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

## SUPPLEMENTARY INFORMATION

**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, 10$^{th}$ 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

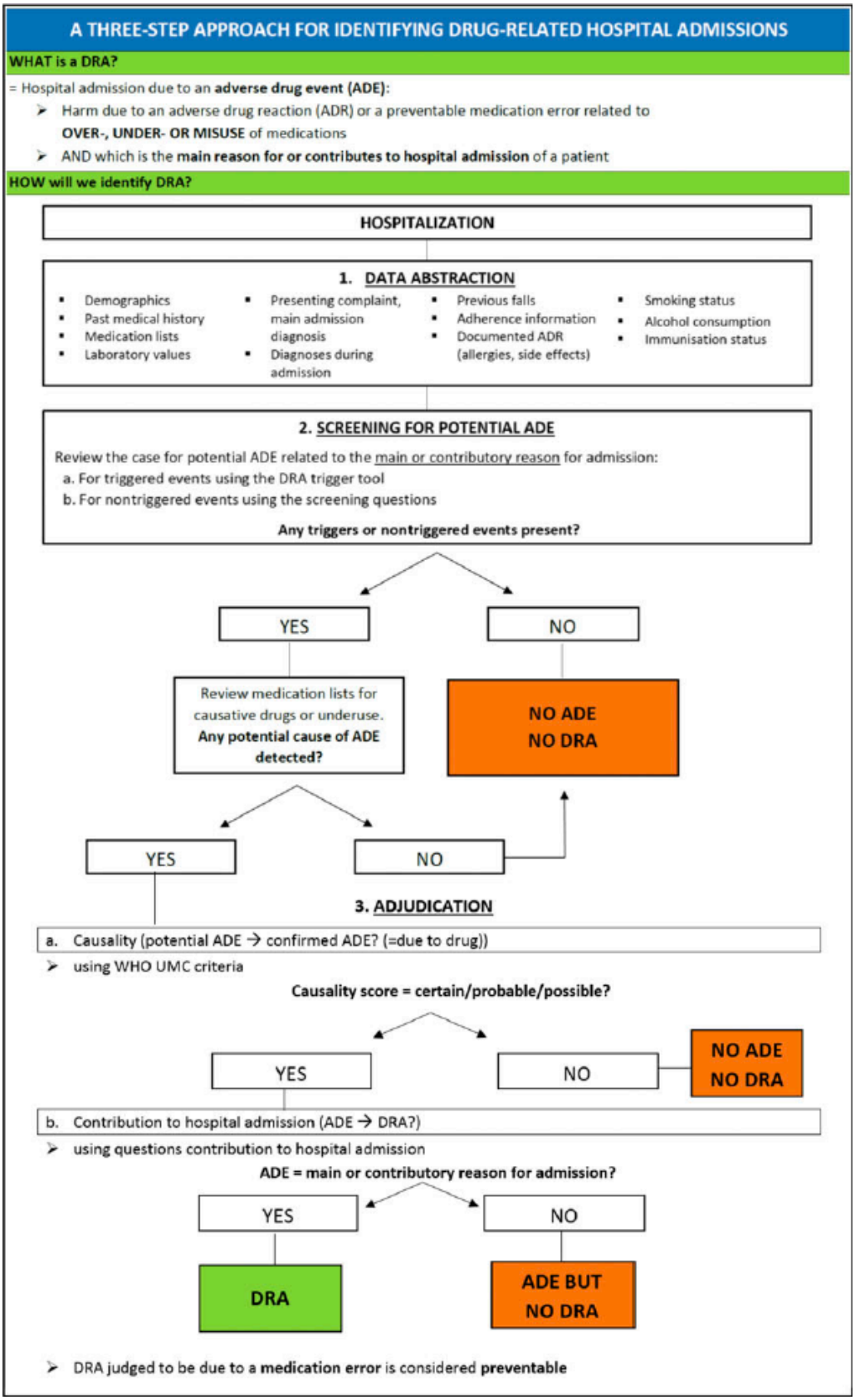
**Appendix 3:** Global and individual performances of triggers for detecting drug-related hospital admissions and preventable drug-related hospital admissions during follow-up

**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

**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 (Thevelin S et al., Br J Clin Pharmacol 2018)



## TRIGGER TOOL TO SCREEN FOR DRUG-RELATED HOSPITAL ADMISSIONS IN OLDER PERSONS

| Trigger on admission up to 48h of admission | Suspected causative drugs or causes for underuse |
|---|---|
| ***Diagnoses*** | |
| **Fall and/or fracture** | **Use** of any of the following drugs?<br>☐ Benzodiazepines<br>☐ Non-benzodiazepine hypnotics e.g. zopiclone, zolpidem<br>☐ Antipsychotics<br>☐ Antidepressants<br>☐ Sedating antihistamines<br>☐ Opioids<br>☐ Anticholinergics[$$] (cfr. Table A1)<br>☐ Other (*Please specify*): |
| | **Use** of any drugs causing orthostatic hypotension?<br>☐ Calcium channel blockers<br>☐ Diuretics<br>☐ α1-receptor blockers<br>☐ Nitrates<br>☐ β-blockers<br>☐ ACE-inhibitors<br>☐ Angiotensin receptor blockers<br>☐ Direct renin inhibitors (e.g. aliskiren)<br>☐ Anti-Parkinson drugs<br>☐ Antidepressants (mainly tricyclic)<br>☐ Antipsychotics<br>☐ Gliflozines (SGLT2-inhibitors)<br>☐ Other (*Please specify*): |
| | If a fall is caused by hypoglycaemia, look for **use** of drugs contributing to hypoglycaemia (check trigger hypoglycaemia) |
| | **Underuse** of any of the following drugs in patients with known osteoporosis and/or history of fragility fracture(s) and/or Bone Mineral Density T-scores of -2.5 or lower in multiple sites?<br>☐ 800 IU Vitamin D/d (+ 1000-1200 mg calcium/day if dietary intake is <1200-1000mg/day)<br>☐ Bone anti-resorptive therapy ( e.g. bisphosphonates, strontiumranelate,teriparatide, denosumab) |
| | **Underuse** of any of the following drugs in patients on corticosteroid therapy ≥ 3 months?<br>☐ 800 IU Vitamin D/d (+ 1000-1200 mg calcium/day if dietary intake is <1200-1000mg/day)<br>☐ Bisphosphonates |
| | **Underuse** of vitamin D in patients who are housebound and/or experiencing falls or with osteopenia with Bone Mineral Density T-score between -1 and -2.5 in multiple sites? |
| **Confusion/delirium*** | **Use** of any of the following drugs?<br>☐ Benzodiazepines<br>☐ Non-benzodiazepine hypnotics e.g. zopiclone, zolpidem<br>☐ Antipsychotics<br>☐ Anti-epileptics<br>☐ Antihistamines (H1- and H2-receptor blockers)<br>☐ Antidepressants<br>☐ Opioids<br>☐ Dopaminergic agonists<br>☐ Digoxin<br>☐ Fluoroquinolones *(dose adjustment in renal impairment required)*<br>☐ Acetylcholinesterase-inhibitors (new onset confusion in patients with dementia)<br>☐ Other anticholinergics[$$] (cfr. Table A1) (*Please specify*): |
| | **Abrupt discontinuation/rapid dose reduction** of any of the following drugs?<br>☐ Benzodiazepines<br>☐ Non-benzodiazepine hypnotics e.g. zopiclone, zolpidem<br>☐ Corticosteroids<br>☐ Dopaminergic agonists<br>☐ Antidepressants<br>☐ Opioids<br>☐ Lithium<br>☐ Antipsychotics<br>☐ Other (*Please specify*): |
| **Acute renal impairment**** | **Use** of any of the following drugs?<br>☐ Non-steroidal anti-inflammatory drugs<br>☐ ACE-inhibitors<br>☐ Angiotensin receptor blockers<br>☐ Diuretics<br>☐ Sulphonamides<br>☐ Cephalosporins<br>☐ Quinolones (ciprofloxacin)<br>☐ Aminoglycosides<br>☐ Vancomycin<br>☐ Pentamidine<br>☐ Rifampicin<br>☐ Acyclovir, valacyclovir, gancyclovir, valgancyclovir, foscarnet, cidofovir<br>☐ Lithium<br>☐ Calcineurin Inhibitors (e.g. cyclosporine, tacrolimus)<br>☐ Cisplatin<br>☐ Radiology contrast medium<br>☐ Amphotericin<br>☐ Bisphosphonates<br>☐ Other nephrotoxic drugs (*Please specify*): |
| **Dehydration** | Use of any of the following drugs?<br>☐ Diuretics<br>☐ Gliflozines (SGLT2-inhibitors)<br>☐ Laxatives<br>☐ Any drugs causing vomiting<br>☐ Any drugs causing diarrhoea<br>☐ Other (*Please specify*): |

