

SUPPLEMENTARY APPENDICES

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Supplementary appendix 1: High-risk prescribing errors amenable to clinical decision support (13)

Prescribing Error	Error Type
Penicillin containing compound prescribed to a penicillin allergic patient without reasoning (e.g. a mild or non-allergy such as diarrhoea or vomiting entered as an allergy where the indication for penicillin is compelling) (<i>Risk of hypersensitivity reactions</i>)	Allergy
Amiodarone prescribed to a patient with abnormal thyroid function tests (<i>Increased risk of thyroid disorders</i>)	Clinical contraindication
Non-cardioselective beta-adrenoceptor blocking drug prescribed to a patient with chronic obstructive pulmonary disease (<i>Increased risk of bronchospasm</i>)	Clinical contraindication
ACE inhibitor or angiotensin-II receptor antagonist prescribed to a patient with a potassium level ≥ 5.0 mmol/litre (<i>Can cause or exacerbate hyperkalaemia</i>)	Clinical contraindication
Verapamil prescribed to a patient with NYHA Class III or IV heart failure (<i>Risk of precipitating heart failure, exacerbating conduction disorders and causing significant deterioration</i>)	Clinical contraindication
Warfarin prescribed to a patient with a concurrent bleeding disorder (<i>Increased risk of bleeding</i>)	Clinical contraindication
Aspirin prescribed to a patient with a past medical history of peptic ulcer disease without anti-secretory drugs or mucosal protectants (<i>Increased risk of peptic ulceration, and risk of bleeding</i>)	Clinical contraindication
Antiplatelet prescribed to a patient with a concurrent bleeding disorder (<i>Increased risk of bleeding</i>)	Clinical contraindication
Benzodiazepine or benzodiazepine-like drug prescribed to a patient with chronic obstructive pulmonary disease (<i>Risk of respiratory depression</i>)	Clinical contraindication
Antipsychotic, other than risperidone, prescribed to a patient for the management of the behavioural and psychological symptoms of dementia (<i>Increased risk of stroke</i>)	Clinical contraindication
Tricyclic antidepressant prescribed to a patient with dementia (<i>Increased risk of worsening cognitive impairment</i>)	Clinical contraindication
Selective serotonin re-uptake inhibitor prescribed to a patient with epilepsy (<i>Increased risk of seizure threshold being reduced</i>)	Clinical contraindication
Selective serotonin re-uptake inhibitor prescribed to a patient with a history of clinically significant hyponatraemia (non-iatrogenic, sodium < 130 mmol/litre in the previous 2 months) (<i>Increased risk of hyponatraemia</i>)	Clinical contraindication
Prochlorperazine prescribed to a patient with parkinsonism (<i>Risk of exacerbating parkinsonism symptoms</i>)	Clinical contraindication
NSAID prescribed to a patient with chronic renal failure (<i>Increased risk of deteriorating renal function</i>)	Clinical contraindication
NSAID prescribed to a patient with a history of peptic ulcer disease or gastrointestinal bleeding without anti-secretory drugs or mucosal protectants (<i>Increased risk of peptic ulceration and bleeding</i>)	Clinical contraindication
NSAID prescribed to a patient with a history of heart failure (<i>Risk of exacerbation of heart failure</i>)	Clinical contraindication
Glibenclamide prescribed to an older adult with Type 2 diabetes mellitus (<i>Increased risk of hypoglycaemia</i>)	Clinical contraindication

Metformin prescribed to a patient with eGFR < 30 ml/min/1.73m ² (<i>Increased risk of lactic acidosis</i>)	Clinical contraindication
Pioglitazone prescribed to a patient with heart failure (<i>Risk of exacerbation of heart failure</i>) [†]	Clinical contraindication
Diphenoxylate, loperamide, codeine phosphate prescribed as antidiarrhoeal agents for treatment of severe infective gastroenteritis (e.g. bloody diarrhoea, high fever, or severe systemic toxicity) (<i>Increased risk of exacerbation or protraction of infection</i>)	Clinical contraindication
Metoclopramide prescribed to a patient with parkinsonism (<i>Risk of exacerbating parkinsonism symptoms</i>)	Clinical contraindication
Cephalosporin antibiotic prescribed to an older adult (except under the direction of Microbiology or for suspected meningitis) (<i>Increased risk of antibiotic-associated infections</i>)	Clinical contraindication
Vancomycin prescribed intravenously to a patient with renal impairment without dose adjustment (<i>Increased risk of toxicity</i>)	Clinical contraindication
Quinolone antibiotic prescribed to a patient with epilepsy (<i>Increased risk of seizure threshold being reduced</i>)	Clinical contraindication
Nitrofurantoin prescribed to a patient with eGFR < 60 ml/minute/1.73m ² (<i>Risk of peripheral neuropathy and inadequate concentration in urine</i>) [†]	Clinical contraindication
Methotrexate prescribed to a patient with a clinically significant drop in white cell count or platelet count (<i>Risk of bone marrow suppression</i>)	Clinical contraindication
Methotrexate prescribed to a patient with abnormal liver function tests (<i>Risk of liver toxicity</i>)	Clinical contraindication
Potassium chloride supplements continued for longer than is required (reference range 3.5–5.3 mmol/litre) (<i>Increased risk of hyperkalaemia</i>)	Clinical contraindication
Low molecular weight heparin prescribed without the patient's weight being used to calculate the treatment dose (<i>Risk of subtherapeutic or supratherapeutic dosing</i>)	Dosing
Low molecular weight heparin prescribed at a dose exceeding the maximum as stated in the product literature (<i>Risk of bleeding increased</i>)	Dosing
Digoxin prescribed at a dose >125 micrograms daily to a patient with renal impairment (<i>Increased risk of digoxin toxicity</i>)	Dosing
Digoxin prescribed at a dose of >125 micrograms daily to a patient with heart failure who is in sinus rhythm (<i>Increased risk of digoxin toxicity</i>)	Dosing
Low molecular weight heparin prescribed to a patient with renal impairment without dose adjustment (<i>Increased risk of bleeding</i>)	Dosing
Lithium dose not adjusted or omitted in a patient with a lithium concentration above the therapeutic range (> 1.0 mmol/litre) (<i>Risk of lithium toxicity</i>)	Dosing
Paracetamol prescribed at a dose of 4 g over a 24 hour to a patient under 50 kg (<i>Risk of hepatocellular toxicity</i>) [†]	Dosing
Domperidone prescribed at a total daily dose exceeding 30 mg/day in adults > 60 years old (<i>Increased risk of QTc prolongation, serious ventricular arrhythmia and sudden cardiac death</i>) [†]	Dosing
Gentamicin dose calculated based on actual body weight rather than ideal body weight in an obese patient (BMI > 30 kg/m ²) (<i>Risk of excessive dosing and toxicity</i>)	Dosing
Gentamicin prescribed to a patient with renal impairment without dose adjustment (<i>Increased risk of toxicity</i>)	Dosing

