

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information.

Supplement to: Wallis KA, Elley CR, Moyes SA, Lee A, Hikaka JF, Kerse NM (2021) 'Safer Prescribing And Care for the Elderly (SPACE): Cluster randomised controlled trial in general practice'

Table S1: SPACE intervention delivery and GP tick-box selection: Practice size, number of GPs receiving SPACE intervention, number of participants with high-risk prescribing (HRP) at review, and GP tick-box selections indicating intended action.

Practice label	GPs N (FTE)	Practice size	Intervention delivered (n GPs)	HRP (n Patients)	Tick-box: GP selection for patients with HRP (%)				Intervention delivery notes	Rationale for tick-box selection
					Letter n (%)	No letter	No action	No review		
A	4 (3)	Medium	4 (1 via phone)	15	10 (67%)	1	3	1	GPs set alerts, ordered bloods as went through list, some patients “do what they want anyway” and so intervention won’t change	No letter was sent, blood form instead. No action as issue resolved or patient left practice.
C	15 (not known)	Large	1	111	3 (3%)	1	3	104	Only 1 of 15 GPs engaged, although 2 GPs received education.	No letter due to patient dementia or worried about causing anxiety. No action as issue resolved or patient bought OTC PPI.
E	3 (2.5)	Medium	3	22	10 (45%)	1	11	0	GPs were engaged. Set alerts to review with note why. Liked letter to inform patients, liked letter for those patients who just kept phoning for repeats rather	Didn’t send letter to patients who were anxious frequent attenders or demented; No action

									than coming in for r/v with GP. Nurses also involved as they often managed the phone for repeat and follow-up	due to topical NSAID/ PPI already started/ clopidogrel already stopped.
F	10 (5.8)	Large	10	27	11 (41%)	7	9	0	Engaged. Some GPs more engaged than others. Flagged computer to prevent re-starting NSAIDs if had already stopped. Used dashboard and messages. Liked the letter and thought patients would like it as a sign of being proactive.	No letter if don't speak English, or frequent attender. No action if issue already resolved.
K	4 (?)	Medium	4	71	17 (24%)	31	23	0	Required 4 visits to get to all 4 GPs.	No letter c/o prefer to phone or talk during consultation, or fear of upset and breakdown of relationship; No action if issue resolved.
M	12 (9)	Large	no	49	0 (0%)	0	0	49	No response from practice.	
O	4 (3)	Medium	4	34	8 (18%)	14	12	0	Worked with nurse who passed on info to GPs. GP verified PPI recommendations with	No letter as had sent blood test form

									cardiologists and got varying opinions.	already; No action if issue resolved.
Q	6 (2.5)	Medium	6	13	0 (0%)	0	0	13	All GPs reviewed lists together. Didn't send letters but phoned patients themselves or put notes on computer to review.	No letter c/o phoned; No action c/o flagged and HR accepted.
R	2 (1.8)	Small	2	17	4 (24%)	2	7	4	One GP made notes for nurse to enter alerts into the computer system.	Patient due to come in, fear of anxiety. Issue resolved.
S	6 (?)	Medium	6	40	4 (10%)	19	17	0	Engaged. But practice had already participated in SiP.	No letter as phoned patients; No action as issues resolved.
T	1 (1)	Small	1	3	2 (67%)	0	1	0	GP enjoyed being involved and opportunity for refresher.	No action as issue resolved.
U	2 (1.5)	Small	2	7	4 (57%)	2	1	0	Shared patients difficult to allocate to GP.	No letter as patient due in soon. No action as issue resolved.
V	8 (7)	Large	4	58	20 (34%)	18	20	0	GPs pleased to be part of the audit, surprised at level of HRP, lots of patients with gout.	Seeing patient soon. Mild dementia. Issue resolved.
W	1 (1)	Small	1	18	0 (0%)	1	17	0	Most HRP resolved as was short term NSAID.	English second language. Preferred