| | |
|---|---|
| **Bleeding** (i.e. major bleeding and clinically relevant non-major bleeding***) | **Use** of any of the following drugs?<br>☐ Antiplatelets<br>☐ Vitamin K antagonists<br>☐ Direct oral anticoagulants<br>☐ Unfractionated heparin<br>☐ Low molecular weight heparins<br>☐ Selective serotonin reuptake inhibitors<br>☐ Non-steroidal anti-inflammatory drugs<br>☐ Other (*Please specify*): |
| | ☐ **Underuse** of proton pump inhibitors prophylaxis while<br>- NSAIDs monotherapy (≥ 70 years old) or on concurrent NSAIDs and/or antiplatelets and/or corticosteroids<br>- NSAIDs or antiplatelet or corticosteroids monotherapy with a history of peptic ulcer disease/gastrointestinal bleeding while on these drugs |
| **Stroke** | **Underuse** of any of the following drugs in patients with known chronic atrial fibrillation?<br>☐ Vitamin K antagonists<br>☐ Direct oral anticoagulants (except valvular atrial fibrillation) |
| | **Underuse** of adequate antihypertensive therapy?<br>* *Note*: Adequate antihypertensive therapy will be defined according to the recommendations for older patients in the 2013 European ESH/ESH guidelines for the management of arterial hypertension. |
| | **Underuse** of any of the following drugs in patients with history of coronary, cerebral or peripheral vascular disease?<br>☐ Antiplatelets<br>☐ Statins** (unless end-of-life or > 85 years old)<br>***Note*: Evidence for statin treatment above the age of 80-85 years is limited and clinical judgement should guide decisions in the very old, taking into account life expectancy, serious adverse events, possible drug interactions. Low to moderate intensity statin regimens are recommended. (**low**: simvastatin 10mg, pravastatin 10-20mg, fluvastatin 20-40 **moderate**: atorvastatin 10-20mg, Rosuvastatin 5-10mg, Simvastatin 20-40mg, pravastatin 40-80 mg, Fluvastatin 80 mg, Fluvastatin 40 mg BID) |
| **Thromboembolic event (DVT or PE)** | **Underuse** of adequate anticoagulation?<br>☐ Unfractionated heparin<br>☐ Low molecular weight heparins<br>☐ Direct oral anticoagulants<br>☐ Vitamin K antagonists |
| **(Recurrent) myocardial infarction or ischaemic disease** | **Underuse** of cardiovascular secondary prevention?<br>☐ Antiplatelets (unless already anticoagulated)<br>☐ Statins** (unless end-of-life or > 85 years old)<br>☐ β-blocker/ACE-inhibitor or angiotensin receptor blocker /adequate anti-anginal therapy in case of ischaemic disease |
| | **Underuse** of adequate antihypertensive therapy? * |
| **Heart failure exacerbation** | **Use** of any drugs that could precipitate heart failure exacerbation?<br>☐ Non-steroidal anti-inflammatory drugs<br>☐ Corticosteroids<br>☐ Thiazolidinediones (glitazones)<br>☐ Non-dihydropyridine calcium channel blockers (verapamil, diltiazem)<br>☐ Sodium-containing formulations (effervescent, dispersible and soluble medications)<br>☐ Other (*Please specify*): |
| | **Underuse** of any of the following drugs?<br>☐ β-blockers¥<br>☐ ACE-inhibitors¥<br>☐ Diuretics<br>*Note*: ¥ β-blocker and ACE-inhibitors in heart failure due to left ventricular dysfunction |
| **COPD exacerbation** | **Use** of any drugs that could precipitate COPD exacerbation?<br>☐ Benzodiazepines with acute or chronic respiratory failure<br>☐ Opioids<br>☐ Other (*Please specify*): |
| | **Underuse** of any of the following drugs?<br>☐ 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)?<br>☐ A strong opioid in moderate to severe pain if paracetamol, NSAIDs or weak opioids are not appropriate (e.g. because of insufficient pain relief)<br>☐ Short-acting opioids for break-through pain during treatment with long acting opioids<br>☐ Other (*Please specify*): |
| **Gastrointestinal disorders (severe diarrhoea, vomiting)** | **Use** of any of the following drugs?<br>☐ Antibiotics<br>☐ Laxatives<br>☐ Selective serotonin reuptake inhibitors<br>☐ Digoxin<br>☐ Cholinesterase-inhibitors<br>☐ Opioids<br>☐ Non-steroidal anti-inflammatory drugs<br>☐ Chemotherapy (*Please specify*):<br>☐ Other (*Please specify*): |

| | |
|---|---|
| **Major constipation or faecal impaction** | **Use** of any of the following drugs?<br>☐ Chronic (stimulant) laxative use<br>☐ Opioids (look for **underuse of laxatives** with regular opioid use)<br>☐ Calcium antagonists (Mainly verapamil)<br>☐ Calcium<br>☐ Oral iron<br>☐ Aluminium antacids<br>☐ Atypical antipsychotics<br>☐ Tricyclic antidepressants<br>☐ Bladder antimuscarinics<br>☐ Other anticholinergic drugs[$$] (cfr. Table A1)<br>☐ Other (*Please specify*): |
| ***Laboratory values*** | |
| **INR > 5** | Look for evidence of bleeding (see trigger) to determine if an adverse drug event (ADE) has occurred. A raised INR in itself is not an ADE. |
| **Digoxin level > 2ng/ml** | Look for signs or symptoms of digoxin toxicity (bradycardia, nausea, diarrhoea, confusion) to determine if a potential ADE has occurred. Not all levels above normal will result in an ADE. |
| **Hypoglycaemia (blood glucose < 4 mmol/L or 72 mg/dl)** | Look for symptoms such as lethargy, tremor, confusion, faintness or administration of intravenous or oral glucose.<br>**Use** of any of the following drugs?<br>☐ Insulin<br>☐ Oral hypoglycaemic agents (except metformin in monotherapy)<br>☐ MAO – inhibitors<br>☐ β-blockers (masking symptoms of hypoglycaemia) |
| **Hyperglycaemia (blood glucose > 11 mmol/L or 198 mg/dl)** | **Use** of any drugs that may cause or worsen hyperglycaemia?<br>☐ Corticosteroids<br>☐ Atypical antipsychotics (mainly olanzapine & clozapine)<br>☐ Thiazide diuretics *less frequent*<br>☐ β-blockers (except carvedilol and nebivolol) *less frequent*<br>☐ Protease-inhibitors<br>☐ Calcineurin Inhibitors (cyclosporine, sirolimus, tacrolimus)<br>☐ Other (*Please specify*): |
| | In case hyperglycaemia is part of diabetic ketoacidosis or hyperosmolar hyperglycaemic state in a patient, review for **underuse** of insulin or oral hypoglycaemic agents. |
| **Hyperkalaemia ($K^+$ > 5.5 mmol/L)** | **Use** of any the following drugs?<br>☐ Intravenous or oral potassium<br>☐ Potassium-sparing diuretics<br>☐ ACE-inhibitors<br>☐ Angiotensin receptor blockers<br>☐ Direct renin inhibitors (e.g. aliskiren)<br>☐ Non-steroidal anti-inflammatory drugs<br>☐ Heparins (seldom, mainly when treated > 7days and concomitant other risk factors)<br>☐ Trimethoprim-sulfamethoxazole<br>☐ Cyclosporine<br>☐ Tacrolimus<br>☐ Other (*Please specify*): |
| **Hypokalaemia ($K^+$ < 3 mmol/L)** | **Use** of any of the following drugs?<br>☐ Loop diuretics<br>☐ Thiazide and thiazide-like diuretics<br>☐ Corticosteroids<br>☐ Laxatives<br>☐ Salbutamol (IV or aerosol)<br>☐ Theophylline<br>☐ Other (*Please specify*): |
| **Hyponatraemia ($Na^+$ < 130 mmol/L)** | **Use** of any of the following drugs?<br>☐ Diuretics<br>☐ Selective serotonin reuptake inhibitors<br>☐ Tricyclic antidepressants<br>☐ ACE-inhibitors<br>☐ Angiotensin receptor blockers<br>☐ Carbamazepine & oxcarbazepine<br>☐ High dose cyclophosphamide<br>☐ Other (*Please specify*): |
| **White blood cells < 3000 /$mm^3$ or < 3 x $10^3$/µL** | **Use** of any of the following drugs?<br>☐ Carbamazepine & oxcarbazepine<br>☐ Antipsychotics ( mainly clozapine)<br>☐ Thyreostatics<br>☐ Ganciclovir<br>☐ Immunosuppressants<br>☐ Chemotherapy (*Please specify):*<br>☐ Mirtazapine (first 6 weeks of treatment)<br>☐ Voriconazole<br>☐ Other (*Please specify*): |
| **Platelet count < 50000 /$mm^3$ or < 50 x $10^3$/µL** | **Use** of any of the following drugs?<br>☐ Carbamazepine & oxcarbazepine<br>☐ Ganciclovir<br>☐ Unfractionated heparin<br>☐ Low molecular weight heparins<br>☐ Immunosuppressants<br>☐ Thienopyridines (mainly ticlopidine)<br>☐ Quinine sulfate<br>☐ Sulfamides *Less frequent*<br>☐ Chemotherapy (*Please specify):*<br>☐ Other (*Please specify*): |
| **Neutrophils < 1400/$mm^3$ or < 1.4 x $10^3$/µL** | **Use** of any of the following drugs?<br>☐ Ganciclovir<br>☐ Antipsychotics ( mainly clozapine)<br>☐ Thyreostatics<br>☐ Thienopyridines (mainly ticlopidine)<br>☐ Chemotherapy (*Please specify):*<br>☐ 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?<br>☐ Flumazenil in a patient on benzodiazepines<br>☐ Naloxone in a patient on opioids<br>☐ Phytonadione (vitamin K) in a patient on VKA<br>☐ Protamine sulphate in a patient on heparins<br>☐ Oral or intravenous glucose or glucagon in a patient taking hypoglycaemic drugs<br>☐ Potassium supplements in case of hypokalaemia<br>☐ Sodium polystyrene (Kayexalate) in case of hyperkalaemia<br>☐ Adrenaline, antihistamines and corticosteroids (general drug allergy)<br>☐ Acetylcysteine (paracetamol overdose)<br>☐ Digoxin antibodies in a patient with a supratherapeutic digoxin levels<br>☐ Oral metronidazole or vancomycin in a patient who has recently been treated with an antibiotic that may cause *Clostridium difficile* associated diarrhoea |
| **Mention of a (potential) ADE in the medical record** | Assess causality using the WHO-UMC criteria |
| **Abrupt medication stop within 24h of admission** | When medications are stopped or withheld as compared to medications taken at home, look for reasons why this was done. Abruptly stopping medications is a trigger requiring further investigation for cause. A sudden change in patient condition requiring adjustment of medications is often related to an ADE |

ADE, adverse drug event; ADR, adverse drug reaction; COPD, chronic obstructive pulmonary disease; DVT, deep vein thrombosis; ESH/ESC, European Society of Hypertension/European Society of Cardiology; FEV1, forced expiratory volume in 1 second; INR, international normalised ratio, NSAIDS, non-steroidal anti-inflammatory drugs; PE, pulmonary embolism; VKA, Vitamin K antagonists

| SCREENING QUESTIONS FOR NON-TRIGGERED, SPONTANEOUSLY DETECTED EVENTS | |
|---|---|
| 1. Could the main or contributory reason for admission be related to a drug or recent change in medications? | |
| ☐ Adverse drug reaction (non-preventable side effect, first allergic reaction)<br>☐ Overuse of medication(s) (drug without an indication, too long duration of therapy, therapeutic duplication)<br>☐ Inappropriate discontinuation (removal or dosage decrease) leading to physiological withdrawal signs/symptoms or return of the underlying disease signs/symptoms | ☐ Wrong drug<br>☐ Wrong dose (supratherapeutic or subtherapeutic)<br>☐ Clinically significant drug-drug or drug-food interactions<br>☐ Inappropriate monitoring<br>☐ Other (e.g. drug not correctly dispensed/prepared/administered) |
| 2. Could the main or contributory reason for admission be related to underuse? | |
| ☐ Omission of an indicated drug<br>☐ Too short duration of medication therapy | ☐ Suspected adherence concerns |

From : 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.