Gentamicin prescribed to an adult patient with normal renal function in a dose exceeding 7 mg/kg/day (<i>Increased risk of toxicity</i>)	Dosing
Amphotericin B prescribed without stating the brand name and the dose in mg/kg (<i>Risk of fatal overdose due to confusion between lipid based and non-lipid formulations</i>)	Drug name
Brand specific prescribing of tacrolimus preparations (<i>Brands vary in their dosing and pharmacokinetics</i>)	Drug name
Digoxin prescribed concomitantly with a diuretic (<i>Risk of hypokalaemia and subsequent digoxin toxicity</i>)	Drug-drug interaction
Statin prescribed concomitantly with a macrolide antibiotic (<i>Increased risk of myopathy</i>)	Drug-drug interaction
Potassium-sparing diuretic (excluding aldosterone antagonists) prescribed to a patient also receiving an ACE inhibitor or angiotensin-II receptor antagonist (<i>Increased risk of severe hyperkalaemia</i>)	Drug-drug interaction
Amiodarone prescribed concomitantly with simvastatin 40 mg or above (<i>Increased risk of myopathy</i>)	Drug-drug interaction
Verapamil prescribed to a patient concomitantly with a beta-adrenoceptor blocking drug (<i>Increased risk of adverse cardiovascular effects</i>)	Drug-drug interaction
Warfarin prescribed concomitantly with a NSAID (<i>Increased risk of bleeding</i>)	Drug-drug interaction
Clopidogrel prescribed to a patient concomitantly with a NSAID (<i>Increased risk of bleeding</i>)	Drug-drug interaction
Clopidogrel prescribed to a patient concomitantly with omeprazole or esomeprazole (<i>Antiplatelet effect of clopidogrel potentially reduced</i>) [†]	Drug-drug interaction
Macrolide antibiotic prescribed concomitantly with warfarin without appropriate dose adjustment or increased INR monitoring (<i>Increased risk of bleeding</i>)	Drug-drug interaction
Lithium prescribed in conjunction with newly prescribed NSAIDs without dose adjustment or increased monitoring (<i>Increased risk of toxicity</i>) [†]	Drug-drug interaction
Lithium therapy prescribed in conjunction with newly prescribed loop or thiazide diuretics without dose adjustment or increased monitoring (<i>Increased risk of toxicity</i>) [†]	Drug-drug interaction
Tricyclic antidepressant prescribed at the same time as a Monoamine Oxidase Inhibitor (<i>Increased risk of serotonin syndrome</i>)	Drug-drug interaction
Tramadol prescribed concomitantly with a Monoamine Oxidase Inhibitor (<i>Increased risk of serotonin syndrome</i>)	Drug-drug interaction
Selective serotonin re-uptake inhibitor prescribed concomitantly with tramadol (<i>Increased risk of serotonin syndrome</i>)	Drug-drug interaction
Selective serotonin re-uptake inhibitor prescribed concomitantly with aspirin without appropriate prophylaxis with anti-secretory drugs or mucosal protectant (<i>Increased risk of gastrointestinal bleeding</i>)	Drug-drug interaction
Citalopram prescribed concomitantly with other QT prolonging drugs (<i>Increased risk of arrhythmias</i>) [†]	Drug-drug interaction
Tramadol prescribed concomitantly with antiepileptics (<i>Increased risk of seizures in patients with uncontrolled epilepsy</i>) [†]	Drug-drug interaction
Nefopam prescribed concomitantly with antiepileptics (<i>Increased risk of seizures in patients with uncontrolled epilepsy</i>) [†]	Drug-drug interaction

