clin Pract* 2018; 24: 317–322.
20. The Uppsala Monitoring Centre. The use of the WHO-UMC system for standardised case causality assessment. 2013 Available on <https://www.who.int/publications/m/item/WHO-causality-assessment>.
21. Otero MJ, Toscano Guzmán MD, Galván-Banqueri M, Martínez-Sotelo J, Santos-Rubio MD. Utility of a trigger tool (TRIGGER-CHRON) to detect adverse events associated with high-alert medications in patients with multimorbidity. *Eur J Hosp Pharm Sci Pract* 2020; ejhpharm-2019-002126.
22. 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.
23. Hu Q, Qin Z, Zhan M, Chen Z, Wu B, Xu T. Validating the Chinese geriatric trigger tool and analyzing adverse drug event associated risk factors in elderly Chinese patients: A retrospective review. *PLoS ONE* 2020; 15: e0232095.
24. Toscano Guzmán MD, Galván Banqueri M, Otero M José, Sánchez Fidalgo S, Font Noguera I, Pérez Guerrero M conception. Validating a Trigger Tool for Detecting Adverse Drug Events in Elderly Patients With Multimorbidity (TRIGGER-CHRON). *J Patient Saf* 2018;
25. Zerah L, Bihan K, Kohler S, Mariani L-L. Iatrogenesis and neurological manifestations in the elderly. *Rev Neurol (Paris)* 2020; 176: 710–723.
26. Stine JG, Chalasani N. Chronic liver injury induced by drugs: a systematic review. *Liver Int* 2015; 35: 2343–2353.

27. Low EXS, Zheng Q, Chan E, Lim SG. Drug induced liver injury: East versus West - a systematic review and meta-analysis. *Clin Mol Hepatol* 2020; 26: 142–154.
28. Manias E. Detection of medication-related problems in hospital practice: a review. *Br J Clin Pharmacol* 2013; 76: 7–20.
29. Warlé-van Herwaarden MF, Kramers C, Sturkenboom MC, van den Bemt PMLA, De Smet PAGM, Dutch HARM-Wrestling Task Force. Targeting outpatient drug safety: recommendations of the Dutch HARM-Wrestling Task Force. *Drug Saf* 2012; 35: 245–259.
30. Warlé-van Herwaarden MF, Valkhoff VE, Herings RMC *et al.* Quick assessment of drug-related admissions over time (QUADRAT study). *Pharmacoepidemiol Drug Saf* 2015; 24: 495–503.
31. Kempen TGH, Hedström M, Olsson H *et al.* Assessment tool for hospital admissions related to medications: development and validation in older patients. *Int J Clin Pharm* 2019; 41: 198–206.
32. Unbeck M, Schildmeijer K, Henriksson P *et al.* Is detection of adverse events affected by record review methodology? an evaluation of the ‘Harvard Medical Practice Study’ method and the ‘Global Trigger Tool’. *Patient Saf Surg* 2013; 7: 10.
33. Silva M das DG, Martins MAP, Viana L de G *et al.* Evaluation of accuracy of IHI Trigger Tool in identifying adverse drug events: a prospective observational study: Evaluation of accuracy of triggers. *Br J Clin Pharmacol* 2018; 84: 2252–2259.
34. Hu Q, Qin Z, Zhan M, Wu B, Chen Z, Xu T. Development of a trigger tool for the detection of adverse drug events in Chinese geriatric inpatients using the Delphi method. *Int J Clin Pharm* 2019; 41: 1174–1183.
35. Toscano Guzmán MD, Galván Banqueri M, Otero MJ, Alfaro Lara ER, Casajus Lagranja P, Santos Ramos B. Development of a Trigger Tool to Identify Adverse Drug Events in Elderly Patients With Multimorbidity. *J Patient Saf* 2017;

36. Onder G, Petrovic M, Tangiisuran B *et al.* Development and validation of a score to assess risk of adverse drug reactions among in-hospital patients 65 years or older: the GerontoNet ADR risk score. *Arch Intern Med* 2010; 170: 1142–1148.

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.

