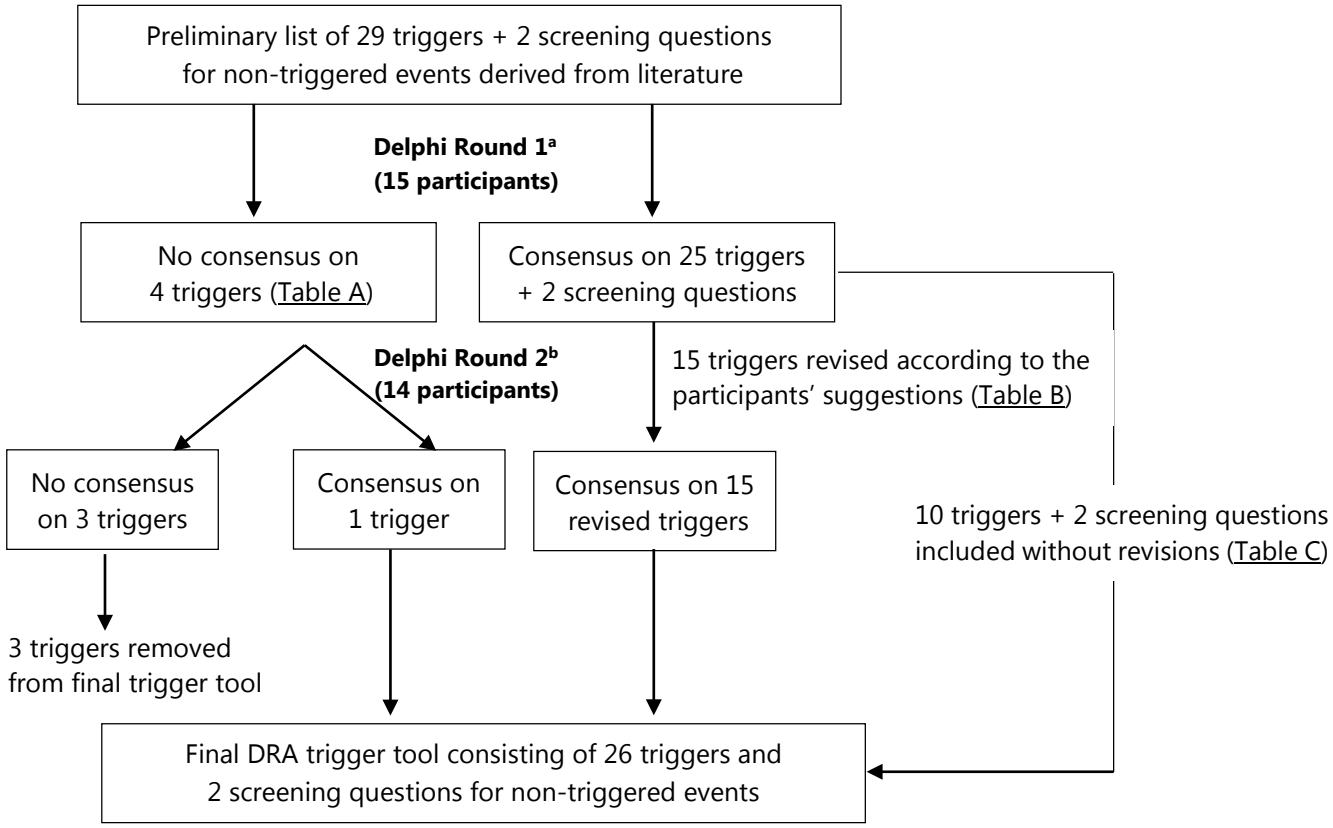
Supporting Information S1: Overview validation trigger tool for drug-related admissions (DRA) in older persons using a 2-round online modified Delphi technique with an international expert panel



[a] In Delphi round 1, participants rated for each trigger and screening question the "relevance to screen for a DRA in older people" on a 5-point Likert scale, ranging from "absolutely irrelevant" to "absolutely relevant". Relevance was defined as "the degree to which the item comprehensively includes the full scope of the outcome it intends to measure". A free-text field was provided for each item, allowing comments to improve trigger design.