Colestyramine prescribed to a patient at the same time as any other oral medication (<i>Risk of poor clinical effect owing to reduced absorption of medications</i>) [†]	Drug-drug interaction
Orlistat prescribed at the same time of day as oral antiepileptics (<i>Orlistat can reduce the absorption of antiepileptics, leading to loss of seizure control</i>)	Drug-drug interaction
Quinolone prescribed to a patient who is also receiving theophylline (<i>Possible increased risk of convulsions</i>)	Drug-drug interaction
Atazanavir prescribed concomitantly with a proton-pump inhibitor (<i>Concentration of atazanavir potentially reduced, reducing therapeutic effect</i>)	Drug-drug interaction
Methotrexate prescribed concomitantly with trimethoprim (<i>Increased risk of haematological toxicity</i>)	Drug-drug interaction
Phenytoin and enteral feeds prescribed to a patient concomitantly (<i>Reduced absorption of phenytoin</i>)	Drug-food interaction
More than one paracetamol-containing product prescribed to a patient at a time (<i>Maximum dose exceeded</i>)	Duplicate therapy
Benzodiazepines prescribed long-term (i.e. more than 2–4 weeks) (<i>Risk of dependence and withdrawal reactions</i>)	Duration
Benzodiazepine or benzodiazepine-like drug prescribed long-term to a patient with depression (<i>Risk of dependence and withdrawal reactions</i>)	Duration
Benzodiazepine-like drugs (e.g. zopiclone) prescribed long-term (i.e. more than 2–4 weeks) (<i>Risk of dependence reactions</i>)	Duration
Antipsychotic prescribed long-term (i.e. > 1 month) to a patient with parkinsonism (<i>Increased risk of worsening of extra-pyramidal side effects</i>)	Duration
Soluble insulin prescribed to a patient on a when required basis (<i>Increased risk of serious episodes of hypoglycaemia and nocturnal hypoglycaemia post dose</i>) [†]	Frequency
Weekly dose of an oral bisphosphonate prescribed daily (<i>Risk of hypocalcaemia</i>) [†]	Frequency
Oral methotrexate prescribed to a patient with an inappropriate frequency (<i>Increased risk of toxicity</i>)	Frequency
Diphenoxylate, loperamide, or codeine phosphate prescribed as antidiarrhoeal agents for treatment of diarrhoea of unknown cause (<i>Increased risk of exacerbating constipation with overflow diarrhoea</i>)	Indication
Vancomycin prescribed intravenously over less than 60 minutes (<i>Rapid infusion of vancomycin can cause severe reactions</i>)	Intravenous rate
Low molecular weight heparin omitted to be prescribed for prophylaxis (<i>Increased risk of thrombosis</i>)	Omission of prophylactic treatment
Regular opiates prescribed without concurrent use of laxatives (<i>Risk of severe constipation</i>) [‡]	Omission of prophylactic treatment
Prescribing of incorrect or inequivalent morphine (opiate) dose via multiple routes. (<i>Risk of toxicity</i>) [‡]	Route
Insulin prescribed to a patient at an inappropriate time, allowing for an administration without food (except once daily long-acting insulins) (<i>Increased risk of hypoglycaemia</i>)	Timing of dose

ACE Angiotensin converting enzyme; BMI Body mass index; eGFR Estimated glomerula filtration rate; NSAIDs Non-steroidal anti-inflammatory drugs; NYHA New York Heart Association

Supplementary appendix 2: Scoring likelihood and severity of the errors occurring (from the UK National Patient Safety Agency Risk Matrix)

Consequence	Likelihood				
	1 Rare <i>This will probably never occur</i>	2 Unlikely <i>Do not expect it to occur but it is possible it may do</i>	3 Possible <i>This might occasionally occur</i>	4 Likely <i>This will probably occur</i>	5 Almost certain <i>This will undoubtedly occur, possibly frequently</i>
5 Catastrophic <i>Leads to death, multiple permanent injuries, or irreversible health effects</i>	5	10	15	20	25
4 Major <i>Major injury leading to long-term incapacity/ disability</i>	4	8	12	16	20
3 Moderate <i>Moderate injury requiring intervention</i>	3	6	9	12	15
2 Minor <i>Minor injury or illness requiring minor intervention</i>	2	4	6	8	10
1 Insignificant <i>No risk of patient injury or harm and no intervention required</i>	1	2	3	4	5

Risk Rating Score			
1-3 Low risk	4-6 Moderate risk	8-12 High risk	15-25 Extreme risk

Supplementary appendix 3: Summary of the opportunities for error and high-risk errors occurring across all sites pre- and post-CPOE

Prescribing error	Pre-CPOE			Post-CPOE		
	N _{Opp}	N _{Err}	Error rate	N _{Opp}	N _{Err}	Error rate
Regular opiates prescribed without concurrent use of laxatives (<i>Risk of severe constipation</i>)	486	55	11.3%	438	37	8.4%
Benzodiazepines prescribed long-term (i.e. more than 2-4 weeks) (<i>Risk of dependence and withdrawal reactions</i>)	129	40	31.0%	122	38	31.1%
Digoxin prescribed concomitantly with a diuretic (<i>Risk of hypokalaemia and subsequent digoxin toxicity</i>)	76	39	51.3%	59	25	42.4%
Insulin prescribed to a patient at an inappropriate time, allowing for an administration without food (except once daily long-acting insulins) (<i>Increased risk of hypoglycaemia</i>)	104	28	26.9%	113	50	44.2%
Citalopram prescribed concomitantly with other QT prolonging drugs (<i>Increased risk of arrhythmias</i>)	161	28	17.4%	141	19	13.5%
Clopidogrel prescribed to a patient concomitantly with omeprazole or esomeprazole (<i>Antiplatelet effect of clopidogrel potentially reduced</i>)	409	27	6.6%	366	14	3.8%
Paracetamol prescribed at a dose of 4 g over a 24 hour to a patient under 50 kg (<i>Risk of hepatocellular toxicity</i>)	841	25	3.0%	863	29	3.4%
Selective serotonin re-uptake inhibitor prescribed concomitantly with tramadol (<i>Increased risk of serotonin syndrome</i>)	161	24	14.9%	141	5	3.5%
Potassium-sparing diuretic (excluding aldosterone antagonists) prescribed to a patient also receiving an ACE inhibitor or angiotensin-II receptor antagonist (<i>Increased risk of severe hyperkalaemia</i>)	334	23	6.9%	272	22	8.1%
Statin prescribed concomitantly with a macrolide antibiotic (<i>Increased risk of myopathy</i>)	434	20	4.6%	406	6	1.5%
ACE inhibitor or angiotensin-II receptor antagonist prescribed to a patient with a potassium level >5.0 mmol/litre (<i>Can cause or exacerbate hyperkalaemia</i>)	334	19	5.7%	272	19	7.0%
Benzodiazepine-like drugs (e.g. Zopiclone) prescribed long-term (i.e. more than 2-4 weeks) (<i>Risk of dependence reactions</i>)	129	19	14.7%	122	8	6.6%
Benzodiazepine or benzodiazepine-like drug prescribed long-term to a patient with depression (<i>Risk of dependence and withdrawal reactions</i>)	129	16	12.4%	122	5	4.1%
Low molecular weight heparin prescribed at a dose exceeding the maximum as stated in the product literature (<i>Risk of bleeding increased</i>)	712	15	2.1%	438	1	0.2%
More than one paracetamol-containing product prescribed to a patient at a time (<i>Maximum dose exceeded</i>)	841	14	1.7%	863	20	2.3%