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/mm ³	12	12	1.00 [0.74 – 1.00]	8	0.67 [0.35 – 0.90]
Platelet count < 50000/mm ³	7	7	1.00 [0.59 – 1.00]	5	0.71 [0.29 – 0.96]
Neutrophils < 1400/mm ³	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	673	0.87 [0.84 – 0.89]	518	0.66 [0.62 – 0.69]
For preventable DRAs, at least one trigger	716			219	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.

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		
<i>Diagnoses</i>			
Fall and/or fracture and/or orthostatic hypotension	<p>Use of any of the following drugs?</p> <table border="0" style="width: 100%;"> <tr> <td style="vertical-align: top; width: 50%;"> <input type="checkbox"/> Benzodiazepines <input type="checkbox"/> Non-benzodiazepine hypnotics e.g. zopiclone, zolpidem <input type="checkbox"/> Antipsychotics <input type="checkbox"/> Antidepressants </td> <td style="vertical-align: top; width: 50%;"> <input type="checkbox"/> Sedating antihistamines <input type="checkbox"/> Opioids <input type="checkbox"/> Anticholinergics <input type="checkbox"/> Other (<i>Please specify</i>): </td> </tr> </table>	<input type="checkbox"/> Benzodiazepines <input type="checkbox"/> Non-benzodiazepine hypnotics e.g. zopiclone, zolpidem <input type="checkbox"/> Antipsychotics <input type="checkbox"/> Antidepressants	<input type="checkbox"/> Sedating antihistamines <input type="checkbox"/> Opioids <input type="checkbox"/> Anticholinergics <input type="checkbox"/> Other (<i>Please specify</i>):
	<input type="checkbox"/> Benzodiazepines <input type="checkbox"/> Non-benzodiazepine hypnotics e.g. zopiclone, zolpidem <input type="checkbox"/> Antipsychotics <input type="checkbox"/> Antidepressants	<input type="checkbox"/> Sedating antihistamines <input type="checkbox"/> Opioids <input type="checkbox"/> Anticholinergics <input type="checkbox"/> Other (<i>Please specify</i>):	
	<p>Use of any drugs that cause orthostatic hypotension?</p> <table border="0" style="width: 100%;"> <tr> <td style="vertical-align: top; width: 50%;"> <input type="checkbox"/> Direct renin inhibitors (e.g. aliskiren) <input type="checkbox"/> Anti-Parkinson drugs <input type="checkbox"/> Antidepressants (mainly tricyclic) <input type="checkbox"/> Antipsychotics <input type="checkbox"/> Calcium channel blockers <input type="checkbox"/> Diuretics <input type="checkbox"/> β blockers </td> <td style="vertical-align: top; width: 50%;"> <input type="checkbox"/> ACE inhibitors <input type="checkbox"/> Angiotensin receptor blockers <input type="checkbox"/> Nitrates <input type="checkbox"/> Gliflozines (SGLT2-inhibitors) <input type="checkbox"/> α1-receptor blockers <input type="checkbox"/> Other (<i>Please specify</i>): </td> </tr> </table>	<input type="checkbox"/> Direct renin inhibitors (e.g. aliskiren) <input type="checkbox"/> Anti-Parkinson drugs <input type="checkbox"/> Antidepressants (mainly tricyclic) <input type="checkbox"/> Antipsychotics <input type="checkbox"/> Calcium channel blockers <input type="checkbox"/> Diuretics <input type="checkbox"/> β blockers	<input type="checkbox"/> ACE inhibitors <input type="checkbox"/> Angiotensin receptor blockers <input type="checkbox"/> Nitrates <input type="checkbox"/> Gliflozines (SGLT2-inhibitors) <input type="checkbox"/> α 1-receptor blockers <input type="checkbox"/> Other (<i>Please specify</i>):