[b] In Delphi round 2, a summary of the findings from round 1 was fed back to the participants. Participants re-evaluated the triggers for which there was no consensus in round 1 on the 5-point Likert scale, taking into account the groups' responses (Table A). Participants also rated the revised triggers on the 5-point Likert scale (Table B). The triggers and screening questions that were accepted unanimously in round 1, were not included in round 2 (Table C).

Table A: Triggers for which there was no consensus after round 1 and which were re-evaluated in round 2

Triggers (n=4)	Round 1	Expert panels' comments and suggestions	Round 2
	Median[a] score [IQR]		Median[a] score [IQR]
Rash [b]	4 [3-5]	▪ "Rash is no indication for admission" ▪ "Very unspecific term, the rash itself is unlikely to be the cause of admission, maybe better screen for allergic reaction" ▪ "Rash (and other allergic reactions like angio-oedema, bronchospasm, anaphylaxis) are triggers for DRPs in all patients, not specifically in older patients and are maybe more frequent in younger patients. I would suggest to leave the item out of the list." ▪ "More a situation in which the patient would go to the family physician, not requiring hospital admission" ▪ "Check the medication if rash but rash does not lead to hospital admission"	4 [2.25-5]
Clostridium difficile toxin positive stool [b]	4 [3.5-5]	▪ "Will not be very frequent" ▪ "Relevant if associated to diarrhoea, dehydration, abdominal pain, fever, which are reasons for admission. *Clostridium difficile* positive stool is not a sufficient reason." ▪ "Maybe it is related to antibiotic therapy, but it is a known effect and not easy to prevent. We could add proton pump inhibitors to medications that could cause a *Clostridium difficile* infection." ▪ "Not sure about this one"	4 [3-4.75]
Theophylline > 20 µg/ml [b]	4 [3-4]	▪ "Theophylline is less prescribed these days" ▪ "Rarely used in our country" ▪ "We don't use theophylline" ▪ "Not necessarily resulting in hospital admission, maybe not sensitive enough?" ▪ "Not seen in our patients" ▪ "Symptoms are more important, or make a general trigger abnormal blood levels of drugs with narrow therapeutic range"	4 [3-4]
Neutrophils < 1400/mm^3 [c]	4 [3.5-4.5]	▪ "Add symptoms" ▪ "Would remove this question, how many patients do we have on these agents" ▪ "Neutropenia is likely often associated with drug use, but probably not the reason for hospitalisation. E.g. for chemotherapy, fever in neutropenia would be the reason, so maybe better screen for such terms?" ▪ "Add thyreostatics, antipsychotics (atypical – OK mainly clozapine)"	4 [4-4]

[a] Score on the 5-point Likert scale, with 5 indicating "absolutely relevant" to screen for a drug-related admission in older persons and 1 indicating "absolutely irrelevant". Cut-off values for consensus measurement: consensus that a trigger should be retained if median ≥ 4 and 25th percentile ≥ 4, consensus that a trigger should be removed median ≤ 3 and 75th percentile < 3, no consensus for triggers that failed to meet either of the latter cut-off values.

[b] Triggers for which there was no consensus after round 2, were not included in the final trigger tool

[c] Trigger included in the final trigger tool

Note: The list of causative drugs or causes for underuse associated to each trigger is not shown here but was also shown to the participants.