Selective serotonin re-uptake inhibitor prescribed to a patient with a history of clinically significant hyponatraemia (non-iatrogenic , sodium <130 mmol/litre in the previous 2 months) (<i>Increased risk of hyponatraemia</i>)	161	14	8.7%	141	2	1.4%
Soluble insulin prescribed to a patient on a when required basis (<i>Increased risk of serious episodes of hypoglycaemia and nocturnal hypoglycaemia post dose</i>)	104	13	12.5%	113	16	14.2%
Benzodiazepine or benzodiazepine-like drug prescribed to a patient with COPD (<i>Risk of respiratory depression</i>)	129	12	9.3%	122	11	9.0%
Selective serotonin re-uptake inhibitor prescribed to a patient with epilepsy (<i>Increased risk of seizure threshold being reduced</i>)	161	11	6.8%	141	5	3.5%
Low molecular weight heparin prescribed to a patient with renal impairment without dose adjustment (<i>Increased risk of bleeding</i>)	712	10	1.4%	438	5	1.1%
Prescribing of incorrect or inequivalent morphine (opiate) dose via multiple routes (<i>Risk of toxicity</i>)	486	10	2.1%	438	1	0.2%
Selective serotonin re-uptake inhibitor prescribed concomitantly with aspirin without appropriate prophylaxis with anti-secretory drugs or mucosal protectant (<i>Increased risk of gastrointestinal bleeding</i>)	161	8	5.0%	141	11	7.8%
Vancomycin prescribed intravenously over less than 60 minutes (<i>Rapid infusion of vancomycin can cause severe reactions</i>)	22	7	31.8%	16	4	25.0%
Clopidogrel prescribed to a patient concomitantly with a NSAID (<i>Increased risk of bleeding</i>)	409	7	1.7%	366	2	0.5%
Antipsychotic, other than risperidone, prescribed to a patient for the management of the behavioural and psychological symptoms of dementia (<i>Increased risk of stroke</i>)	66	6	9.1%	61	6	9.8%
Antiplatelet prescribed to a patient with a concurrent bleeding disorder (<i>Increased risk of bleeding</i>)	409	6	1.5%	366	4	1.1%
Domperidone prescribed at a total daily dose exceeding 30 mg/day in adults > 60 years old (<i>Increased risk of QTc prolongation, serious ventricular arrhythmia and sudden cardiac death</i>)	21	6	28.6%	9	0	0.0%
Tramadol prescribed concomitantly with antiepileptics (<i>Increased risk of seizures in patients with uncontrolled epilepsy</i>)	486	5	1.0%	438	4	0.9%
Aspirin prescribed to a patient with a past medical history of peptic ulcer disease without anti-secretory drugs or mucosal protectants (<i>Increased risk of peptic ulceration, and risk of bleeding</i>)	409	4	1.0%	366	4	1.1%
Penicillin containing compound prescribed to a penicillin allergic patient without reasoning (e.g. a mild or non-allergy such as diarrhoea or vomiting entered as an allergy where the indication for penicillin is compelling) (<i>Risk of hypersensitivity reactions</i>)	244	4	1.6%	232	1	0.4%
Cephalosporin antibiotic prescribed to an older adult (except under the direction of Microbiology or for suspected meningitis) (<i>Increased risk of antibiotic-associated infections</i>)	27	4	14.8%	7	0	0.0%
Weekly dose of an oral bisphosphonate prescribed daily (<i>Risk of hypocalcaemia</i>)	74	4	5.4%	71	0	0.0%

Gentamicin prescribed to a patient with renal impairment without dose adjustment (<i>Increased risk of toxicity</i>)	46	3	6.5%	23	2	8.7%
Nitrofurantoin prescribed to a patient with eGFR < 60 ml/minute/1.73m ² (<i>Risk of peripheral neuropathy and inadequate concentration in urine</i>)	13	3	23.1%	1	0	0.0%
Warfarin prescribed concomitantly with a NSAID (<i>Increased risk of bleeding</i>)	106	3	2.8%	82	0	0.0%
Tricyclic antidepressant prescribed to a patient with dementia (<i>Increased risk of worsening cognitive impairment</i>)	79	2	2.5%	56	4	7.1%
Macrolide antibiotic prescribed concomitantly with warfarin without appropriate dose adjustment or increased INR monitoring (<i>Increased risk of bleeding</i>)	106	2	1.9%	82	2	2.4%
Gentamicin prescribed to an adult patient with normal renal function in a dose exceeding 7 mg/kg/day (<i>Increased risk of toxicity</i>)	46	2	4.3%	23	1	4.3%
Amiodarone prescribed to a patient with abnormal thyroid function tests (<i>Increased risk of thyroid disorders</i>)	24	2	8.3%	19	0	0.0%
Digoxin prescribed at a dose >125 micrograms daily to a patient with renal impairment (<i>Increased risk of digoxin toxicity</i>)	76	2	2.6%	59	0	0.0%
Metformin prescribed to a patient with eGFR < 30 mls/min/1.73m ² (<i>Increased risk of lactic acidosis</i>)	115	2	1.7%	104	0	0.0%
Methotrexate prescribed to a patient with abnormal liver function tests (<i>Risk of liver toxicity</i>)	11	2	18.2%	11	0	0.0%
NSAID prescribed to a patient with a history of heart failure (<i>Risk of exacerbation of heart failure</i>)	88	2	2.3%	74	0	0.0%
NSAID prescribed to a patient with chronic renal failure (<i>Increased risk of deteriorating renal function</i>)	88	2	2.3%	74	0	0.0%
Non-cardioselective beta-adrenoceptor blocking drug prescribed to a patient with COPD (<i>Increased risk of bronchospasm</i>)	306	1	0.3%	336	2	0.6%
Antipsychotic prescribed long-term (i.e. > 1 month) to a patient with parkinsonism (<i>Increased risk of worsening of extra-pyramidal side effects</i>)	66	1	1.5%	61	1	1.6%
Amiodarone prescribed concomitantly with simvastatin 40 mg or above (<i>Increased risk of myopathy</i>)	24	1	4.2%	19	0	0.0%
Brand specific prescribing of tacrolimus preparations (<i>Brands vary in their dosing and pharmacokinetics</i>)	5	1	20.0%	8	0	0.0%
Diphenoxylate, loperamide, or codeine phosphate prescribed as antidiarrhoeal agents for treatment of diarrhoea of unknown cause (<i>Increased risk of exacerbating constipation with overflow diarrhoea</i>)	65	1	1.5%	37	0	0.0%
Glibenclamide prescribed to an older adult with Type 2 diabetes mellitus (<i>Increased risk of hypoglycaemia</i>)	2	1	50.0%	0	0	NA
Methotrexate prescribed to a patient with a clinically significant drop in white cell count or platelet count (<i>Risk of bone marrow suppression</i>)	11	1	9.1%	11	0	0.0%