	<input type="checkbox"/> Direct renin inhibitors (e.g. aliskiren) <input type="checkbox"/> Anti-Parkinson drugs <input type="checkbox"/> Antidepressants (mainly tricyclic) <input type="checkbox"/> Antipsychotics <input type="checkbox"/> Calcium channel blockers <input type="checkbox"/> Diuretics <input type="checkbox"/> β blockers	<input type="checkbox"/> ACE inhibitors <input type="checkbox"/> Angiotensin receptor blockers <input type="checkbox"/> Nitrates <input type="checkbox"/> Gliflozines (SGLT2-inhibitors) <input type="checkbox"/> α 1-receptor blockers <input type="checkbox"/> Other (<i>Please specify</i>):	
<p>If a fall is caused by hypoglycaemia, look for use of drugs that contribute to hypoglycaemia</p>			
<p>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?</p> <table border="0" style="width: 100%;"> <tr> <td style="vertical-align: top; width: 50%;"> <input type="checkbox"/> 800 IU Vitamin D/d (+ 1000-1200 mg calcium/day if dietary intake is <1200-1000mg/day) </td> <td style="vertical-align: top; width: 50%;"> <input type="checkbox"/> Bone anti-resorptive therapy (e.g. bisphosphonates, strontium, ranelate, teriparatide, or denosumab) </td> </tr> </table>		<input type="checkbox"/> 800 IU Vitamin D/d (+ 1000-1200 mg calcium/day if dietary intake is <1200-1000mg/day)	<input type="checkbox"/> Bone anti-resorptive therapy (e.g. bisphosphonates, strontium, ranelate, teriparatide, or denosumab)
<input type="checkbox"/> 800 IU Vitamin D/d (+ 1000-1200 mg calcium/day if dietary intake is <1200-1000mg/day)	<input type="checkbox"/> Bone anti-resorptive therapy (e.g. bisphosphonates, strontium, ranelate, teriparatide, or denosumab)		

	<p>Underuse of any of the following drugs in patients on corticosteroid therapy ≥ 3 months?</p> <p><input type="checkbox"/> 800 IU Vitamin D/d (+ 1000-1200 mg calcium/day if dietary intake is $<1200-1000\text{mg/day}$) <input type="checkbox"/> Bisphosphonates</p> <p>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?</p>																						
<p>Confusion/delirium</p>	<p>Use of any of the following drugs?</p> <table border="0"> <tr> <td><input type="checkbox"/> Benzodiazepines</td> <td><input type="checkbox"/> Opioids</td> </tr> <tr> <td><input type="checkbox"/> Non-benzodiazepine hypnotics e.g. zopiclone, zolpidem</td> <td><input type="checkbox"/> Dopaminergic agonists</td> </tr> <tr> <td><input type="checkbox"/> Antipsychotics</td> <td><input type="checkbox"/> Acetylcholinesterase-inhibitors (new-onset confusion in patients with dementia)</td> </tr> <tr> <td><input type="checkbox"/> Antiepileptics</td> <td><input type="checkbox"/> Digoxin</td> </tr> <tr> <td><input type="checkbox"/> Antihistamines (H1- and H2-receptor blockers)</td> <td><input type="checkbox"/> Fluoroquinolones (<i>dose adjustment in renal impairment required</i>)</td> </tr> <tr> <td><input type="checkbox"/> Antidepressants</td> <td><input type="checkbox"/> Other anticholinergics</td> </tr> </table> <p>Abrupt discontinuation/rapid dose reduction of any of the following drugs?</p> <table border="0"> <tr> <td><input type="checkbox"/> Benzodiazepines</td> <td><input type="checkbox"/> Antidepressants</td> </tr> <tr> <td><input type="checkbox"/> Non-benzodiazepine hypnotics e.g. zopiclone, zolpidem</td> <td><input type="checkbox"/> Lithium</td> </tr> <tr> <td><input type="checkbox"/> Antipsychotics</td> <td><input type="checkbox"/> Opioids</td> </tr> <tr> <td><input type="checkbox"/> Dopaminergic agonists</td> <td><input type="checkbox"/> Corticosteroids</td> </tr> <tr> <td></td> <td><input type="checkbox"/> Other (<i>Please specify</i>):</td> </tr> </table>	<input type="checkbox"/> Benzodiazepines	<input type="checkbox"/> Opioids	<input type="checkbox"/> Non-benzodiazepine hypnotics e.g. zopiclone, zolpidem	<input type="checkbox"/> Dopaminergic