**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

| | **ICD10 codes** |
|---|---|
| Dementia | F00; F01; F02; F03; F05.1; G30; G31.1 |
| Depression | F32; F33 |
| Stroke | I63;I69;I74;G45;G46 |
| Hypertension | I10; I15 |
| Diabetes | E10–E14; G590; G632; G730; G990; H280; H360; I792; L97; M142; M146; N083; G590; G632; G730; G990; H280; H360; I792; L97; M142; M146; N083 |
| Non-valvular atrial fibrillation | I48 |
| Coronary heart disease | I20-I25 |
| Heart failure | I11.0; I13.0; I13.2; I13.9; I50; K76.1; J81 |
| Chronic renal failure | N18;I12.0; I13.1; I13.2; E10.2; E11.2; E13.2; E14.2;N08.3; Z49.0-Z49.2; Z94.0; Z99.2 |
| Chronic hepatic disease | R18; I85; K70; K71.4; K71.5; K71.7; K72; K73; K74; K76.1; B18; C22; C78.7 |
| COPD | J43; J44 |
| Cancer | C00-C26;C30-C34;C37-C41;C43; C45-C58; C60-C76;C81-C85;C88; C90-C97; C77-C80 |
| History of hospitalization for major bleeding | I60-I62; S063; S064; S065; S066; K250; K252; K254; K256; K260; K262; K264; K266; K270; K272; K274; K276; K280; K282; K284; K286; K290; K920; K921; K922; I850; N02; R31; J942; R040; R041; R042; R048; R049; D62; K661; K624; M250; R58; N920; N921; N924; N938; N939; N920; N950; H113; H356; H431; H450; H922; I312 |
| Venous thrombo-embolism | I26; I80-I82 |

Abbreviations: COPD: chronic obstructive pulmonary disease

**Charlson score**

| | **ICD10 codes** | Points |
|---|---|---|
| Coronary heart disease | I20-I25 | 1 |
| Heart failure | I11.0; I13.0; I13.2; I13.9; I50; K76.1; J81 | 1 |
| Peripheral vascular disease | I70;I71;I731;I738;I739;I771;I790;I792;K551;K558;K559; Z958;Z959 | 1 |
| Cerebrovascular disease | G45;G46;H340;I60-I69 | 1 |
| Dementia | F00; F01; F02; F03; F05.1; G30; G31.1 | 1 |
| Chronic pulmonary disease | I278;I279;J40-J47;J60-J67;J684;J701;J703 | 1 |
| Connective tissue disease | M05;M06;M315;M32;M33;M34;M351;M353;M360 | 1 |
| Ulcer disease | K25-K28 | 1 |
| Mild liver disease | B18;K700-K703;K709;K713K715;K717;K73;K74;K760;K762-764;K768;K769;Z944 | 1 |
| Diabetes | E100;E101;E106;E108;E109;E110;E111;E116;E118;E119;E120;E121;E126;E128-E131;E136;E138-E141; E146;E148; E149 | 1 |
| Hemiplegia | G041;G114;G801;G802;G81;G82; G830; G831-G834;G839 | 2 |
| Moderate or severe renal disease | I120;I131;N032-N037;N052-N057;N18;N19;N250;Z490;Z491;Z492;Z940;Z992 | 2 |
| Diabetes with end-organ damage | E102-E105;E107;E112-E115;E117;E122-E125;E127;E132-E135;E137;E142-E145;E147 | 2 |
| Any tumor (except for malignant neoplasm of skin) | C00-C26;C30-C34;C37-C41;C43; C45-C58; C60-C76;C81-C85;C88; C90-C97 | 2 |
| Moderate or severe liver disease | I850;I859;I864;I982;K704;K711; K721;K729; K765-K767 | 3 |
| Metastatic solid tumor | C77-C80 | 6 |
| HIV-AIDS | B20-B22;B24;Z21 | 6 |
| Age (years) | | |
| - 50 – 59 | | 1 |
| - 60 – 69 | | 2 |
| - 70 – 79 | | 3 |
| - 80 – 89 | | 4 |
| - 99 - 99 | | 5 |

| | ATC codes |
|---|---|
| Oral antithrombotics | B01AC06; B01AC04; B01AC22; B01AC24; B01AC07; B01AC30; B01AA03; B01AA07; B01AA12; B01AF01; B01AF02; B01AE07 |
| Analgesics[1] | N02 |
| NSAIDs[2] | M01A |
| Psycholeptics[3] | N05 |
| Psychoanaleptics[4] | N06 |
| Antidiabetic drugs | A10 |
| Diuretics | C03 |
| Beta-blocking agents | C07 |
| Agents acting on the renin angiotensin system | C09 |
| Calcium channel blockers | C08 |
| Lipid modifying agents | C10 |

[1] : Analgesics = opioids (N02A), other analgesics and antipyretics (N02B), antimigraine preparations (N02C)

[2] : Nonsteroidal anti-inflammatory drug

[3] : Psycholeptics = antipsychotics (NO5A), anxiolytics (NO5B), hypnotics and sedatives (N05C)

[4] : Psychoanaleptics = antidepressants (N06A), psychostimulants (N06B), psycholeptics and psychoanaleptics in combination (N06C), anti-dementia drugs (N06D)

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

| | Number of triggers | Numbers of confirmed DRA | PPV [CI 95%] | Numbers of confirmed preventable DRA** | PPV [CI 95%] |
|---|---|---|---|---|---|
| **TRIGGER – DIAGNOSES*** | | | | | |
| Fall/fracture | 122 | 82 | 0.67 [0.58 – 0.75] | 38 | 0.31 [0.23 – 0.40] |
| Confusion/delirium | 63 | 27 | 0.43 [0.30 – 0.56] | 6 | 0.10 [0.04 – 0.20] |
| Acute renal impairment | 166 | 48 | 0.29 [0.29 – 0.36] | 19 | 0.11 [0.07 – 0.17] |
| Dehydration | 54 | 29 | 0.54 [0.40 – 0.67] | 10 | 0.19 [0.09 – 0.31] |
| Bleeding | 90 | 76 | 0.84 [0.75 – 0.91] | 19 | 0.21 [0.13 – 0.31] |
| Stroke | 10 | 7 | 0.70 [0.35 – 0.93] | 6 | 0.60 [0.26 – 0.88] |
| Thromboembolic event | 3 | 1 | 0.33 [0.01 – 0.91] | 1 | 0.33 [0.01 – 0.91] |
| Myocardial infarction or ischaemic disease | 32 | 18 | 0.56 [0.38 – 0.74] | 18 | 0.56 [0.38 – 0.74] |
| Heart failure exacerbation | 101 | 66 | 0.65 [0.55 – 0.75] | 56 | 0.55 [0.45 – 0.65] |
| COPD exacerbation | 60 | 37 | 0.62 [0.48 – 0.74] | 18 | 0.30 [0.19 – 0.43] |
| Uncontrolled non-neuropathic pain | 36 | 22 | 0.61 [0.43 – 0.77] | 18 | 0.50 [0.33 – 0.67] |
| Gastrointestinal disorders | 66 | 27 | 0.41 [0.29 – 0.54] | 4 | 0.06 [0.02 – 0.15] |
| Major constipation or faecal impaction | 40 | 14 | 0.35 [0.21 – 0.52] | 9 | 0.23 [0.11 – 0.38] |
| **At least one 'diagnoses' trigger** | 622 | 381 | 0.61 [0.57 – 0.65] | 179 | 0.29 [0.25 – 0.33] |
| **TRIGGER - LABORATORY VALUES*** | | | | | |
| INR > 5 | 8 | 6 | 0.75 [0.35 – 0.97] | 4 | 0.50 [0.16 – 0.84] |
| Digoxin level > 2 ng/ml | 0 | 0 | | 0 | |
| Hypoglycaemia | 11 | 4 | 0.36 [0.11 – 0.69] | 2 | 0.18 [0.02 – 0.52] |
| Hyperglycaemia | 50 | 6 | 0.12 [0.05 – 0.24] | 3 | 0.06 [0.01 – 0.17] |
| Hyperkalaemia | 36 | 11 | 0.31 [0.16 – 0.48] | 2 | 0.06 [0.01 – 0.19] |

| | Number of triggers | Numbers of confirmed DRA | PPV [CI 95%] | Numbers of confirmed preventable DRA** | PPV [CI 95%] |
|---|---|---|---|---|---|
| Hypokalaemia | 10 | 2 | 0.20 [0.03 – 0.56] | 2 | 0.20 [0.03 – 0.56] |
| Hyponatremia | 57 | 18 | 0.32 [0.20 – 0.45] | 7 | 0.12 [0.05 – 0.24] |
| WBC < 3000/mm3 | 12 | 8 | 0.67 [0.35 – 0.90] | 0 | 0 |
| Platelet count < 50000/mm3 | 7 | 5 | 0.71 [0.29 – 0.96] | 0 | 0 |
| Neutrophils < 1400/mm3 | 9 | 6 | 0.67 [0.30 – 0.93] | 0 | 0 |
| **At least one 'laboratory values' trigger** | 169 | 53 | 0.31 [0.24 – 0.39] | 20 | 0.12 [0.07 – 0.18] |
| **TRIGGER – OTHERS** | | | | | |
| Antidote use or treatments that suggest a potential ADE | 21 | 16 | 0.76 [0.53 – 0.92] | 8 | 0.38 [0.18 – 0.62] |
| Mention of a potential ADE in the medical record | 136 | 96 | 0.71 [0.62 – 0.78] | 26 | 0.19 [0.13 – 0.27] |
| Abrupt medication stops with 24 h of admission | 119 | 77 | 0.65 [0.55 – 0.73] | 24 | 0.20 [0.13 – 0.29] |
| **At least one 'others' trigger** | 205 | 134 | 0.65 [0.58 – 0.72] | 39 | 0.19 [0.14 – 0.25] |
| **TOTAL** | | | | | |
| **At least one trigger** | **716** | **471*** ** | **0.66 [0.62 – 0.69]** | **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 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