											to phone patients.
AC	4 (3.3)	Medium	4	26	0 (0%)	14	12	0	Met separately with each GP.	Issues resolved. GPs made notes, didn't like letters. Issues resolved, or HRP chosen.	
AD	3 (3)	Medium	3	31	5 (16%)	7	19	0	Pleased to be involved and reminded. Pleased about MOPS.	No letter if coming in soon. No action if resolved.	
AF	5 (2.2)	Medium	5	17	1 (6%)	13	3	0	Very happy to have pharmacist visit and education.	Didn't like the idea of sending letters.	
AH	1 (1)	Small	1	9	0 (0%)	5	4	0	GP liked being updated as felt things changed all the time and difficult to keep up.	Didn't like letters, knew patients well and preferred to talk.	
AJ	6 (3.3)	Medium	no	26	0 (0%)	0	0	26	Impossible to pin down the doctors. Manager was going to pass on lists to GPs.		
AL	3 (1.5)	Small	3	19	8 (%)	5	6	0	Very engaged practice & GPs and keen to chat.	Happy for some to send letters.	
Total				613	97	151	168	197	Overall: Difficulty getting time with GPs; Difficulty allocating patient to list of one GP when registered to the practice as a group;		
				HRP	Letter	No letter	No action	No review			

FTE = full time equivalent; GP = general practitioner; HRP = number of patients identified with high-risk prescriptions during the previous 14 weeks; MOPS = maintenance of professional standards points towards re-accreditation; NSAID = nonsteroidal anti-inflammatory drug; OTC = over the counter; PPI = proton pump inhibitor; Pts = patients; SIP = 'Safety in Practice' – an initiative targeting NSAID/anti-platelet prescribing in general practice

NB: M and AJ did not receive any part of intervention due to no response from practice after randomisation. Only 1/15 GPs received the intervention in practice C.

- **Letter** = automated letter from GP to patient inviting patient to discuss their medication at their next appointment
- **No letter** = no letter but to discuss and possibly change when patient next in, +/- reminder note in patient record
- **No action** = no need to change anything as HRP resolved or patient moved
- **No review** = no one-on-one session with pharmacist and GP reviewing patient list

Table S2: Per protocol analysis: changes in proportion of participants with high-risk prescribing in SPACE vs control group at 6 and 12 months

	Baseline		Six months		Twelve months		Odds ratio at 6 months	p-value	Odds ratio at 12 months	p-value
	SPACE	Control	SPACE	Control	SPACE	Control	SPACE vs control		SPACE vs control	
<i>Primary outcome:</i>										
Combined Risk Factor	574/7861 (7.3%)	905/14006 (6.5%)	422/7446 (5.7%)	753/13203 (5.7%)	348/6831 (5.1%)	609/11821 (5.2%)	0.94 (0.82, 1.08)	0.4	1.03 (0.88, 1.20)	0.7
<i>Secondary outcomes:</i>										
Gastrointestinal	285/5766 (4.9%)	476/10410 (4.6%)	196/5246 (3.7%)	418/9430 (4.4%)	125/3175 (3.9%)	315/6360 (5.0%)	0.76 (0.64, 0.92)	0.004	0.75 (0.60, 0.94)	0.01
Renal	347/4297 (8.1%)	528/7559 (7.0%)	244/3482 (7.0%)	383/6119 (6.3%)	214/3096 (6.9%)	308/5210 (5.9%)	1.01 (0.83, 1.23)	0.9	1.16 (0.94, 1.43)	0.2
Heart Failure	15/395 (3.8%)	35/845 (4.1%)	12/356 (3.4%)	21/759 (2.8%)	10/311 (3.2%)	27/638 (4.2%)	1.50 (0.71, 3.18)	0.3	0.65 (0.30, 1.41)	0.3

*Adjusted for clustering by practice

Table S3: Analysis by original random group assignment: changes in proportion of participants with high-risk prescribing in SPACE vs control group at 6 and 12 months