agonists	<input type="checkbox"/> Antipsychotics	<input type="checkbox"/> Acetylcholinesterase-inhibitors (new-onset confusion in patients with dementia)	<input type="checkbox"/> Antiepileptics	<input type="checkbox"/> Digoxin	<input type="checkbox"/> Antihistamines (H1- and H2-receptor blockers)	<input type="checkbox"/> Fluoroquinolones (<i>dose adjustment in renal impairment required</i>)	<input type="checkbox"/> Antidepressants	<input type="checkbox"/> Other anticholinergics	<input type="checkbox"/> Benzodiazepines	<input type="checkbox"/> Antidepressants	<input type="checkbox"/> Non-benzodiazepine hypnotics e.g. zopiclone, zolpidem	<input type="checkbox"/> Lithium	<input type="checkbox"/> Antipsychotics	<input type="checkbox"/> Opioids	<input type="checkbox"/> Dopaminergic agonists	<input type="checkbox"/> Corticosteroids		<input type="checkbox"/> Other (<i>Please specify</i>):
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<input type="checkbox"/> Dopaminergic agonists	<input type="checkbox"/> Corticosteroids																						
	<input type="checkbox"/> Other (<i>Please specify</i>):																						
<p>Acute renal impairment</p>	<p>Use of any of the following drugs?</p> <table border="0"> <tr> <td><input type="checkbox"/> Lithium</td> <td><input type="checkbox"/> Rifampicin</td> </tr> <tr> <td><input type="checkbox"/> ACE inhibitors</td> <td><input type="checkbox"/> Acyclovir, valacyclovir, gancyclovir, valgancyclovir, foscarnet, cidofovir</td> </tr> <tr> <td><input type="checkbox"/> Angiotensin receptor blockers</td> <td><input type="checkbox"/> Amphotericin</td> </tr> <tr> <td><input type="checkbox"/> Diuretics</td> <td><input type="checkbox"/> Calcineurin inhibitors (e.g. cyclosporine, tacrolimus)</td> </tr> <tr> <td><input type="checkbox"/> Sulphonamides</td> <td><input type="checkbox"/> Cisplatin</td> </tr> <tr> <td><input type="checkbox"/> Cephalosporins</td> <td><input type="checkbox"/> Radiology contrast medium</td> </tr> <tr> <td><input type="checkbox"/> Quinolones (ciprofloxacin)</td> <td><input type="checkbox"/> Bisphosphonates</td> </tr> <tr> <td><input type="checkbox"/> Aminoglycosides</td> <td><input type="checkbox"/> Non-steroidal anti-inflammatory drugs</td> </tr> <tr> <td><input type="checkbox"/> Vancomycin</td> <td><input type="checkbox"/> Other nephrotoxic drugs (<i>Please specify</i>):</td> </tr> <tr> <td><input type="checkbox"/> Pentamidine</td> <td></td> </tr> </table>	<input type="checkbox"/> Lithium	<input type="checkbox"/> Rifampicin	<input type="checkbox"/> ACE inhibitors	<input type="checkbox"/> Acyclovir, valacyclovir, gancyclovir, valgancyclovir, foscarnet, cidofovir	<input type="checkbox"/> Angiotensin receptor blockers	<input type="checkbox"/> Amphotericin	<input type="checkbox"/> Diuretics	<input type="checkbox"/> Calcineurin inhibitors (e.g. cyclosporine, tacrolimus)	<input type="checkbox"/> Sulphonamides	<input type="checkbox"/> Cisplatin	<input type="checkbox"/> Cephalosporins	<input type="checkbox"/> Radiology contrast medium	<input type="checkbox"/> Quinolones (ciprofloxacin)	<input type="checkbox"/> Bisphosphonates	<input type="checkbox"/> Aminoglycosides	<input type="checkbox"/> Non-steroidal anti-inflammatory drugs	<input type="checkbox"/> Vancomycin	<input type="checkbox"/> Other nephrotoxic drugs (<i>Please specify</i>):	<input type="checkbox"/> Pentamidine			
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<input type="checkbox"/> Vancomycin	<input type="checkbox"/> Other nephrotoxic drugs (<i>Please specify</i>):																						