Metoclopramide prescribed to a patient with parkinsonism (<i>Risk of exacerbating parkinsonism symptoms</i>)	83	1	1.2%	98	0	0.0%
Pioglitazone prescribed to a patient with heart failure (<i>Risk of exacerbation of heart failure</i>)	5	1	20.0%	2	0	0.0%
Quinolone antibiotic prescribed to a patient with epilepsy (<i>Increased risk of seizure threshold being reduced</i>)	27	1	3.7%	10	0	0.0%
Tricyclic antidepressant prescribed at the same time as a Monoamine Oxidase Inhibitor (<i>Increased risk of serotonin syndrome</i>)	3	1	33.3%	0	0	NA
Vancomycin prescribed intravenously to a patient with renal impairment without dose adjustment (<i>Increased risk of toxicity</i>)	22	1	4.5%	16	0	0.0%
Prochlorperazine prescribed to a patient with parkinsonism (<i>Risk of exacerbating parkinsonism symptoms</i>)	15	0	0.0%	28	2	7.1%
Potassium chloride supplements continued for longer than is required (reference range 3.5-5.3 mmol/litre) (<i>Increased risk of hyperkalaemia</i>)	58	0	0.0%	55	1	1.8%
Warfarin prescribed to a patient with a concurrent bleeding disorder (<i>Increased risk of bleeding</i>)	106	0	0.0%	82	1	1.2%
Amphotericin B prescribed without stating the brand name and the dose in mg/kg (<i>Risk of fatal overdose due to confusion between lipid based and non-lipid formulations</i>)	0	0	NA	0	0	NA
Atazanavir prescribed concomitantly with a proton-pump inhibitor (<i>Concentration of atazanavir potentially reduced, reducing therapeutic effect</i>)	1	0	0.0%	0	0	NA
Colestyramine prescribed to a patient at the same time as any other oral medication (<i>Risk of poor clinical effect owing to reduced absorption of medications</i>)	1	0	0.0%	0	0	NA
Digoxin prescribed at a dose of >125 micrograms daily to a patient with heart failure who is in sinus rhythm (<i>Increased risk of digoxin toxicity</i>)	76	0	0.0%	59	0	0.0%
Diphenoxylate, loperamide, codeine phosphate prescribed as antidiarrhoeal agents for treatment of severe infective gastroenteritis (e.g. bloody diarrhoea, high fever, or severe systemic toxicity) (<i>Increased risk of exacerbation or protraction of infection</i>)	65	0	0.0%	35	0	0.0%
Gentamicin dose calculated based on actual body weight rather than ideal body weight in an obese patient (BMI > 30 kg/m ²) (<i>Risk of excessive dosing and toxicity</i>)	46	0	0.0%	23	0	0.0%
Lithium dose not adjusted or omitted in a patient with a lithium concentration above the therapeutic range (> 1.0 mmol/litre) (<i>Risk of lithium toxicity</i>)	4	0	0.0%	2	0	0.0%
Lithium prescribed in conjunction with newly prescribed NSAIDs without dose adjustment or increased monitoring (<i>Increased risk of toxicity</i>)	4	0	0.0%	2	0	0.0%

Lithium therapy prescribed in conjunction with newly prescribed loop or thiazide diuretics without dose adjustment or increased monitoring (<i>Increased risk of toxicity</i>)	4	0	0.0%	2	0	0.0%
Methotrexate prescribed concomitantly with trimethoprim (<i>Increased risk of haematological toxicity</i>)	11	0	0.0%	11	0	0.0%
Nefopam prescribed concomitantly with antiepileptics (<i>Increased risk of seizures in patients with uncontrolled epilepsy</i>)	0	0	NA	0	0	NA
NSAID prescribed to a patient with a history of peptic ulcer disease or gastrointestinal bleeding without anti-secretory drugs or mucosal protectants (<i>Increased risk of peptic ulceration and bleeding</i>)	88	0	0.0%	74	0	0.0%
Oral methotrexate prescribed to a patient with an inappropriate frequency (<i>Increased risk of toxicity</i>)	11	0	0.0%	11	0	0.0%
Orlistat prescribed at the same time of day as oral antiepileptics (<i>Orlistat can reduce the absorption of antiepileptics, leading to loss of seizure control</i>)	0	0	NA	0	0	NA
Phenytoin and enteral feeds prescribed to a patient concomitantly (<i>Reduced absorption of phenytoin</i>)	6	0	0.0%	10	0	0.0%
Quinolone prescribed to a patient who is also receiving theophylline (<i>Possible increased risk of convulsions</i>)	27	0	0.0%	10	0	0.0%
Tramadol prescribed concomitantly with a Monoamine Oxidase Inhibitor (<i>Increased risk of serotonin syndrome</i>)	3	0	0.0%	0	0	NA
Verapamil prescribed to a patient concomitantly with a beta-adrenoceptor blocking drug (<i>Increased risk of adverse cardiovascular effects</i>)	4	0	0.0%	6	0	0.0%
Verapamil prescribed to a patient with NYHA Class III or IV heart failure (<i>Risk of precipitating heart failure, exacerbating conduction disorders and causing significant deterioration</i>)	4	0	0.0%	6	0	0.0%