	Baseline		Six months		Twelve months		Odds ratio at	p-value	Odds ratio at	p-value
	SPACE	Control	SPACE	Control	SPACE	Control	6 months SPACE vs control		12months SPACE vs control	
<i>Primary outcome:</i>										
Combined Risk Factor	886 / 12060 (7.3%)	593 / 9807 (6.0%)	703 / 11411 (6.2%)	472 / 9238 (5.1%)	573 / 10582 (5.4%)	384 / 8070 (4.8%)	1.21 (1.06, 1.38)	0.005	1.14 (0.98, 1.33)	0.09
<i>Secondary outcomes:</i>										
Gastrointestinal	459 / 8989 (5.1%)	302 / 7187 (4.2%)	354 / 8175 (4.3%)	260 / 6501 (4.0%)	236 / 5155 (4.6%)	204 / 4380 (4.7%)	1.01 (0.85, 1.20)	0.9	0.88 (0.72, 1.09)	0.2
Renal	534 / 6520 (8.2%)	341 / 5336 (6.4%)	392 / 5325 (7.4%)	235 / 4276 (5.5%)	339 / 4801 (7.1%)	183 / 3505 (5.2%)	1.25 (1.04, 1.51)	0.02	1.25 (1.01, 1.55)	0.04
Heart Failure	24 / 642 (3.7%)	26 / 598 (4.3%)	23 / 582 (4%)	10 / 533 (1.9%)	22 / 510 (4.3%)	15 / 439 (3.4%)	3.72 (1.58, 8.75)	0.003	1.78 (0.86, 3.72)	0.1

*Adjusted for clustering by practice

Table S4: Number of ‘participants with high-risk prescribing at baseline’ hospitalised with related diagnoses in SPACE compared with control group in the 12 months following baseline adjusting for hospitalisations in the 12 months prior to baseline, patient age at baseline and number of prescribed medications at baseline.

	12 months before baseline		12 months after baseline		Odds ratio	p-value
	SPACE	Control	SPACE	Control		
Combined Risk Factor	15/828 (1.81%)	27/651 (4.15%)	24/828 (2.90%)	33/651 (5.07%)	0.68 (0.39, 1.19)	0.2
Gastrointestinal	6/427 (1.41%)	5/334 (1.50%)	4/427 (0.94%)	9/334 (2.69%)	0.36 (0.11, 1.20)	0.1
Renal	2/503 (0.40%)	5/372 (1.34%)	5/503 (0.99%)	5/372 (1.34%)	0.69 (0.15, 3.21)	0.6
Heart Failure	1/21 (4.76%)	1/29 (3.45%)	2/21 (9.52%)	2/29 (6.90%)	1.55 (0.16, 14.80)	0.7

Table S5: Number of related hospitalisations in ‘participants’ in SPACE compared with control group in the 12 months following baseline adjusting for hospitalisations in the 12 months prior to baseline, patient age at baseline and number of prescribed medications at baseline.

	12 months before baseline		12 months after baseline		Rate Ratio	p-value
	SPACE	Control	SPACE	Control		
Combined Risk Factor	464 (40)	433 (42)	498 (43)	503 (49)	0.95 (0.84, 1.07)	0.4
Gastrointestinal	127 (15)	128 (17)	131 (15)	115 (15)	1.03 (0.80, 1.33)	0.8
Renal	90 (14)	82 (15)	86 (14)	106 (19)	0.78 (0.58, 1.03)	0.08
Heart Failure	137 (224)	103 (165)	87 (142)	100 (160)	0.88 (0.66, 1.18)	0.4

The numbers in brackets are admissions per thousand person-years

Table S6: Number of related hospitalisations in ‘participants with high-risk prescribing at baseline’ in SPACE compared with control groups in the 12 months following baseline adjusting for hospitalisations in the 12 months prior to baseline, patient age at baseline and number of prescribed medications at baseline.