Table B: Triggers for which there was consensus after round 1 but were revised according to the expert panels' suggestions and revisions were re-evaluated in round 2

Triggers (n=15)	Round 1 Median[a] score [IQR]	Revisions made according to the expert panels' suggestions	Round 2 Median[a] score [IQR]
Fall and/or fracture	5 [4-5]	▪ Inclusion of a list of clinically relevant anticholinergics ▪ Drugs that may cause orthostatic hypotention: addition of antidepressants (mainly tricyclic), antipsychotics, gliflozines (SGLT2-inhibitors) ▪ Underuse: modification of 'calcium and vitamin D' to '800 IU vitamin D/day (+ calcium if dietary intake is <1200-1000mg/day)' as it is the Vitamin D that is the essential treatment in osteopenia, osteoporosis and the recent information in the literature indicates that supplemental calcium may even be detrimental if the dietary content of calcium is already adequate	5 [4-5]
Confusion	5 [4.5-5]	▪ Inclusion of a list of clinically relevant anticholinergics ▪ Causative drugs: addition of non-benzodiazepine hypnotics, dopaminergic agonists, digoxin, fluoroquinolones, acetylcholinesterase-inhibitors ▪ Abrupt stop/rapid dose reduction: addition of antipsychotics	5 [4-5]
Acute renal impairment	4 [4-5]	▪ Causative drugs: addition of bisphosphonates, quinolones, antiviral agents ▪ Modification of cyclosporine to the whole class of calcineurin inhibitors (e.g. cyclosporine, tacrolimus)	5 [4.25-5]
Dehydration	4 [4-5]	▪ Causative drugs: addition of laxatives, gliflozines (SGLT-2 inhibitors), any drugs causing diarrhea, any drugs causing vomiting	5 [4-5]
Bleeding	5 [4.5-5]	▪ Differentiation of heparins into fractionated and non-fractionated heparins ▪ Addition of the following two items to 'Underuse of proton inhibitors prophylaxis while on': 1) Concurrent use of non-steroidal anti-inflammatory drugs (NSAIDs) and/or antiplatelets and/or corticosteroids 2) NSAIDs or antiplatelet or corticosteroids monotherapy with a history of peptic ulcer disease/gastro-intestinal bleeding	5 [5-5]
Stroke	4 [4-5]	▪ Addition of a definition of underuse of adequate antihypertensive therapy in older patients ▪ Addition of a definition of underuse of statins in older patients ▪ Removal of 'underuse of antiplatelets when anticoagulants are contra-indicated' because aspiring for stroke prevention is considered ineffective	5 [4-5]
Heart failure exacerbation	4 [4-5]	▪ Causative drugs: addition of 'sodium-containing formulations (effervescent, dispersible and soluble medications)', modification of 'calcium channel blockers' to 'non-dihydropyridine calcium channel blockers (verapamil, diltiazem)'	4.5 [4-5]
Chronic Obstructive Pulmonary Disease (COPD) exacerbation	4 [4-4.5]	▪ Causative drugs: addition of opioids ▪ Removal of non-selective β-blockers from causative drugs given recent evidence showing β-blockers are appropriate in COPD and associated with significantly reduced mortality	4 [4-4]

Table B: Triggers for which there was consensus after round 1 but were revised according to the expert panels' suggestions and revisions were re-evaluated in round 2