N_{opp} represents the number of error-opportunities generated, whilst N_{err} is the number of errors that were found to have occurred. Error rates were generated by dividing the latter by the former, with

“NA” representing cases where this rate was incalculable due to a denominator of zero.

ACE Angiotensin converting enzyme; BMI Body mass index; CPOE Computerised physician order entry; #eGFR Estimated glomerula filtration rate; NSAIDs Non-steroidal anti-inflammatory drugs; NYHA New York Heart Association

Supplementary appendix 4: Clinical decision support configured at each site for each of the 78 errors

Prescribing Error	Error Type	Level of CDS		
		Site 1	Site 2	Site 3
Penicillin containing compound prescribed to a penicillin allergic patient without reasoning (e.g. a mild or non-allergy such as diarrhoea or vomiting entered as an allergy where the indication for penicillin is compelling) (Risk of hypersensitivity reactions)	Allergy	Interruptive	Interruptive	Interruptive
ACE inhibitor or angiotensin-II receptor antagonist prescribed to a patient with a potassium level >5.0 mmol/litre (Can cause or exacerbate hyperkalaemia)	Clinical contraindication	None	None	None
Amiodarone prescribed to a patient with abnormal thyroid function tests (Increased risk of thyroid disorders)	Clinical contraindication	Interruptive	None	None
Antiplatelet prescribed to a patient with a concurrent bleeding disorder (Increased risk of bleeding)	Clinical contraindication	None	None	None
Antipsychotic, other than risperidone, prescribed to a patient for the management of the behavioural and psychological symptoms of dementia (Increased risk of stroke)	Clinical contraindication	None	None	None
Aspirin prescribed to a patient with a past medical history of peptic ulcer disease without anti-secretory drugs or mucosal protectants (Increased risk of peptic ulceration, and risk of bleeding)	Clinical contraindication	None	None	None
Benzodiazepine or benzodiazepine-like drug prescribed to a patient with chronic obstructive pulmonary disease(Risk of respiratory depression)	Clinical contraindication	None	None	None

Cephalosporin antibiotic prescribed to an older adult (except under the direction of Microbiology or for suspected meningitis) (Increased risk of antibiotic-associated infections)	Clinical contraindication	None	None	None
Diphenoxylate, loperamide, codeine phosphate prescribed as antidiarrhoeal agents for treatment of severe infective gastroenteritis (e.g. bloody diarrhoea, high fever, or severe systemic toxicity) (Increased risk of exacerbation or protraction of infection)	Clinical contraindication	None	None	None
Glibenclamide prescribed to an older adult with Type 2 diabetes mellitus (Increased risk of hypoglycaemia)	Clinical contraindication	None	None	None
Metformin prescribed to a patient with eGFR < 30 ml/min/1.73m ² (Increased risk of lactic acidosis)	Clinical contraindication	None	None	None
Methotrexate prescribed to a patient with a clinically significant drop in white cell count or platelet count (Risk of bone marrow suppression)	Clinical contraindication	Passive	None	None
Methotrexate prescribed to a patient with abnormal liver function tests (Risk of liver toxicity)	Clinical contraindication	None	None	None
Metoclopramide prescribed to a patient with parkinsonism (Risk of exacerbating parkinsonism symptoms)	Clinical contraindication	None	None	None
Nitrofurantoin prescribed to a patient with eGFR < 60 ml/minute/1.73m ² (Risk of peripheral neuropathy and inadequate concentration in urine) †	Clinical contraindication	None	None	None
Non-cardioselective beta-adrenoceptor blocking drug prescribed to a patient with COPD (Increased risk of bronchospasm)	Clinical contraindication	Interruptive	None	None

NSAID prescribed to a patient with a history of heart failure (Risk of exacerbation of heart failure)	Clinical contraindication	None	None	None
NSAID prescribed to a patient with a history of peptic ulcer disease or gastrointestinal bleeding without anti-secretory drugs or mucosal protectants (Increased risk of peptic ulceration and bleeding)	Clinical contraindication	None	None	None
NSAID prescribed to a patient with chronic renal failure (Increased risk of deteriorating renal function)	Clinical contraindication	None	None	None
Pioglitazone prescribed to a patient with heart failure (Risk of exacerbation of heart failure) †	Clinical contraindication	None	None	None
Potassium chloride supplements continued for longer than is required (reference range 3.5–5.3 mmol/litre) (Increased risk of hyperkalaemia)	Clinical contraindication	None	None	None
Prochlorperazine prescribed to a patient with parkinsonism (Risk of exacerbating parkinsonism symptoms)	Clinical contraindication	None	None	None
Quinolone antibiotic prescribed to a patient with epilepsy (Increased risk of seizure threshold being reduced)	Clinical contraindication	None	None	None
Selective serotonin re-uptake inhibitor prescribed to a patient with a history of clinically significant hyponatraemia (non-iatrogenic , sodium <130 mmol/litre in the previous 2 months) (Increased risk of hyponatraemia)	Clinical contraindication	None	None	None
Selective serotonin re-uptake inhibitor prescribed to a patient with epilepsy (Increased risk of seizure threshold being reduced)	Clinical contraindication	None	None	None
Tricyclic antidepressant prescribed to a patient with dementia (Increased risk of worsening cognitive impairment)	Clinical contraindication	None	None	None