<input type="checkbox"/> Pentamidine																							

Dehydration	<p>Use of any of the following drugs?</p> <ul style="list-style-type: none"> <input type="checkbox"/> Diuretics <input type="checkbox"/> Gliflozines (SGLT2-inhibitors) <input type="checkbox"/> Laxatives <input type="checkbox"/> Any drugs causing vomiting <input type="checkbox"/> Any drugs causing diarrhoea <input type="checkbox"/> Other (<i>Please specify</i>):
Bleeding (i.e. major bleeding and clinically relevant non-major bleeding)	<p>Use of any of the following drugs?</p> <ul style="list-style-type: none"> <input type="checkbox"/> Selective serotonin reuptake inhibitors <input type="checkbox"/> Antiplatelets <input type="checkbox"/> Vitamin K antagonists <input type="checkbox"/> Direct oral anticoagulants <input type="checkbox"/> Unfractionated heparin Low molecular weight heparins <input type="checkbox"/> Non-steroidal anti-inflammatory drugs <input type="checkbox"/> Other (<i>Please specify</i>): <p>Underuse of proton pump inhibitors prophylaxis while</p> <ul style="list-style-type: none"> - 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	<p>Underuse of any of the following drugs in patients with known chronic atrial fibrillation?</p> <ul style="list-style-type: none"> <input type="checkbox"/> Vitamin K antagonists <input type="checkbox"/> Direct oral anticoagulants (except valvular atrial fibrillation) <p>Underuse of adequate antihypertensive therapy?</p> <p>Underuse of any of the following drugs in patients with history of coronary, cerebral, or peripheral vascular disease?</p> <ul style="list-style-type: none"> <input type="checkbox"/> Antiplatelets <input type="checkbox"/> Statins (unless end-of-life or > 85 years old)
Thromboembolic event (DVT or PE)	<p>Underuse of adequate anticoagulation?</p> <ul style="list-style-type: none"> <input type="checkbox"/> Unfractionated heparin <input type="checkbox"/> Low molecular weight heparins <input type="checkbox"/> Direct oral anticoagulants <input type="checkbox"/> Vitamin K antagonists
Heart failure exacerbation	<p>Use of any drugs that could precipitate a heart failure exacerbation?</p> <ul style="list-style-type: none"> <input type="checkbox"/> Non-dihydropyridine calcium (verapamil, diltiazem) <input type="checkbox"/> Thiazolidinediones (glitazones) <input type="checkbox"/> Non-steroidal anti-inflammatory drugs <input type="checkbox"/> Corticosteroids <input type="checkbox"/> Sodium-containing formulations <input type="checkbox"/> Other (<i>Please specify</i>): <p>Underuse of any of the following drugs?</p> <ul style="list-style-type: none"> <input type="checkbox"/> β blockers[¥] <input type="checkbox"/> ACE inhibitors[¥] <input type="checkbox"/> Diuretics <p><i>Note</i> [¥] β blockers and ACE inhibitors in heart failure due to left ventricular dysfunction</p>

Recurrent myocardial infarction or ischaemic disease	Underuse of cardiovascular secondary prevention?	
	<input type="checkbox"/> Antiplatelets (unless already anticoagulated) <input type="checkbox"/> Statins (unless end-of-life or > 85 years old)	<input type="checkbox"/> β blocker/ACE inhibitor or angiotensin receptor blocker /adequate anti-anginal therapy in case of ischaemic disease
COPD exacerbation	Underuse of adequate antihypertensive therapy?	
	Use of any drugs that could precipitate a COPD exacerbation?	
	<input type="checkbox"/> Benzodiazepines with acute or chronic respiratory failure <input type="checkbox"/> Opioids	<input type="checkbox"/> Other (<i>Please specify</i>):
Uncontrolled (non-neuropathic) pain	Underuse of any of the following drugs?	