	12 months before baseline		12 months after baseline		Rate Ratio	p-value
	SPACE	Control	SPACE	Control		
Combined Risk Factor	23 (28)	33 (51)	28 (34)	45 (69)	0.63 (0.39, 1.02)	0.06
Gastrointestinal	7 (16)	6 (18)	4 (9)	9 (27)	0.37 (0.11, 1.23)	0.1
Renal	2 (4)	5 (13)	6 (12)	5 (13)	0.70 (0.15, 3.19)	0.6
Heart Failure	1 (48)	2 (69)	2 (95)	5 (172)	0.52 (0.10, 2.86)	0.4

The numbers in brackets are admissions per thousand person-years

Table S7: ICD 10 codes used to identify hospitalisations for gastrointestinal diagnoses, acute kidney injury and heart failure diagnoses potentially related to NSAID/antiplatelet medication

Gastrointestinal hospitalisations:

K21	Gastro-esophageal reflux disease
K21.0	Gastro-esophageal reflux disease with oesophagitis
K21.9	Gastro-esophageal reflux disease without oesophagitis
K25	Gastric Ulcer, site unspecified
K25.0	Acute gastric ulcer, site unspecified, with hemorrhage
K25.1	Acute gastric ulcer, site unspecified, with perforation
K25.2	Acute gastric ulcer, site unspecified, with both hemorrhage and perforation
K25.3	Acute gastric ulcer, site unspecified, without hemorrhage or perforation
K25.4	Chronic or unspecified gastric ulcer, site unspecified, with hemorrhage
K25.5	Chronic or unspecified gastric ulcer, site unspecified, with perforation
K25.6	Chronic or unspecified gastric ulcer, site unspecified, with both hemorrhage and perforation
K25.7	Chronic gastric ulcer, site unspecified, without hemorrhage or perforation
K25.9	Gastric ulcer, site unspecified, unspecified as acute or chronic, without hemorrhage or perforation
K26	Duodenal Ulcer, site unspecified
K26.0	Acute duodenal ulcer, site unspecified, with hemorrhage
K26.1	Acute duodenal ulcer, site unspecified, with perforation
K26.2	Acute duodenal ulcer, site unspecified, with both hemorrhage and perforation
K26.3	Acute duodenal ulcer, site unspecified, without hemorrhage or perforation
K26.4	Chronic or unspecified duodenal ulcer, site unspecified, with hemorrhage
K26.5	Chronic or unspecified duodenal ulcer, site unspecified, with perforation
K26.6	Chronic or unspecified duodenal ulcer, site unspecified, with both hemorrhage and perforation
K26.7	Chronic duodenal ulcer, site unspecified, without hemorrhage or perforation
K26.9	Duodenal ulcer, site unspecified, unspecified as acute or chronic, without hemorrhage or perforation
K27	Peptic Ulcer, site unspecified
K27.0	Acute peptic ulcer, site unspecified, with hemorrhage
K27.1	Acute peptic ulcer, site unspecified, with perforation
K27.2	Acute peptic ulcer, site unspecified, with both hemorrhage and perforation
K27.3	Acute peptic ulcer, site unspecified, without hemorrhage or perforation
K27.4	Chronic or unspecified peptic ulcer, site unspecified, with hemorrhage
K27.5	Chronic or unspecified peptic ulcer, site unspecified, with perforation
K27.6	Chronic or unspecified peptic ulcer, site unspecified, with both hemorrhage and perforation
K27.7	Chronic peptic ulcer, site unspecified, without hemorrhage or perforation