Triggers (n=15)	Round 1 Median[a] score [IQR]	Revisions made according to the expert panels' suggestions	Round 2 Median[b] score [IQR]
Major constipation or faecal impaction	4 [4-5]	▪ Inclusion of a list of clinically relevant anticholinergics ▪ Causative drugs: addition of calcium, atypical antipsychotics ▪ Modification of causative drug 'verapamil' to 'calcium antagonists (mainly verapamil)' in general as other calcium antagonists are not free from constipation as side effect either ▪ Modification of 'chronic laxative use' to 'chronic (stimulant) laxative use' because stimulant laxatives are particularly associated with myenteric plexus damage and consequent chronic constipation	4 [4-5]
Hyperkalaemia (K^+ > 5.5 mmol/L)	5 [4-5]	▪ Heparins: addition of the remark 'seldom, mainly when treated ≥ 7 days and concomitant other risk factors' ▪ Removal of digoxin	5 [4-5]
Hypokalaemia (K^+ < 3 mmol/L)	4 [4-5]	▪ Causative drugs: addition of laxatives, salbutamol ▪ Modification of 'thiazide diuretics' to 'thiazide and thiazide-like diuretics' (e.g. indapamide, chlortalidone) ▪ Removal of antithrombotics as hypokalaemia is not frequent with these medications	5 [4.25-5]
Hyponatraemia (Na^+ < 130 mmol/L)	4 [4-5]	▪ Causative drugs: addition of tricyclic antidepressants, high dose cyclophosphamide ▪ Modification of cut-off threshold from Na^+ <135 mmol/L to <130 mmol/L ▪ Removal of colchicine, non-steroidal inflammatory drugs and proton pump inhibitors because hyponatraemia is not frequent with these medications	4 [4-5]
White blood cells < 3000/mm^3	4 [4-4.5]	▪ Causative drugs: addition of voriconazole, thyreostatics and mirtazapine (first 6 weeks of treatment) ▪ Modification of 'clozapine' to 'antipsychotics (mainly clozapine)' as all antipsychotics may cause leucopenia	4 [4-4.75]
Platelet count < 50 000/mm^3	4 [4-4]	▪ Causative drugs: addition of unfractionated heparin, quinine sulfate, sulphamides	4 [4-4.75]
Antidote use or treatment that suggests a potential adverse drug event	5 [4-5]	▪ Modification of trigger name 'antidote use' to 'antidote use or treatment that suggest a potential adverse drug event' ▪ Addition of 'potassium supplements in case of hypokalaemia' and 'sodium polystyrene (Kayexalate) in case of hyperkalaemia'	5 [4-5]

[a] Score on the 5-point Likert scale, with 5 indicating "absolutely relevant" to screen for a drug-related admission in older persons and 1 indicating "absolutely irrelevant". Cut-off values for consensus measurement: consensus that a trigger should be retained if median ≥ 4 and 25th percentile ≥ 4, consensus that a trigger should be removed median ≤ 3 and 75th percentile < 3, no consensus for triggers that failed to meet either of the latter cut-off values. [b] In round 2 the revised triggers were evaluated.

Note: The list of causative drugs or causes for underuse associated to each trigger is not shown here but was also shown to the participants.

Table C: Triggers for which there was consensus after round 1 and were included without revisions in the final trigger tool

Triggers (n=10) and screening questions (n=2)	Median[a] score Round 1 [IQR]
Thromboembolic event (deep vein thrombosis or pulmonary embolism)	4 [4-5]
(Recurrent) myocardial infarction or ischaemic disease	4 [4-4.5]
Uncontrolled (non-neuropathic) pain	4 [4-5]
Gastro-intestinal disorders (severe diarrhoea, vomiting)	4 [4-5]
International Normalized Ratio > 5	4 [4-5]
Digoxin level > 2ng/ml	4 [4-4]
Hypoglycaemia (blood glucose < 4 mmol/L or 72 mg/dl	5 [4-5]
Hyperglycaemia (blood glucose > 11 mmol/L or 198 mg/dl)	4 [4-4.5]
Mention of a (potential) adverse drug event in the medical record	5 [4.5-5]
Abrupt medication stop within 24 hours of admission	4 [4-5]
Screening question adverse drug reaction/overuse/misuse	5 [4-5]
Screening question underuse	4 [4-5]

[a] Score on the 5-point Likert scale, with 5 indicating "absolutely relevant" to screen for a drug-related admission in older persons and 1 indicating "absolutely irrelevant". Cut-off values for consensus measurement: consensus that a trigger should be retained if median ≥ 4 and 25th percentile ≥ 4, consensus that a trigger should be removed median ≤ 3 and 75th percentile < 3, no consensus for triggers that failed to meet either of the latter cut-off values.