Vancomycin prescribed intravenously to a patient with renal impairment without dose adjustment (Increased risk of toxicity)	Clinical contraindication	None	None	None
Verapamil prescribed to a patient with NYHA Class III or IV heart failure (Risk of precipitating heart failure, exacerbating conduction disorders and causing significant deterioration)	Clinical contraindication	Interruptive	None	None
Warfarin prescribed to a patient with a concurrent bleeding disorder (Increased risk of bleeding)	Clinical contraindication	Interruptive	None	None
Digoxin prescribed at a dose >125 micrograms daily to a patient with renal impairment (Increased risk of digoxin toxicity)	Dosing	Interruptive	None	None
Digoxin prescribed at a dose of >125 micrograms daily to a patient with heart failure who is in sinus rhythm (Increased risk of digoxin toxicity)	Dosing	None	None	None
Domperidone prescribed at a total daily dose exceeding 30 mg/day in adults > 60 years old (Increased risk of QTc prolongation, serious ventricular arrhythmia and sudden cardiac death) †	Dosing	Passive	None	None
Gentamicin dose calculated based on actual body weight rather than ideal body weight in an obese patient (BMI > 30 kg/m ²) (Risk of excessive dosing and toxicity)	Dosing	None	Interruptive	None
Gentamicin prescribed to a patient with renal impairment without dose adjustment (Increased risk of toxicity)	Dosing	None	None	None
Gentamicin prescribed to an adult patient with normal renal function in a dose exceeding 7 mg/kg/day (Increased risk of toxicity)	Dosing	None	None	None

Lithium dose not adjusted or omitted in a patient with a lithium concentration above the therapeutic range (> 1.0 mmol/litre) (Risk of lithium toxicity)	Dosing	None	None	None
Low molecular weight heparin prescribed at a dose exceeding the maximum as stated in the product literature (Risk of bleeding increased)	Dosing	Interruptive	None	None
Low molecular weight heparin prescribed to a patient with renal impairment without dose adjustment (Increased risk of bleeding)	Dosing	Interruptive	None	None
Paracetamol prescribed at a dose of 4 g over a 24 hour to a patient under 50 kg (Risk of hepatocellular toxicity) [†]	Dosing	Interruptive	None	None
Amphotericin B prescribed without stating the brand name and the dose in mg/kg (Risk of fatal overdose due to confusion between lipid based and non-lipid formulations)	Drug name	Interruptive	Interruptive	Interruptive
Brand specific prescribing of tacrolimus preparations (Brands vary in their dosing and pharmacokinetics)	Drug name	Interruptive	Interruptive	Interruptive
Amiodarone prescribed concomitantly with simvastatin 40 mg or above (Increased risk of myopathy)	Drug-drug interaction	None	Interruptive	Interruptive
Atazanavir prescribed concomitantly with a proton-pump inhibitor (Concentration of atazanavir potentially reduced, reducing therapeutic effect)	Drug-drug interaction	None	Interruptive	Interruptive
Citalopram prescribed concomitantly with other QT prolonging drugs (Increased risk of arrhythmias) †	Drug-drug interaction	None	Interruptive	Interruptive
Clopidogrel prescribed to a patient concomitantly with a NSAID (Increased risk of bleeding)	Drug-drug interaction	None	Interruptive	Interruptive

Clopidogrel prescribed to a patient concomitantly with omeprazole or esomeprazole (Antiplatelet effect of clopidogrel potentially reduced)†	Drug-drug interaction	None	Interruptive	Interruptive
Colestyramine prescribed to a patient at the same time as any other oral medication (Risk of poor clinical effect owing to reduced absorption of medications) †	Drug-drug interaction	Passive	None	None
Digoxin prescribed concomitantly with a diuretic (Risk of hypokalaemia and subsequent digoxin toxicity)	Drug-drug interaction	None	Interruptive	Interruptive
Lithium prescribed in conjunction with newly prescribed NSAIDs without dose adjustment or increased monitoring (Increased risk of toxicity)†	Drug-drug interaction	None	Interruptive	Interruptive
Lithium therapy prescribed in conjunction with newly prescribed loop or thiazide diuretics without dose adjustment or increased monitoring (Increased risk of toxicity) †	Drug-drug interaction	None	Interruptive	Interruptive
Macrolide antibiotic prescribed concomitantly with warfarin without appropriate dose adjustment or increased INR monitoring (Increased risk of bleeding)	Drug-drug interaction	None	Interruptive	Interruptive
Methotrexate prescribed concomitantly with trimethoprim (Increased risk of haematological toxicity)	Drug-drug interaction	None	Interruptive	Interruptive
Nefopam prescribed concomitantly with antiepileptics (Increased risk of seizures in patients with uncontrolled epilepsy) †	Drug-drug interaction	None	Interruptive	Interruptive
Orlistat prescribed at the same time of day as oral antiepileptics (Orlistat can reduce the absorption of antiepileptics, leading to loss of seizure control)	Drug-drug interaction	None	None	None