	<input type="checkbox"/> Single or dual inhaled bronchodilator therapy (i.e. a β 2 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)?	
	<input type="checkbox"/> A strong opioid in moderate to severe pain if paracetamol, NSAIDs, or weak opioids are not appropriate (e.g. because of insufficient pain relief)	<input type="checkbox"/> Short-acting opioids for break-through pain during treatment with long-acting opioids <input type="checkbox"/> Other (<i>Please specify</i>):
Gastrointestinal disorders (severe diarrhoea and vomiting)	Use of any of the following drugs?	
	<input type="checkbox"/> Opioids <input type="checkbox"/> Selective serotonin reuptake inhibitors <input type="checkbox"/> Cholinesterase inhibitors <input type="checkbox"/> Digoxin <input type="checkbox"/> Antibiotics	<input type="checkbox"/> Laxatives <input type="checkbox"/> Non-steroidal anti-inflammatory drugs <input type="checkbox"/> Chemotherapy (<i>Please specify</i>): <input type="checkbox"/> Other (<i>Please specify</i>):
Major constipation or faecal impaction	Use of any of the following drugs?	
	<input type="checkbox"/> Atypical antipsychotics <input type="checkbox"/> Tricyclic antidepressants <input type="checkbox"/> Opioids (look for underuse of laxatives with regular opioid use) <input type="checkbox"/> Calcium antagonists (mainly verapamil) <input type="checkbox"/> Chronic (stimulant) laxative use	<input type="checkbox"/> Calcium <input type="checkbox"/> Oral iron <input type="checkbox"/> Aluminium antacids <input type="checkbox"/> Bladder antimuscarinics <input type="checkbox"/> Other anticholinergic drugs <input type="checkbox"/> Other (<i>Please specify</i>):

Infection	Underuse of any of the following drugs? <input type="checkbox"/> Vaccines (haemophilus, pneumococcal, influenza)	Use of any of the following drugs? <input type="checkbox"/> Immunosuppressants <input type="checkbox"/> Chemotherapy <input type="checkbox"/> Corticosteroids
Liver disorders	Use of any of the following drugs? <input type="checkbox"/> Tricyclic antidepressants <input type="checkbox"/> Antiepileptics (carbamazepine, phenytoin, valproate) <input type="checkbox"/> Methyldopa <input type="checkbox"/> Amiodarone <input type="checkbox"/> Lipid-lowering agents <input type="checkbox"/> Antibiotics (amoxicillin-clavulanate, flucloxacillin, ciprofloxacin, minocycline, nitrofurantoin, sulphamide, macrolide)	<input type="checkbox"/> Antituberculosis drugs (isoniazide, rifampicin, pyrazinamide) <input type="checkbox"/> Antiretroviral drugs: zidovudine, stavudine <input type="checkbox"/> Acetaminophen <input type="checkbox"/> NSAIDs <input type="checkbox"/> Allopurinol <input type="checkbox"/> Chemotherapy <input type="checkbox"/> Immunosuppressants
Seizures or movement disorders	Use of any of the following drugs? <input type="checkbox"/> Antipsychotics <input type="checkbox"/> Antidepressants <input type="checkbox"/> Antiepileptics (carbamazepine, phenytoin, valproate) <input type="checkbox"/> Lithium <input type="checkbox"/> Anti-Parkinson's drugs <input type="checkbox"/> Amiodarone	Abrupt discontinuation/rapid dose reduction of any of the following drugs? <input type="checkbox"/> Anti-Parkinson's drugs <input type="checkbox"/> Benzodiazepines <input type="checkbox"/> Antiepileptics
Laboratory values		
Hypokalaemia (K ⁺ < 3 mmol/L)	Use of any of the following drugs? <input type="checkbox"/> Loop diuretics <input type="checkbox"/> Thiazides and thiazide-like diuretics <input type="checkbox"/> Corticosteroids	<input type="checkbox"/> Laxatives <input type="checkbox"/> Salbutamol (IV or aerosol) <input type="checkbox"/> Theophylline <input type="checkbox"/> Other (<i>Please specify</i>):
Hyponatraemia (Na ⁺ < 130 mmol/L)	Use of any of the following drugs? <input type="checkbox"/> Selective serotonin reuptake inhibitors <input type="checkbox"/> Diuretics <input type="checkbox"/> ACE inhibitors <input type="checkbox"/> Angiotensin receptor blockers	<input type="checkbox"/> Tricyclic antidepressants <input type="checkbox"/> Carbamazepine and oxcarbazepine <input type="checkbox"/> High-dose cyclophosphamide <input type="checkbox"/> Other (<i>Please specify</i>):

Pancytopenia or anomaly on one of the 3 lines: leucopenia, thrombopenia, anaemia	Use of any of the following drugs?	