**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

| | Number of triggers | Numbers of confirmed ADE | PPV [CI 95%] to detect ADE | Numbers of confirmed DRA | PPV [CI 95%] to detect DRA |
|---|---|---|---|---|---|
| **TRIGGER – DIAGNOSES*** | | | | | |
| **Fall/fracture** | | | | | |
| **All** | **122** | **95** | **0.78 [0.69 – 0.85]** | **82** | **0.67 [0.58 – 0.75]** |
| Belgium | 21 | 19 | 0.90 [0.70 – 0.99] | 16 | 0.77 [0.53 – 0.92] |
| Ireland | 29 | 19 | 0.66 [0.46 – 0.82] | 13 | 0.45 [0.26 – 0.65] |
| The Netherlands | 16 | 10 | 0.63 [0.35 – 0.85] | 10 | 0.63 [0.35 – 0.85] |
| Switzerland | 56 | 47 | 0.84 [0.72 – 0.93] | 43 | 0.77 [0.64 – 0.87] |
| **Confusion/delirium** | | | | | |
| **All** | **63** | **39** | **0.62 [0.49 – 0.74]** | **27** | **0.43 [0.30 – 0.56]** |
| Belgium | 6 | 4 | 0.67 [0.22 – 0.96] | 1 | 0.17 [0.004 – 0.64] |
| Ireland | 20 | 6 | 0.30 [0.11 – 0.54] | 2 | 0.10 [0.01 – 0.32] |
| The Netherlands | 14 | 9 | 0.65 [0.35 – 0.87] | 6 | 0.43 [0.18 -0.71] |
| Switzerland | 23 | 20 | 0.87 [0.66 – 0.97] | 18 | 0.78 [0.56 – 0.92] |
| **Acute renal impairment** | | | | | |
| **All** | **166** | **136** | **0.82 [0.75 – 0.87]** | **48** | **0.29 [0.29 – 0.36]** |
| Belgium | 54 | 47 | 0.87 [0.75 – 0.95] | 15 | 0.28 [0.16 – 0.42] |
| Ireland | 17 | 7 | 0.41 [0.18 – 0.67] | 4 | 0.23 [0.07 – 0.50] |
| The Netherlands | 28 | 23 | 0.82 [0.63 – 0.94] | 13 | 0.46 [0.27 – 0.66] |
| Switzerland | 67 | 59 | 0.88 [0.78 – 0.95] | 16 | 0.24 [0.14 – 0.36] |

| | Number of triggers | Numbers of confirmed ADE | PPV [CI 95%] to detect ADE | Numbers of confirmed DRA | PPV [CI 95%] to detect DRA |
|---|---|---|---|---|---|
| **Dehydration** | | | | | |
| **All** | **54** | **44** | **0.81 [0.69 – 0.91]** | **29** | **0.54 [0.40 – 0.67]** |
| Belgium | 10 | 10 | 1.00 [0.69 – 1.00] | 5 | 0.50 [0.19 – 0.81] |
| Ireland | 16 | 7 | 0.44 [0.20 – 0.70] | 3 | 0.19 [0.04 – 0.46] |
| The Netherlands | 10 | 10 | 1.00 [0.69 – 1.00] | 5 | 0.50 [0.19 – 0.81] |
| Switzerland | 18 | 17 | 0.95 [0.73 – 0.99] | 16 | 0.89 [0.65 – 0.99] |
| **Bleeding** | | | | | |
| **All** | **90** | **88** | **0.98 [0.92 – 1.00]** | **76** | **0.84 [0.75 – 0.91]** |
| Belgium | 11 | 11 | 1.00 [0.72 – 1.00] | 10 | 0.91 [0.59 – 0.99] |
| Ireland | 14 | 13 | 0.93 [0.66 – 0.99] | 9 | 0.64 [0.35 – 0.87] |
| The Netherlands | 25 | 24 | 0.96 [0.80 – 0.99] | 19 | 0.76 [0.55 – 0.91] |
| Switzerland | 40 | 40 | 1.00 [0.99 – 1.00] | 38 | 0.95 [0.83 – 0.99] |
| **Stroke** | | | | | |
| **All** | **10** | **7** | **0.70 [0.35 – 0.93]** | **7** | **0.70 [0.35 – 0.93]** |
| Belgium | 1 | 1 | 1.00 [0.02 – 1.00] | 1 | 1.00 [0.02 – 1.00] |
| Ireland | 4 | 3 | 0.75 [0.19 – 0.99] | 3 | 0.75 [0.19 – 0.99] |
| The Netherlands | 1 | 1 | 1.00 [0.02 – 1.00] | 1 | 1.00 [0.02 – 1.00] |
| Switzerland | 4 | 2 | 0.50 [0.07 – 0.93] | 2 | 0.50 [0.07 – 0.93] |
| **Thromboembolic event** | | | | | |
| **All** | **3** | **2** | **0.67 [0.09 – 0.99]** | **1** | **0.33 [0.01 – 0.91]** |
| Belgium | 0 | 0 | NA | 0 | NA |
| Ireland | 1 | 1 | 1.00 [0.02 – 1.00] | 0 | 0.00 [0.00 – 0.97] |
| The Netherlands | 1 | 1 | 1.00 [0.02 – 1.00] | 1 | 1.00 [0.02 – 1.00] |
| Switzerland | 1 | 0 | 0.00 [0.00 – 0.97] | 0 | 0.00 [0.00 – 0.97] |

| | Number of triggers | Numbers of confirmed ADE | PPV [CI 95%] to detect ADE | Numbers of confirmed DRA | PPV [CI 95%] to detect DRA |
|---|---|---|---|---|---|
| **Myocardial infarction or ischaemic disease** | | | | | |
| **All** | **32** | **28** | **0.88 [0.71 – 0.96]** | **18** | **0.56 [0.38 – 0.74]** |
| Belgium | 18 | 16 | 0.89 [0.65 – 0.99] | 9 | 0.50 [0.26 – 0.74] |
| Ireland | 5 | 4 | 0.80 [0.28 – 0.99] | 3 | 0.60 [0.15 – 0.95] |
| The Netherlands | 7 | 6 | 0.86 [0.42 – 0.99] | 5 | 0.71 [0.29 – 0.96] |
| Switzerland | 2 | 2 | 1.00 [0.99 – 1.00] | 1 | 0.50 [0.01 – 0.99] |
| **Heart failure exacerbation** | | | | | |
| **All** | **101** | **73** | **0.72 [0.62 – 0.81]** | **66** | **0.65 [0.55 – 0.75]** |
| Belgium | 22 | 18 | 0.82 [0.60 – 0.95] | 18 | 0.82 [0.59 – 0.94] |
| Ireland | 12 | 11 | 0.92 [0.61 – 0.99] | 10 | 0.83 [0.52 – 0.98] |
| The Netherlands | 28 | 15 | 0.54 [0.34 – 0.73] | 15 | 0.54 [0.34 – 0.72] |
| Switzerland | 39 | 29 | 0.74 [0.58 – 0.87] | 23 | 0.59 [0.42 – 0.74] |
| **COPD exacerbation** | | | | | |
| **All** | **60** | **40** | **0.68 [0.53 – 0.78]** | **37** | **0.62 [0.48 – 0.74]** |
| Belgium | 1 | 0 | 0.00 [0.00 – 0.97] | 0 | 0.00 [0.00 – 0.97 |
| Ireland | 8 | 5 | 0.62 [0.24 – 0.91] | 5 | 0.62 [0.24 – 0.91] |
| The Netherlands | 45 | 29 | 0.65 [0.49 – 0.78] | 26 | 0.58 [0.42 – 0.72] |
| Switzerland | 6 | 6 | 1.00 [0.54 – 1.00] | 6 | 1.00 [0.54 – 1.00] |
| **Uncontrolled non-neuropathic pain** | | | | | |
| **All** | **36** | **30** | **0.83 [0.67 – 0.94]** | **22** | **0.61 [0.43 – 0.77]** |
| Belgium | 14 | 9 | 0.65 [0.35 – 0.87] | 6 | 0.43 [0.18 – 0.71] |
| Ireland | 3 | 3 | 1.00 [0.98 – 1.00] | 2 | 0.67 [0.09 – 0.99] |
| The Netherlands | 11 | 10 | 0.91 [0.59 – 0.99] | 9 | 0.82 [0.48 – 0.98] |
| Switzerland | 8 | 8 | 1.00 [0.63 – 1.00] | 5 | 0.63 [0.25 – 0.92] |