Potassium-sparing diuretic (excluding aldosterone antagonists) prescribed to a patient also receiving an ACE inhibitor or angiotensin-II receptor antagonist (Increased risk of severe hyperkalaemia)	Drug-drug interaction	None	Interruptive	Interruptive
Quinolone prescribed to a patient who is also receiving theophylline (Possible increased risk of convulsions)	Drug-drug interaction	None	Interruptive	Interruptive
Selective serotonin re-uptake inhibitor prescribed concomitantly with aspirin without appropriate prophylaxis with anti-secretory drugs or mucosal protectant (Increased risk of gastrointestinal bleeding)	Drug-drug interaction	None	Interruptive	Interruptive
Selective serotonin re-uptake inhibitor prescribed concomitantly with tramadol (Increased risk of serotonin syndrome)	Drug-drug interaction	None	Interruptive	Interruptive
Statin prescribed concomitantly with a macrolide antibiotic (Increased risk of myopathy)	Drug-drug interaction	None	Interruptive	Interruptive
Tramadol prescribed concomitantly with a Monoamine Oxidase Inhibitor (Increased risk of serotonin syndrome)	Drug-drug interaction	None	Interruptive	Interruptive
Tramadol prescribed concomitantly with antiepileptics (Increased risk of seizures in patients with uncontrolled epilepsy) †	Drug-drug interaction	None	Interruptive	Interruptive
Tricyclic antidepressant prescribed at the same time as a Monoamine Oxidase Inhibitor (Increased risk of serotonin syndrome)	Drug-drug interaction	None	Interruptive	Interruptive
Verapamil prescribed to a patient concomitantly with a beta-adrenoceptor blocking drug (Increased risk of adverse cardiovascular effects)	Drug-drug interaction	None	Interruptive	Interruptive

Warfarin prescribed concomitantly with a NSAID (Increased risk of bleeding)	Drug-drug interaction	None	Interruptive	Interruptive
Phenytoin and enteral feeds prescribed to a patient concomitantly (Reduced absorption of phenytoin)	Drug-food interaction	None	None	None
More than one paracetamol-containing product prescribed to a patient at a time (Maximum dose exceeded)	Duplicate therapy	None	None	Interruptive
Antipsychotic prescribed long-term (i.e. > 1 month) to a patient with parkinsonism (Increased risk of worsening of extra-pyramidal side effects)	Duration	None	None	None
Benzodiazepine or benzodiazepine-like drug prescribed long-term to a patient with depression (Risk of dependence and withdrawal reactions)	Duration	None	None	None
Benzodiazepine-like drugs (e.g. Zopiclone) prescribed long-term (i.e. more than 2–4 weeks) (Risk of dependence reactions)	Duration	None	None	None
Benzodiazepines prescribed long-term (i.e. more than 2–4 weeks) (Risk of dependence and withdrawal reactions)	Duration	None	None	None
Oral methotrexate prescribed to a patient with an inappropriate frequency (Increased risk of toxicity)	Frequency	Interruptive	Interruptive	None
Soluble insulin prescribed to a patient on a when required basis (Increased risk of serious episodes of hypoglycaemia and nocturnal hypoglycaemia post dose) †	Frequency	Interruptive	None	None
Weekly dose of an oral bisphosphonate prescribed daily (Risk of hypocalcaemia) †	Frequency	Interruptive	Interruptive	None

Diphenoxylate, loperamide, or codeine phosphate prescribed as antidiarrhoeal agents for treatment of diarrhoea of unknown cause (Increased risk of exacerbating constipation with overflow diarrhoea)	Indication	None	None	None
Vancomycin prescribed intravenously over less than 60 minutes (Rapid infusion of vancomycin can cause severe reactions)	Intravenous rate	Passive	None	Interruptive
Regular opiates prescribed without concurrent use of laxatives (Risk of severe constipation)‡	Omission of prophylactic treatment	None	None	None
Prescribing of incorrect or inequivalent morphine (opiate) dose via multiple routes. (Risk of toxicity)‡	Route	None	None	Passive
Insulin prescribed to a patient at an inappropriate time, allowing for an administration without food (except once daily long-acting insulins) (Increased risk of hypoglycaemia)	Timing of dose	Passive	None	None

ACE Angiotensin converting enzyme; BMI Body mass index; eGFR Estimated glomerula filtration rate; NSAIDs Non-steroidal anti-inflammatory drugs; NYHA New York Heart Association

Supplementary appendix 5: Errors occurring pre-implementation and post-implementation considering the level of decision support

Site	Level of CDS	N _{Ind}	Pre-CPOE			Post-CPOE			Relative Risk (95% CI)	P-value
			N _{Opp}	N _{Err}	Error rate	N _{Opp}	N _{Err}	Error rate		
1	None	59	2742	117	4.3%	1924	57	3.0%	0.69 (0.50 – 0.96)	0.023
	Passive	5	57	19	33.3%	40	15	37.5%	1.13 (0.61 – 2.02)	0.673
	Interruptive	14	1068	31	2.9%	670	2	0.3%	0.10 (0.02 – 0.44)	<0.001
2	None	51	3177	106	3.3%	3207	160	5.0%	1.50 (1.18 – 1.97)	0.001
	Passive	0	0	-	-	0	-	-	-	-
	Interruptive	27	1336	73	5.5%	1320	40	3.0%	0.55 (0.37 – 0.82)	0.002
3	None	51	1699	122	7.2%	1532	59	3.9%	0.54 (0.39 – 0.73)	<0.001
	Passive	1	133	8	6.0%	129	0	0.0%	0.00 (0.00 – 0.68)	0.007
	Interruptive	26	1100	86	7.8%	1004	57	5.7%	0.73 (0.52 – 1.02)	0.056
Total	None	161	7618	345	4.5%	6663	276	4.1%	0.91 (0.78 – 1.07)	0.267
	Passive	6	190	27	14.2%	169	15	8.9%	0.62 (0.33 – 1.18)	0.139
	Interruptive	67	3504	190	5.4%	2994	99	3.3%	0.61 (0.48 – 0.78)	<0.001

N_{Ind} represents the number of IMPACT pre-defined errors in each group, N_{Opp} is the number of error-opportunities generated, and N_{Err} is the number of errors that were found to have occurred. p-Values are from Fisher's exact tests, with bold values significant at p<0.05.

CDS Clinical decision support; CPOE Computerised physician order entry; CI Confidence interval