	<input type="checkbox"/> Carbamazepine and oxcarbazepine, <input type="checkbox"/> Antipsychotics (mainly clozapine) <input type="checkbox"/> Mirtazapine (first six weeks of treatment) <input type="checkbox"/> Heparin <input type="checkbox"/> Thienopyridines (mainly ticlopidine) <input type="checkbox"/> Sulfamides <input type="checkbox"/> Voriconazole	<input type="checkbox"/> Ganciclovir <input type="checkbox"/> Immunosuppressants <input type="checkbox"/> Chemotherapy (<i>Please specify</i>): <input type="checkbox"/> Quinine sulphate <input type="checkbox"/> Thyreostatics <input type="checkbox"/> Other (<i>Please specify</i>):
Other		
Antidote use or treatments that suggest a potential ADE	Use of any of the following drugs on the day of admission?	
	<input type="checkbox"/> Oral metronidazole or vancomycin in a patient who has recently been treated with an antibiotic that may cause <i>Clostridium difficile</i> -associated diarrhoea <input type="checkbox"/> Flumazenil in a patient on benzodiazepines <input type="checkbox"/> Naloxone in a patient on opioids <input type="checkbox"/> Phytonadione (vitamin K) in a patient on VKA <input type="checkbox"/> Protamine sulphate in a patient on heparins <input type="checkbox"/> Oral or IV glucoses or glucagon in a patient taking hypoglycaemic drugs	<input type="checkbox"/> Potassium supplements in case of hypokalaemia <input type="checkbox"/> Sodium polystyrene (Kayexalate) in case of hyperkalaemia <input type="checkbox"/> Adrenaline, antihistamines, and corticosteroids (general drug allergy) <input type="checkbox"/> Acetylcysteine (paracetamol overdose) <input type="checkbox"/> Digoxin antibodies in a patient with supratherapeutic digoxin levels

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	<table border="0"> <tr> <td>Use of any of the following drugs on the day of admission: metronidazole/vancomycin naloxone</td> <td> vitamin K protamine sulphate sodium polystyrene Adrenaline Antihistamines Corticosteroids </td> </tr> </table>	Use of any of the following drugs on the day of admission: metronidazole/vancomycin naloxone	vitamin K protamine sulphate sodium polystyrene Adrenaline Antihistamines Corticosteroids
Use of any of the following drugs on the day of admission: metronidazole/vancomycin naloxone	vitamin K protamine sulphate sodium polystyrene Adrenaline Antihistamines Corticosteroids		

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 ($\geq 5\%$) 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	<table border="0"> <tr> <td>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</td> <td> ACE inhibitors Angiotensin receptor blockers Anticholinergic Alpha1 receptor blockers Underuse of any of the following drugs: Vitamin D Bone-antiresorptive therapy </td> </tr> </table>	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
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	<table border="0"> <tr> <td>Use or stopping of any of the following drugs: Benzodiazepines and analogues Antipsychotics</td> <td> Antiepileptics Antidepressants Dopaminergic agents Opioids </td> </tr> </table>	Use or stopping of any of the following drugs: Benzodiazepines and analogues Antipsychotics	Antiepileptics Antidepressants Dopaminergic agents Opioids
Use or stopping of any of the following drugs: Benzodiazepines and analogues Antipsychotics	Antiepileptics Antidepressants Dopaminergic agents Opioids		