- K27.9 Peptic ulcer, site unspecified, unspecified as acute or chronic, without hemorrhage or perforation
- K28 Gastrojejunal ulcer, site unspecified
- K28.0 Acute gastrojejunal ulcer, site unspecified, with hemorrhage
- K28.1 Acute gastrojejunal ulcer, site unspecified, with perforation
- K28.2 Acute gastrojejunal ulcer, site unspecified, with both hemorrhage and perforation
- K28.3 Acute gastrojejunal ulcer, site unspecified, without hemorrhage or perforation
- K28.4 Chronic or unspecified gastrojejunal ulcer, site unspecified, with hemorrhage
- K28.5 Chronic or unspecified gastric ulcer, site unspecified, with perforation
- K28.6 Chronic or unspecified gastrojejunal ulcer, site unspecified, with both hemorrhage and perforation
- K28.7 Chronic gastrojejunal ulcer, site unspecified, without hemorrhage or perforation
- K28.9 Gastrojejunal ulcer, site unspecified, unspecified as acute or chronic, without hemorrhage or perforation
- K29.0 Acute gastritis
- K29.3 Chronic superficial gastritis
- K29.4 Chronic atrophic gastritis
- K29.5 Unspecified chronic gastritis
- K29.6 Other gastritis
- K29.7 Gastritis, unspecified
- K29.8 Duodenitis
- K29.9 Gastroduodenitis unspecified
- K30 Functional dyspepsia
- K92.0 Haematemesis
- K92.1 Melaena
- K92.2 Gastrointestinal haemorrhage, unspecified

Acute Kidney Injury hospital outcomes:

- N14 Drug- and heavy-metal-induced tubulo-interstitial and tubular conditions
- N14.1 Nephropathy induced by other drugs, medicaments and biological substances
- N14.2 Nephropathy induced by unspecified drug, medicament or biological substance
- N17 Acute renal failure
- N17.0 Acute renal failure with tubular necrosis
- N17.1 Acute renal failure with acute cortical necrosis
- N17.2 Acute renal failure with medullary necrosis
- N17.8 Other acute renal failure
- N17.9 Acute renal failure, unspecified
- N19 Unspecified kidney failure

N99.0 Postprocedural renal failure
R34 Anuria and oliguria
R94.4 Abnormal results of kidney function studies

Heart Failure hospitalisation outcomes:

I11.0 Heart failure due to hypertension
I13 Hypertensive heart and chronic kidney disease
I13.0 Hypertensive heart and chronic kidney disease with heart failure and stage 1 through stage 4 chronic kidney disease, or unspecified chronic kidney disease
I13.2 Hypertensive heart and chronic kidney disease with heart failure and with stage 5 chronic kidney disease, or end stage renal disease
I50 Heart failure
I50.1 Left ventricular failure, unspecified
I50.2 Systolic (congestive) heart failure
I50.20 Unspecified systolic (congestive) heart failure
I50.21 Acute systolic (congestive) heart failure
I50.22 Chronic systolic (congestive) heart failure
I50.23 Acute on chronic systolic (congestive) heart failure
I50.3 Diastolic (congestive) heart failure
I50.30 Unspecified diastolic (congestive) heart failure
I50.31 Acute diastolic (congestive) heart failure
I50.32 Chronic diastolic (congestive) heart failure
I50.33 Acute on chronic diastolic (congestive) heart failure
I50.4 Combined systolic (congestive) and diastolic (congestive) heart failure
I50.40 Unspecified combined systolic (congestive) and diastolic (congestive) heart failure
I50.41 Acute combined systolic (congestive) and diastolic (congestive) heart failure
I50.42 Chronic combined systolic (congestive) and diastolic (congestive) heart failure
I50.43 Acute on chronic combined systolic (congestive) and diastolic (congestive) heart failure
I50.8 Other heart failure
I50.81 Right heart failure
I50.810 Right heart failure unspecified
I50.811 Acute right heart failure
I50.812 Chronic right heart failure
I50.813 Acute on chronic right heart failure
I50.814 Right heart failure due to left heart failure
I50.82 Biventricular heart failure
I50.83 High output heart failure
I50.84 End stage heart failure

150.89 Other heart failure
150.9 Heart failure, unspecified