| | Number of triggers | Numbers of confirmed ADE | PPV [CI 95%] to detect ADE | Numbers of confirmed DRA | PPV [CI 95%] to detect DRA |
|---|---|---|---|---|---|
| **Gastrointestinal disorders** | | | | | |
| **All** | **66** | **44** | **0.67 [0.54 – 0.78]** | **27** | **0.41 [0.29 – 0.54]** |
| Belgium | 8 | 6 | 0.75 [0.35 – 0.97] | 1 | 0.13 [0.003 – 0.53] |
| Ireland | 20 | 5 | 0.25 [0.09 – 0.49] | 2 | 0.10 [0.01 – 0.32] |
| The Netherlands | 21 | 18 | 0.86 [0.64 – 0.97] | 10 | 0.48 [0.26 – 0.70] |
| Switzerland | 17 | 15 | 0.88 [0.64 – 0.98] | 14 | 0.82 [0.57 – 0.96] |
| **Major constipation or faecal impaction** | | | | | |
| **All** | **40** | **34** | **0.85 [0.70 – 0.94]** | **14** | **0.35 [0.21 – 0.52]** |
| Belgium | 9 | 7 | 0.78 [0.40 – 0.97] | 4 | 0.44 [0.14 – 0.79] |
| Ireland | 16 | 13 | 0.81 [0.54 – 0.96] | 3 | 0.19 [0.04 – 0.46] |
| The Netherlands | 7 | 6 | 0.86 [0.42 – 0.99] | 3 | 0.43 [0.10 – 0.82] |
| Switzerland | 8 | 8 | 1.00 [0.63 – 1.00] | 4 | 0.50 [0.16 – 0.85] |
| **At least one diagnoses trigger** | | | | | |
| **All** | **622** | **506** | **0.81 [0.78 – 0.84]** | **381** | **0.61 [0.57 – 0.65]** |
| Belgium | 119 | 105 | 0.88 [0.81 – 0.93] | 69 | 0.58 [0.49 – 0.67] |
| Ireland | 114 | 77 | 0.67 [0.58 – 0.76] | 55 | 0.48 [0.39 – 0.58] |
| The Netherlands | 169 | 127 | 0.75 [0.68 – 0.81] | 103 | 0.61 [0.53 – 0.68] |
| Switzerland | 220 | 197 | 0.89 [0.85 – 0.93] | 154 | 0.70 [0.64 – 0.76] |
| **TRIGGER – LABORATORY VALUES*** | | | | | |
| **INR** | | | | | |
| **All** | **8** | **8** | **1.00 [0.63 – 1.00]** | **6** | **0.75 [0.35 – 0.97]** |
| Belgium | 3 | 3 | 1.00 [0.29 – 1.00] | 2 | 0.67 [0.09 – 0.99] |
| Ireland | 0 | 0 | NA | 0 | NA |
| The Netherlands | 3 | 3 | 1.00 [0.29 – 1.00] | 3 | 1.00 [0.29 – 1.00] |
| Switzerland | 2 | 2 | 1.00 [0.16 – 1.00] | 1 | 0.50 [0.01 – 0.98] |

| | Number of triggers | Numbers of confirmed ADE | PPV [CI 95%] to detect ADE | Numbers of confirmed DRA | PPV [CI 95%] to detect DRA |
|---|---|---|---|---|---|
| **Hypoglycaemia** | | | | | |
| **All** | **11** | **8** | **0.73 [0.39 – 0.94]** | **4** | **0.36 [0.11 – 0.69]** |
| Belgium | 2 | 1 | 0.50 [0.01 – 0.98] | 1 | 0.50 [0.01 – 0.98] |
| Ireland | 6 | 4 | 0.67 [0.22 – 0.96] | 1 | 0.17 [0.004 – 0.64] |
| The Netherlands | 1 | 1 | 1.00 [0.02 – 1.00] | 1 | 1.00 [0.02 – 1.00] |
| Switzerland | 2 | 2 | 1.00 [0.16 – 1.00] | 1 | 0.50 [0.01 – 0.98] |
| **Hyperglycaemia** | | | | | |
| **All** | **50** | **34** | **0.68 [0.53 – 0.80]** | **6** | **0.12 [0.05 – 0.24]** |
| Belgium | 14 | 8 | 0.57 [0.29 – 0.83] | 0 | 0.00 [0.00 – 0.23] |
| Ireland | 9 | 6 | 0.67 [0.30 – 0.92] | 2 | 0.22 [0.03 – 0.60] |
| The Netherlands | 12 | 8 | 0.67 [0.35 – 0.90] | 2 | 0.17 [0.02 – 0.48] |
| Switzerland | 15 | 12 | 0.80 [0.52 – 0.96] | 2 | 0.13 [0.02 – 0.41] |
| **Hyperkalaemia** | | | | | |
| **All** | **36** | **29** | **0.81 [0.64 – 0.92]** | **11** | **0.31 [0.16 – 0.48]** |
| Belgium | 10 | 9 | 0.90 [0.56 – 0.99] | 2 | 0.20 [0.02 – 0.56] |
| Ireland | 8 | 6 | 0.75 [0.35 – 0.97] | 2 | 0.25 [0.03 – 0.65] |
| The Netherlands | 12 | 9 | 0.75 [0.43 – 0.94] | 6 | 0.50 [0.21 – 0.79] |
| Switzerland | 6 | 5 | 0.83 [0.36 – 0.99] | 1 | 0.17 [0.004 – 0.64] |
| **Hypokalaemia** | | | | | |
| **All** | **10** | **9** | **0.90 [0.55 – 1.00]** | **2** | **0.20 [0.03 – 0.56]** |
| Belgium | 2 | 1 | 0.50 [0.1 – 0.98] | 0 | 0.00 [0.00 – 0.84] |
| Ireland | 1 | 1 | 1.00 [0.02 – 1.00] | 0 | 0.00 [0.00 – 0.97] |
| The Netherlands | 1 | 1 | 1.00 [0.02 – 1.00] | 0 | 0.00 [0.00 – 0.97] |
| Switzerland | 6 | 6 | 1.00 [0.54 – 1.00] | 2 | 0.33 [0.04 – 0.78] |

| | Number of triggers | Numbers of confirmed ADE | PPV [CI 95%] to detect ADE | Numbers of confirmed DRA | PPV [CI 95%] to detect DRA |
|---|---|---|---|---|---|
| **Hyponatremia** | | | | | |
| **All** | **57** | **45** | **0.79 [0.66 – 0.89]** | **18** | **0.32 [0.20 – 0.45]** |
| Belgium | 11 | 10 | 0.91 [0.58 – 0.99] | 5 | 0.45 [0.17 – 0.77] |
| Ireland | 21 | 11 | 0.52 [0.30 – 0.74] | 4 | 0.19 [0.05 – 0.42] |
| The Netherlands | 13 | 12 | 0.92 [0.64 – 0.99] | 6 | 0.43 [0.19 – 0.75] |
| Switzerland | 12 | 12 | 1.00 [0.73 – 1.00] | 3 | 0.25 [0.06 – 0.57] |
| **WBC < 3000/mm3** | | | | | |
| **All** | **12** | **12** | **1.00 [0.74 – 1.00]** | **8** | **0.67 [0.35 – 0.90]** |
| Belgium | 3 | 3 | 1.00 [0.29 – 1.00] | 3 | 1.00 [0.29 – 1.00 |
| Ireland | 0 | 0 | NA | 0 | NA |
| The Netherlands | 2 | 2 | 1.00 [0.99 – 1.00] | 1 | 0.50 [0.01 – 0.99] |
| Switzerland | 7 | 7 | 1.00 [0.99 – 1.00] | 4 | 0.57 [0.18 – 0.90] |
| **Platelet count < 50000/mm3** | | | | | |
| **All** | **7** | **7** | **1.00 [0.59 – 1.00]** | **5** | **0.71 [0.29 – 0.96]** |
| Belgium | 2 | 2 | 1.00 [0.16 – 1.00] | 2 | 1.00 [0.16 – 1.00] |
| Ireland | 0 | 0 | NA | 0 | NA |
| The Netherlands | 1 | 1 | 1.00 [0.02 – 1.00] | 1 | 1.00 [0.02 – 1.00] |
| Switzerland | 4 | 4 | 1.00 [0.99 – 1.00] | 2 | 0.50 [0.06 – 0.93] |
| **Neutrophils < 1400/mm3** | | | | | |
| **All** | **9** | **9** | **1.00 [0.66 – 1.00]** | **6** | **0.67 [0.30 – 0.93]** |
| Belgium | 1 | 1 | 1.00 [0.02 – 1.00] | 1 | 1.00 [0.02 – 1.00] |
| Ireland | 0 | 0 | NA | 0 | NA |
| The Netherlands | 2 | 2 | 1.00 [0.16 – 1.00] | 1 | 0.50 [0.01 – 0.99] |
| Switzerland | 6 | 6 | 1.00 [0.99 – 1.00] | 4 | 0.67 [0.22 – 0.96] |