Acute renal impairment	<table border="0"> <tr> <td>Use of any of the following drugs: ACE inhibitors Angiotensin receptor blockers</td> <td> Diuretics Sulphonamides </td> </tr> </table>	Use of any of the following drugs: ACE inhibitors Angiotensin receptor blockers	Diuretics Sulphonamides
Use of any of the following drugs: ACE inhibitors Angiotensin receptor blockers	Diuretics Sulphonamides		
Dehydration	<table border="0"> <tr> <td>Use of any of the following drugs: Diuretics Laxatives</td> <td> Any drugs causing vomiting Any drugs causing diarrhoea </td> </tr> </table>	Use of any of the following drugs: Diuretics Laxatives	Any drugs causing vomiting Any drugs causing diarrhoea
Use of any of the following drugs: Diuretics Laxatives	Any drugs causing vomiting Any drugs causing diarrhoea		
Bleeding	<table border="0"> <tr> <td>Use of any of the following drugs: Antiplatelets Anticoagulants</td> <td></td> </tr> </table>	Use of any of the following drugs: Antiplatelets Anticoagulants	
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	<u>Underuse of:</u> Oral anticoagulants in patients with known chronic atrial fibrillation	<u>Underuse of:</u> Antiplatelets or statins in patients with history of coronary, cerebral, or peripheral vascular disease
Thromboembolic event	<u>Underuse of adequate anticoagulation</u>	
(Recurrent) myocardial infarction or ischaemic disease	<u>Underuse of cardiovascular secondary prevention</u> Antiplatelets Statins	Beta blockers / ACE inhibitors or angiotensin receptor blocker / adequate anti-anginal therapy in case of ischaemic disease
Heart failure exacerbation	<u>Underuse of any of the following drugs</u> Beta blockers ACE inhibitors Diuretics	<u>Use of any of the following drugs:</u> NSAIDs Corticosteroids
Gastrointestinal disorders (diarrhoea, vomiting)	<u>Use of any of the following drugs:</u> Opioids Antibiotics	Chemotherapy Laxatives
Major constipation	<u>Use of any of the following drugs:</u> Opioids	Oral iron Laxatives <u>Underuse of laxatives</u>
COPD exacerbation	<u>Use of any of the following drugs:</u> Benzodiazepines Opioids	<u>Underuse of any of the following drugs:</u> Single or dual inhaled bronchodilator therapy
Infection	<u>Underuse of any of the following drugs</u> Vaccines (haemophilus, pneumococcal, influenza)	<u>Use of any of the following drugs:</u> 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	<u>Underuse of any of the following drugs:</u> Opioids	
Liver disorders*	<u>Use of any of the following drugs:</u> Tricyclic antidepressants Antiepileptics (carbamazepine, phenytoin, valproate) Methyldopa Amiodarone Lipid-lowering agents Antibiotics (amoxicillin/clavulanate, ciprofloxacin, minocycline, nitrofurantoin, sulfonamide, and macrolide)	Antituberculosis drugs (isoniazid, rifampicin, pyrazinamide) Antiretroviral drugs (zidovudine, stavudine) Acetaminophen Immunosuppressants Chemotherapy NSAIDs Allopurinol
Seizures and movement disorders*	<u>Use of any of the following drugs:</u> Antipsychotics Antiepileptics Antidepressants Anti-Parkinson’s drugs	<u>Abrupt withdrawal from:</u> Anti-Parkinson’s drugs Antiepileptics Benzodiazepines <u>Use of any of the following drugs:</u> Lithium Amiodarone
TRIGGERS – ‘ABNORMAL LABORATORY VALUES’		
Hypokalaemia	<u>Use of any of the following drugs:</u>	Diuretics Laxatives
Hyponatraemia	<u>Use of any of the following drugs:</u> SSRI	ACE inhibitors and angiotensin receptor blockers Diuretics
Pancytopenia or anomaly on one of the 3 lines	<u>Use of any of the following drugs:</u>	Immunosuppressants Chemotherapy