| | Number of triggers | Numbers of confirmed ADE | PPV [CI 95%] to detect ADE | Numbers of confirmed DRA | PPV [CI 95%] to detect DRA |
|---|---|---|---|---|---|
| **At least one laboratory trigger** | | | | | |
| **All** | **169** | **136** | **0.80 [0.74 – 0.86]** | **53** | **0.31 [0.24 – 0.39]** |
| Belgium | 39 | 31 | 0.80 [0.64 – 0.91] | 13 | 0.33 [0.19 – 0.50] |
| Ireland | 41 | 26 | 0.63 [0.47 – 0.78] | 7 | 0.17 [0.07 – 0.32] |
| The Netherlands | 40 | 34 | 0.85 [0.70 – 0.94] | 18 | 0.45 [0.29 – 0.61] |
| Switzerland | 49 | 45 | 0.92 [0.80 – 0.98] | 15 | 0.31 [0.18 – 0.45] |
| **TRIGGER – OTHERS*** | | | | | |
| **Antidote** | | | | | |
| **All** | **21** | **19** | **0.90 [0.70 – 0.99]** | **16** | **0.76 [0.53 – 0.92]** |
| Belgium | 3 | 2 | 0.67 [0.09 – 0.99] | 2 | 0.67 [0.09 – 0.99] |
| Ireland | 0 | 0 | NA | 0 | NA |
| The Netherlands | 11 | 10 | 0.91 [0.59 – 0.99] | 10 | 0.91 [0.59 – 0.99] |
| Switzerland | 7 | 7 | 1.00 [0.59 – 1.00] | 4 | 0.57 [0.18 – 0.90] |
| **Mention of a potential ADE in the medical record** | | | | | |
| **All** | **136** | **128** | **0.94 [0.89 – 0.97]** | **96** | **0.71 [0.62 – 0.78]** |
| Belgium | 33 | 32 | 0.97 [0.84 – 0.99] | 27 | 0.82 [0.65 – 0.93] |
| Ireland | 15 | 13 | 0.87 [0.60 – 0.98] | 7 | 0.47 [0.21 – 0.73] |
| The Netherlands | 34 | 30 | 0.88 [0.72 – 0.97] | 21 | 0.62 [0.44 – 0.78] |
| Switzerland | 54 | 53 | 0.98 [0.90 – 1.00] | 41 | 0.76 [0.63 – 0.87] |
| **Abrupt medication stops with 24 h of admission** | | | | | |
| **All** | **119** | **107** | **0.90 [0.83 – 0.95]** | **77** | **0.65 [0.55 – 0.73]** |
| Belgium | 29 | 28 | 0.97 [0.82 – 0.99] | 24 | 0.83 [0.64 – 0.94] |

| | Number of triggers | Numbers of confirmed ADE | PPV [CI 95%] to detect ADE | Numbers of confirmed DRA | PPV [CI 95%] to detect DRA |
|---|---|---|---|---|---|
| Ireland | 17 | 14 | 0.82 [0.57 – 0.96] | 5 | 0.30 [0.10 – 0.56] |
| The Netherlands | 38 | 31 | 0.82 [0.66 – 0.92] | 22 | 0.58 [0.41 – 0.74] |
| Switzerland | 35 | 34 | 0.97 [0.85 – 0.99] | 26 | 0.74 [0.57 – 0.87] |
| **At least one other trigger** | | | | | |
| **All** | **205** | **191** | **0.93 [0.89 – 0.96]** | **134** | **0.65 [0.58 – 0.72]** |
| Belgium | 45 | 43 | 0.96 [0.85 – 0.99] | 36 | 0.80 [0.65 – 0.90] |
| Ireland | 31 | 26 | 0.84 [0.66 – 0.94] | 11 | 0.36 [0.19 – 0.55] |
| The Netherlands | 60 | 53 | 0.89 [0.77 – 0.95] | 37 | 0.62 [0.48 – 0.74] |
| Switzerland | 69 | 69 | 1.00 [0.95 – 1.00] | 50 | 0.73 [0.60 – 0.82] |
| **TOTAL AT LEAST ONE TRIGGER** | | | | | |
| **All** | **716** | **621**** | **0.87 [0.84 – 0.89]** | **471**** | **0.66 [0.62 – 0.69]** |
| Belgium | 136 | 127 | 0.93 [0.88 – 0.97] | 90 | 0.66 [0.58 – 0.74] |
| Ireland | 135 | 108 | 0.80 [0.72 – 0.86] | 75 | 0.56 [0.47 – 0.64] |
| The Netherlands | 192 | 151 | 0.79 [0.72 – 0.84] | 120 | 0.62 [0.55 – 0.69] |
| Switzerland | 253 | 235 | 0.93 [0.89 – 0.96] | 186 | 0.73 [0.67 – 0.79] |

*A trigger is positive when the diagnosis or lab value AND a potential causative drug (or drug lacking in case of underuse) are present.
** Number of ADE / DRA identified from triggered events and therefore included in the PPV calculation

**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

| Triggers | Drugs involved<br>N (%) | Additional information and revised proposal |
|---|---|---|
| **Diagnoses** | | |
| Fall / fracture<br>(N = 82)<br><br>+ orthostatic hypotension | Use of any of the following drugs:<br>Benzodiazepines: 13 (16%)<br>Non Benzodiazepine hypnotics: 8 (10%)<br>Antipsychotics: 4 (5%)<br>Antidepressants: 14 (17%)<br>Sedating antihistamines: 0 (0%)<br>Opioids: 6 (7%)<br>Anticholinergic drugs: 16 (20%)<br>Calcium channel blockers: 6 (7%)<br>Diuretics: 17 (21%)<br>Alpha1 receptor blockers: 8 (10%)<br>Nitrates: 0 (0%)<br>Beta blockers: 22 (27%)<br>ACE inhibitors: 10 (12%)<br>Angiotensin receptor blockers: 5 (6%)<br>Direct renin inhibitors: 0 (0%)<br>Anti-parkinson drugs: 4 (5%)<br>Gliflozines: 0 (0%)<br>Drug induced hypoglycemia: 1 (1%)<br>Others: 10 (12%) | Others (N = 10):<br>- Azathioprin, proton pump inhibitor<br>- VKA DOAC and aspirin (consequences of the fall)<br><br>Most prevalent (≥ 5%):<br>- Use of any of the following drugs: Benzodiazepines, Non Benzodiazepine hypnotics, Antidepressants, Antipsychotics, Opioids, Anticholinergic drugs, Calcium channel blockers, Diuretics, Alpha1 receptor blockers, Beta blockers, ACE inhibitors, Angiotensin receptor blockers, Anti-parkinson drugs<br>- Underuse of any of the following drugs: Vitamin D, Bone-antiresorptive therapy<br><br>The same drugs were used in the revised version of the tool (Table 3) |

| | | |
|---|---|---|
| | Underuse of any of the following drugs:<br>Vitamin D: 11 (13%)<br>Bone-antiresorptive therapy: 9 (11%) | |
| Confusion/delirium (N = 27) | Use or stop of any of the following drugs:<br>Benzodiazepines: 4 (15%)<br>Non Benzodiazepines: 2 (7%)<br>Antipsychotics: 4 (15%)<br>Anti-epileptics: 3 (11%)<br>Antihistamines: 0 (0%)<br>Antidepressants: 2 (7%)<br>Opioids: 6 (22%)<br>Dopaminergic agents: 3 (11%)<br>Digoxin: 0 (0%)<br>Fluoroquinolones: 0 (0%)<br>Acetylcholinesterase-inhibitors: 0 (0%)<br>Other anticholinergic drugs: 0 (0%)<br>Corticosteroids: 1 (4%)<br>Lithium: 1 (4%)<br>Others: 3 (11%) | Others (N = 3): NSAIDs, diuretics, Beta blockers, Baclofen<br><br>Most prevalent (≥ 5%):<br>- Use or underuse of any of the following drugs: Benzodiazepines, Non Benzodiazepine hypnotics, Antipsychotics, Anti-epileptics, Antidepressants, Opioids, Dopaminergic agents<br><br>The same drugs were used in the revised version of the tool (Table 3) |
| Acute renal impairment (N = 48) | Use of any of the following drugs:<br>NSAIDs: 1 (2%)<br>ACE inhibitors: 10 (21%)<br>Angiotensin receptor blockers: 7 (15%)<br>Diuretics: 31 (65%)<br>Sulphonamides: 3 (6%)<br>Cephalosporins: 1 (2%)<br>Quinolones: 2 (4%)<br>Aminoglycosides: 0 (0%) | Others (N = 1): Nitrofurantoin, etanercept<br><br>More prevalent (≥ 5%):<br>- Use of any of the following drugs: ACE inhibitors, Angiotensin receptor blockers, Diuretics, Sulphonamides<br><br>The same drugs were used in the revised version of the tool (Table 3) |

| | | |
|---|---|---|
| | Vancomycin: 1 (2%)<br>Pentamidine: 0 (0%)<br>Rifampicin: 0 (0%)<br>Acyclovir, valacyclovir, ganciclovir, valganciclovir, foscarnet, cidofovir: 1 (2%)<br>Lithium: 0 (0%)<br>Calcineurin inhibitors: 2 (4%)<br>Cisplatin: 1 (2%)<br>Radiology contrast medium: 0 (0%)<br>Amphotericin: 0 (0%)<br>Bisphosphonates: 0 (0%)<br>Other nephrotoxic drugs: 2 (4%) | |
| Dehydration<br>(N = 29) | <u>Use of any of the following drugs:</u><br>Diuretics: 19 (66%)<br>Gliflozines: 0 (0%)<br>Laxatives: 3 (10%)<br>Any drugs causing vomiting: 6 (21%)<br>Any drugs causing diarrhea: 7 (24%)<br>Other: 0 (0%) | <u>More prevalent (≥ 5%):</u><br>- Use of any of the following drugs: Diuretics, Any drugs causing diarrhea (including laxatives), Any drugs causing vomiting<br><br><u>The same drugs were used in the revised version of the tool (Table 3)</u> |
| Bleeding<br>(N= 76) | <u>Use of any of the following drugs:</u><br>Antiplatelets: 29 (38%)<br>Vitamin K antagonists: 15 (20%)<br>Direct oral anticoagulant: 25 (33%)<br>Unfractioned heparin: 0 (0%)<br>Low molecular weight heparins: 5 (7%)<br>SSRI: 3 (4%)<br>NSAIDs: 2 (3%)<br>Other: 4 (5%) | <u>Others (N = 4):</u> Corticosteroids<br><br><u>More prevalent (≥ 5%):</u><br>- Use of any of the following drugs: Antiplatelets, Vitamin K antagonists, Direct oral anticoagulant, Low molecular weight heparins<br><br><u>The same drugs were used in the revised version of the tool (Table 3)</u> |

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| | Underuse of any of the following drugs:<br>PPI with VKA or DOA 0 (0%) | |
| Stroke<br>(N = 7) | Underuse of oral anticoagulant drugs in patients with known chronic atrial fibrillation: 4 (57%)<br><br>Underuse of adequate antihypertensive therapy: 0 (0%)<br><br>Underuse of any of the following drugs in patients with history of coronary, cerebral or peripheral vascular disease<br>- Antiplatelets: 1 (14%)<br>- Statins: 1 (14%)<br><br>Other: 1 (14%) | Others (N = 1): NSAIDs<br><br>More prevalent (≥ 5%):<br>- Underuse of oral anticoagulant drugs in patients with known chronic atrial fibrillation<br>- Underuse of antiplatelets and / or statins in patients with history of coronary, cerebral or peripheral vascular disease<br><br>The same drugs were used in the revised version of the tool (Table 3) |
| Thromboembolic event<br>(N = 1) | Underuse of adequate anticoagulation:<br>Vitamin K antagonists: 1 (100%)<br>Direct oral anticoagulant: 0 (0%)<br>Unfractioned heparin: 0 (0%)<br>Low molecular weight heparins: 0 (0%) | More prevalent (≥ 5%):<br>- Underuse of vitamin K antagonists<br><br>The same drugs were used in the revised version of the tool (Table 3) |
| (Recurrent) myocardial infarction or ischaemic disease<br>(N = 18) | Underuse of cardiovascular secondary prevention<br>Antiplatelets: 6 (33%)<br>Statins: 5 (28%)<br>Beta blockers / ACE inhibitors or Angiotensin receptor blocker / adequate anti-anginal therapy in case of ischemic disease: 6 (34%) | More prevalent (≥ 5%):<br>- Underuse of cardiovascular secondary prevention<br><br>The same drugs were used in the revised version of the tool (Table 3) |
| Heart failure exacerbation | Use of any of the following drugs:<br>NSAIDs: 3 (5%) | Others (N = 4): use of beta blockers (bradycardia), Carfilzomib, Tadalafil |

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| (N = 66) | Corticosteroids: 7 (11%)<br>Thiazolidinediones: 0 (0%)<br>Non-dihydropyridine calcium channel blockers: 0 (0%)<br>Sodium containing formulations: 0 (0%)<br>Other: 4 (6%)<br><br><u>Underuse of any of the following drugs</u><br>Beta blockers: 9 (14%)<br>ACE inhibitors: 29 (44%)<br>Diuretics: 17 (26%) | <u>More prevalent (≥ 5%):</u><br>- Use of any of the following drugs: NSAIDs, Corticosteroids<br>- Underuse of any of the following drugs: Beta blockers, ACE inhibitors, Diuretics<br><br><u>The same drugs were used in the revised version of the tool (Table 3)</u> |
| COPD exacerbation (N = 37) | <u>Use of any of the following drugs:</u><br>Benzodiazepines: 6 (16%)<br>Opioids: 14 (38%)<br>Other: 11 (29%)<br><br><u>Underuse of any of the following drugs</u><br>Single or dual inhaled bronchodilatator therapy: 5 (13%) | <u>Others (N = 11):</u> escitalopram, methotrexate, risperidone, protom pump inhibitor, metoprolol<br><br><u>More prevalent (≥ 5%):</u><br>- Use of any of the following drugs: Benzodiazepines, Opioids<br>- Underuse of any of the following drugs: Single or dual inhaled bronchodilatator therapy<br><br><u>The same drugs were used in the revised version of the tool (Table 3)</u> |
| Uncontrolled (non-neuropathic) pain (N = 22) | <u>Underuse of adequate pain treatment:</u><br>Strong opioid in moderate to severe pain if paracetamol, NSAIDS or weak opioids are not appropriate & Short-acting opioids for break-through pain during treatment with long acting opioids (difference not made): 10 (45%)<br><br>Other: 0% | <u>More prevalent (≥ 5%):</u> Underuse of adequate pain treatment (opioids)<br><br><u>The same drugs were used in the revised version of the tool (Table 3)</u> |

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| | *some of the events had no medication reported | |
| Gastrointestinal disorders (diarrhea, vomiting)<br>(N = 27) | Use of any of the following drugs:<br>Antibiotics: 5 (19%)<br>Laxatives: 3 (11%)<br>SSRI: 0 (0%)<br>Digoxin: 1 (4%)<br>Cholinesterase-inhibitors: 0 (0%)<br>Opioids: 7 (26%)<br>NSAIDs: 0 (0%)<br>Chemotherapy: 2 (7%)<br>Other: 4 (15%) | Others (N = 4): Metformin, oral iron, calcium<br><br>More prevalent (≥ 5%): Antibiotics, Laxatives, Opioids, Chemotherapy<br><br>The same drugs were used in the revised version of the tool (Table 3) |
| Major constipation<br>(N = 14) | Use of any of the following drugs:<br>Chronic laxative: 0 (0%)<br>Opioids: 4 (29%)<br>Calcium antagonists: 0 (0%)<br>Calcium: 0 (0%)<br>Oral iron: 2 (14%)<br>Aluminium antiacids: 0 (0%)<br>Atypical antipsychotics: 0 (0%)<br>Tricyclic antidepressant: 0 (0%)<br>Bladder antimuscarinics: 0 (0%)<br>Other anticholinergic drugs: 1 (7%)<br>Other: 0 (0%)<br><br>Underuse of laxatives: 6 (43%)<br><br>*some of the events had no medication reported | More prevalent (≥ 5%):<br>- Use of any of the following drugs: Opioids, Oral iron, anticholinergic drugs<br>- Underuse of any of the following drugs: laxatives<br><br>The same drugs were used in the revised version of the tool (Table 3) |

| Abnormal laboratory values | | |
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| INR > 5<br>(N = 6) | Bleeding + INR > 5 : 5 (83%) | New proposal:<br>- Remove this trigger which does not provide more than the trigger bleeding |
| Digoxin lever > 2 ng/ml<br>(N = 0) | Looks sign or symptoms of digoxin toxicity: bradycardia, nausea, diarrhea, confusion | New proposal:<br>- Remove this trigger which does not provide more than the triggers confusion, nausea, diarrhea, and antidote |
| Hypoglycaemia<br>(N = 4) | Use of any of the following drugs:<br>Insulin: 3 (75%)<br>Oral hypoglycemic agent: 1 (25%)<br>MAO-inhibitors: 0 (0%)<br>Beta-Blockers: 0 (0%) | New proposal:<br>- Remove this trigger which does not provide more than the trigger antidote |
| Hyperglycaemia<br>(N = 6) | Use of any of the following drugs:<br>Corticosteroids: 3 (50%)<br>Atypical antipsychotics: 0 (0%)<br>Thiazide diuretics: 0 (0%)<br>Beta blockers: 0 (0%)<br>Protease inhibitors: 0 (0%)<br>Calcineurin inhibitors: 0 (0%)<br>Other: 0 (0%)<br><br>Underuse of any of the following drugs<br>Underuse of insulin: 2 (33%)<br>Underuse of oral hypoglycemic agents: 2 (33%) | More prevalent (≥ 5%):<br>- Use of any of the following drugs: Corticosteroids<br>- Underuse of any of the following drugs: insulin, oral hypoglycemic agents<br><br>New proposal:<br>- Remove this trigger : Positive predictive value for detecting DRAs < 0.20. |
| Hyperkalaemia<br>(N = 11) | Use of any of the following drugs:<br>Intravenous or oral potassium: 0 (0%)<br>Potassium sparing diuretics: 4 (36%)<br>ACE inhibitors: 6 (55%) | Others (N = 2): Entresto, Pentozol<br><br>More prevalent (≥ 5 %):<br>- Use of any of the following drugs: Potassium sparing diuretics, |

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| | Angiotensin receptor blockers: 1 (9%)<br>Direct renin inhibitors: 0 (0%)<br>NSAIDSs: 0 (0%)<br>Heparins: 0 (0%)<br>Trimethoprim-sulfamethoxazole: 0 (0%)<br>Cyclosporine: 0 (0%)<br>Tacrolimus: 0 (0%)<br>Others: 2 (18%) | ACE inhibitors, Angiotensin receptor blockers<br><br>New proposal:<br>- Remove this trigger which does not provide more than the triggers acute renal impairment and antidote |
| Hypokalaemia<br>(N = 2) | Use of any of the following drugs:<br>Loop diuretics: 0 (0%)<br>Thiazide and thiazide like diuretics: 0 (0%)<br>Corticosteroids: 0 (0%)<br>Laxatives: 0 (0%)<br>Salbutamol: 0 (0%)<br>Theophylline: 0 (0%)<br>Other: 2 (100%) | Others (N = 2): Amoxicillin (Diarrhea)<br><br>More prevalent (≥ 5 %): None<br><br>The same drugs were used in the revised version of the tool (Table 3) |
| Hyponatremia<br>(N = 18) | Use of any of the following drugs:<br>Diuretics: 11 (61%)<br>SSRI: 3 (17%)<br>Tricyclic antidepressant: 0 (0%)<br>ACE-inhibitors: 2 (11%)<br>Angiotensin receptor blockers: 2 (11%)<br>Carbamazepine and oxcarbazepine: 0 (0%)<br>Cyclophosphamide: 0 (0%)<br>Other: 3 (17%) | Others (N = 3): Denosumab, NSAIDS, gliclazide<br><br>More prevalent (≥ 5%):<br>- Use of any of the following drugs: Diuretics, SSRI, ACE-inhibitors, Angiotensin receptor blockers<br><br>The same drugs were used in the revised version of the tool (Table 3) |
| WBC < 3000/mm3<br>(N = 8) | Use of any of the following drugs:<br>Carbamazepine and oxcarbazepine: 0 (0%)<br>Antipsychotics: 0 (0%) | More prevalent (≥ 5%): Immunosuppressants, Chemotherapy<br><br>New proposal: Remove this trigger : cf trigger Neutrophil |

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| | Thyreostatics: 0 (0%)<br>Ganciclovir: 0 (0%)<br>Immunosuppressants: 3 (38%)<br>Chemotherapy: 5 (62%)<br>Mirtazapine: 0 (0%)<br>Voriconazole: 0 (0%)<br>Other: 0 (0%) | |
| Platelet count < 50000/mm3<br>(N = 5) | Use of any of the following drugs:<br>Carbamazepine and oxcarbazepine: 0 (0%)<br>Ganciclovir: 0 (0%)<br>Unfractionned heparin: 0 (0%)<br>Low molecular weight heparin: 0 (0%)<br>Immunosuppressants: 3 (60%)<br>Thienopyridines: 0 (0%)<br>Quinine sulfate: 0 (0%)<br>Sulfamides: 0 (0%)<br>Chemotherapy: 2 (40%)<br>Other: 0 (0%) | More prevalent (≥ 5%): Immunosuppressants, Chemotherapy<br><br>New proposal: Remove this trigger : cf trigger Neutrophil |
| Neutrophils < 1400/mm3<br>(N = 6) | Use of any of the following drugs:<br>Ganciclovir: 0 (0%)<br>Antipsychotics: 0 (0%)<br>Thyreostatics: 0 (0%)<br>Thienopyridines: 0 (0%)<br>Chemotherapy: 6 (100%)<br>Other: 0 (0%) | More prevalent (≥ 5%): Chemotherapy<br><br>New proposal: Remove this trigger : because the causes of these 3 triggers are very similar, and because there are strong correlations between these triggers, we propose to group these triggers (allowing us to add the trigger anemia): "Pancytopenia or anomaly on one of the 3 lines : leucopenia, thrombopenia, anemia"<br><br>The same drugs used in each previous trigger were used in the revised version of the tool (Table 3) |

| Others | | |
|---|---|---|
| Antidote use or treatments that suggest a potential ADE<br><br>(N = 16) | Use of any of the following drugs on the day of admission:<br>Flumazenil: 0 (0%)<br>Naloxone: 1 (6%)<br>Vitamin K: 4 (25%)<br>Protamine sulphate: 1 (6%)<br>Glucose or glucagon: 0 (0%)<br>Potassium: 0 (0%)<br>Sodium polystyrene: 3 (19%)<br>Adrenaline, antihistamine, corticosteroids : 1 (6%)<br>Acetylcysteine : 0 (0%)<br>Digoxin antibodies : 0 (0%)<br>Metronidazole/Vancomycin in patients who had recently been treated with antibiotics who may cause Clostridium difficile infection : 1 (6%)<br><br>*some of the events had no medication reported | More prevalent (≥ 5 %): Naloxone, Vitamin K, Protamine sulphate, Sodium polystyrene, Adrenaline, antihistamine, corticosteroids, Metronidazole/Vanco<br><br>The same drugs were used in the revised version of the tool (Table 3) |
| Mention of a (potential) ADE in the medical record (N = 96) | Symptoms reported:<br>Bleeding: 21 (22%)<br>Dehydration: 11 (11%)<br>Infection: 11 (12%)<br>Heart failure exacerbation: 10 (10%)<br>Fall: 10 (10%)<br>Renal impairment: 9 (9%)<br>Confusion: 7 (7%)<br>Liver disorders: 6 (6%)<br>Hypotension: 6 (6%) | More prevalent (≥ 5%): Bleeding, dehydration, infection, heart failure exacerbation, fall, renal impairment, Confusion, Liver disorders, Hypotension<br><br>New proposal: proposition of new triggers<br><br>“Pancytopenia or anomaly on one of the 3 lines : leucopenia, thrombopenia, anemia” (cf neutrophils trigger)<br><br>“Orthostatic hypotension”: add in the title of the trigger fall (cf fall trigger) |

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| | Gastrointestinal disorders: 4 (4%)<br>Bradycardia: 4 (4%)<br>Abnormal movements: 4 (4%)<br>Hyponatremia: 3 (3%)<br>Hyperkaliemia: 2 (2%)<br>Pancytopenia: 2 (2%)<br>Anemia: 1 (1%)<br>Thromboembolic event: 1 (1%)<br>Constipation: 1 (1%)<br>Hypokaliemia: 1 (1%)<br>Thrombopenia: 1 (1%) | Infection<br>- Use of any of the following drugs:<br>  ○ Immunosuppressants and chemotherapy<br>  ○ Corticosteroids<br>- Underuse of any of the following drugs:<br>  ○ Vaccine (haemophilus, Pneumococcal, Influenza)<br><br>Liver disorders (OPERAM trial and literature)<br>- Use of any of the following drugs:<br>  ○ Acetaminophen<br>  ○ Antibiotics : Amoxicillin / clavulanate, flucloxacillin, ciprofloxacin, minocycline, nitrofurantoin, sulfonamides, macrolide<br>  ○ Antituberculosis drugs: isoniazid-rifampicin-pyrazinamide<br>  ○ Antiretroviral drugs: Zidovudine / stavudine<br>  ○ Tricyclic antidepressants<br>  ○ Antiepileptics: Carbamazepine, phenytoin, Valproate<br>  ○ Lipid lowering agents: Fenofibrate, statins<br>  ○ NSAIDs<br>  ○ Immunosuppressants<br>  ○ Chemotherapy<br>  ○ Methyldopa<br>  ○ Amiodarone<br>  ○ Allopurinol<br><br>Seizures or movement disorders (OPERAM trial and literature)<br>- Use of any of the following drugs:<br>  ○ Antipsychotic |

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| | | ○ Antidepressant<br>○ Antiepileptics (Valproate, carbamazepine, phenytoin)<br>○ Lithium<br>○ Anti-parkinson drugs<br>○ Amiodarone<br>- Abrupt withdrawal from:<br>○ Anti-parkinson drugs<br>○ Benzodiazepines<br>○ Antiepileptics |
| Abrupt medication stop within 24 hour of admission<br>(N = 77) | Symptoms reported:<br>Bleeding: 21 (27%)<br>Renal impairment: 13 (17%)<br>Fall: 11 (14%)<br>Dehydration: 9 (12%)<br>Infection: 7 (9%)<br>Hyperkaliemia: 6 (8%)<br>Confusion: 5 (7%)<br>Hyponatremia: 4 (5%)<br>Heart failure exacerbation: 3 (4%)<br>Liver disorders: 3 (4%)<br>Hypotension: 3 (4%)<br>Gastrointestinal disorders: 1 (1%)<br>Abnormal movements: 1 (1%) | More prevalent (≥ 5%): Bleeding, renal impairment , fall, dehydration, Infection, Hyperkaliemia, Confusion, Hyponatremia<br><br>New proposal: remove this trigger and proposition of new triggers<br><br>"Orthostatic hypotension": add in the title of the trigger fall (cf fall trigger)<br>Infection: cf mention of a potential ADE trigger<br>Liver disorders: cf mention of a potential ADE trigger<br>Seizures or movement disorders: cf mention of a potential ADE trigger |
| **Screening questions for non-triggered spontaneously detected event (N = 123)** | | |
| Adverse drug reaction (N = 90):<br>- Infection: 43 (48%) [chemotherapy, immunosuppressants, inhalation pneumonia linked to the use of opioids or hypnotics]<br>- Liver disorders: 6 (7%) | | New proposal: proposition of new triggers<br><br>- Infection: cf mention of a potential ADE trigger : + Add vaccine underuse |

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| - Others → included in the triggers<br><br>Overuse (N = 5) → included in the triggers<br><br>Underuse (N = 28):<br>- Infection: 5 (18%) [underuse of vaccine]<br>- Others → included in the triggers<br><br>Misuse (N = 13)<br>- Seizures and movement disorders: 2 (15%) [Lithium, Levetiracetam]<br>- Others → included in the triggers | - Seizures and movement disorders: cf mention of a potential ADE trigger |

**Abbreviations:** ACE: angiotensin converting enzyme; ATC: Anatomical therapeutic Chemical classification; COPD: chronic obstructive pulmonary disease, DOA: Direct oral anticoagulant, NSAID: Non-steroidal anti-inflammatory drugs, PPI: proton pump inhibitor, SSRI: Selective serotonin reuptake inhibitors, VKA: Vitamin K antagonist

**Appendix 6:** First version and revised version of trigger tool

**The first trigger tool: 26 triggers**

**Diagnoses trigger: N = 13**

- Fall / fracture
- Confusion/delirium
- Acute renal impairment
- Dehydration
- Bleeding
- Stroke
- Thromboembolic event
- (Recurrent) myocardial infarction or ischaemic disease
- Heart failure exacerbation
- COPD exacerbation
- Uncontrolled (non-neuropathic) pain
- Gastrointestinal disorders (diarrhea, vomiting)
- Major constipation

**Laboratory values trigger: N = 10**

- INR > 5
- Digoxin lever > 2 ng/ml
- Hypoglycaemia
- Hyperglycaemia
- Hyperkalaemia
- Hypokalaemia
- Hyponatremia
- WBC < 3000/mm3
- Platelet count < 50000/mm3
- Neutrophils < 1400/mm3

**Other trigger: N = 3**

- Antidote use or treatments that suggest a potential adverse drug event
- Mention of a (potential) ADE in the medical record
- Abrupt medication stop within 24 hour of admission

Red: triggers deleted for the revised version of the tool

**The revised trigger tool: 21 triggers**

**Diagnoses triggers: N = 16**

- Fall / fracture / orthostatic hypotension
- Confusion/delirium
- Acute renal impairment
- Dehydration
- Bleeding
- Stroke
- Thromboembolic event
- (Recurrent) myocardial infarction or ischaemic disease
- Heart failure exacerbation
- COPD exacerbation
- Uncontrolled (non-neuropathic) pain
- Gastrointestinal disorders (diarrhea, vomiting)
- Major constipation
- Infection
- Liver disorders
- Seizures or movement disorders

**Laboratory values triggers: N = 3**

- Hypokalaemia
- Hyponatremia
- Pancytopenia or anomaly on one of the 3 lines: leucopenia, thrombopenia, anaemia

**Other triggers: N = 2**

- Antidote use or treatments that suggest a potential adverse drug event
- Mention of a (potential) ADE in the medical record

Blue: new triggers for the revised version of the trigger tool