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Safer Prescribing And Care for the Elderly (SPACE): cluster randomised controlled trial in general practice

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Ngaire Kerse: co-investigator and general practitioner advised on data analysis and involved in write-up.

Conflicts of interest: The authors declare there are none.

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Keywords: Prescribing, patient safety, family medicine

How this fits in: It is not known how best to support safer prescribing in general practice. This trial tested a brief intervention comprising automated search, pharmacist delivered education and feedback, and automated letter to prompt patients to seek medicines review.

Trial registration: ACTRN12618000034235, January 2018.

Funding: Auckland Medical Research Foundation, New Zealand.

Pragmatic cluster randomised controlled trial in general practice testing a scalable intervention that may be applied to any prescribing topic and that uses automated search of practice records, outreach pharmacist and letter to prompt at-risk patients to seek medicines review.

Table 1: Participant inclusion criteria: patients at increased risk of adverse drug events with NSAIDs or antiplatelet medication at baseline

Type of adverse drug event	***Any of the following clinical criteria***
Gastrointestinal bleed	Prior peptic ulcer diagnosis
	At least 75 years of age
	At least 65 years of age and prescribed aspirin
	Prescribed oral anticoagulant
Renal impairment	Prescribed both renin-angiotensin system blocker and diuretic
	Chronic kidney disease (eGFR <60 at the most recent test)
Cardiac failure	Heart failure ever

eGFR = estimated glomerular filtration rate

NB: 'Prior peptic ulcer' and 'Heart failure' codes are obtained general practice electronic disease coding from the participating practices. Prescribed medication is defined as any prescription for this category of medication in the previous 14 weeks, as identified from the electronic prescribing database of the participating practices. This time-period is used because most regular medication is prescribed on a 12-weekly basis.

Table 2: High-risk prescribing outcome measures

Adverse drug event type	***High-risk prescribing***
Gastrointestinal	NSAID or aspirin without gastro-protection in patient with prior peptic ulcer ***or*** NSAID without gastro-protection in patient 75 years and older ***or*** NSAID without gastro-protection in patient 65 years and older taking aspirin ***or*** Clopidogrel without gastro-protection in patient 65 years and older taking aspirin ***or*** NSAID without gastro-protection in patient taking an oral anticoagulant ***or*** Aspirin or clopidogrel without gastro-protection in patient taking an oral anticoagulant
Renal	NSAID in patient taking both renin-angiotensin system blocker and diuretic ***or*** NSAID in patient with chronic kidney disease (eGFR <60 at the most recent test)
Cardiac	NSAID in patient with history of heart failure
Combined	Any of the above criteria

eGFR = estimated glomerular filtration rate

NB: 'Prior peptic ulcer' and 'Heart failure' codes are obtained general practice electronic disease coding from the participating practices. Prescribed medication is defined as any prescription for this category of medication in the previous 14 weeks, as identified from the electronic prescribing database of the participating practices. This time-period is used because in New Zealand most medication is prescribed for a maximum of 12 weeks.

Table 3: Baseline demographic and clinical characteristics of study participants

	SPACE (N=11,658)	Control (N=10,209)	Total (N=21,867)
Age, mean (SD)	73.6 (11.9)	73.1 (12.0)	73.4 (12.0)
Female n (%)	5997 (51%)	5376 (53%)	11373 (52%)
Ethnicity, n (%):			
NZ* European	7334 (63%)	7008 (69%)	14342 (66%)
Other European	1674 (14%)	902 (9%)	2576 (12%)
NZ Maori	732 (6%)	902 (9%)	1634 (7%)
Pasifika	459 (4%)	451 (4%)	910 (4%)
East Asian	756 (6%)	374 (4%)	1130 (5%)
Indian	341 (3%)	308 (3%)	649 (3%)
Other	362 (3%)	264 (3%)	626 (3%)
Number long-term medications, mean (SD)	5.1 (3.7)	5.6 (3.8)	5.3 (3.8)

*NZ = New Zealand

Table 4: Changes in rate of high-risk prescribing to participants in SPACE vs control practices at 6 and 12 months

	Baseline		Six months		Twelve months		Odds ratio (6 months)[#] (95% CI)	P-value	Odds ratio (12months)[#] (95% CI)	P-value
	SPACE	Control	SPACE	Control	SPACE	Control				
Primary outcome:										
Combined risk factor*	828/11658 (7.1%)	651/10209 (6.4%)	638/11005 (5.8%)	537/9644 (5.6%)	538/9453 (5.7%)	419/9199 (4.6%)	0.99 (0.87, 1.13)	0.9	1.29 (1.11, 1.49)	**0.001**
Secondary outcomes:										
Gastrointestinal	427/8711 (4.9%)	334/7465 (4.5%)	313/7894 (4.0%)	301/6782 (4.4%)	232/5046 (4.6%)	208/4489 (4.6%)	0.81 (0.68, 0.96)	**0.02**	0.91 (0.74, 1.11)	0.4
Renal	503/6268 (8.0%)	372/5588 (6.7%)	365/5124 (7.1%)	262/4477 (5.9%)	314/4318 (7.3%)	208/3988 (5.2%)	1.16 (0.96, 1.39)	0.1	1.35 (1.10, 1.65)	**0.004**
Heart failure	21/613 (3.4%)	29/627 (4.6%)	19/557 (3.4%)	14/558 (2.5%)	17/441 (3.9%)	20/508 (3.9%)	1.84 (0.87, 3.89)	0.1	0.89 (0.44, 1.78)	0.7

*Gastrointestinal, renal or cardiac 'high-risk' prescribing of NSAIDs and/or anticoagulant medication.

[#] Adjusted for clustering by practice

Table 5: Number of participants hospitalised with related diagnoses 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		Odds ratio	p-value
	SPACE	Control	SPACE	Control		
Combined Risk Factor	350/11,658 (3.00%)	359/10,209 (3.52%)	371/11,658 (3.18%)	364/10,209 (3.57%)	0.96 (0.82, 1.11)	0.5*
Gastrointestinal	116/8711 (1.33%)	116/7465 (1.55%)	112/8711 (1.29%)	99/7465 (1.33%)	1.03 (0.78, 1.35)	0.9
Renal	76/6268 (1.21%)	75/5588 (1.34%)	77/6268 (1.23%)	86/5588 (1.54%)	0.84 (0.62, 1.15)	0.3
Heart Failure	90/613 (14.68%)	76/627 (12.12%)	56/613 (9.14%)	66/627 (10.53%)	0.85 (0.57, 1.25)	0.4

*Due to the small number of hospitalisations in each practice, clustering could not be used in any model except this one. When clustering, sex and ethnicity were included in the model the p-value was 0.3

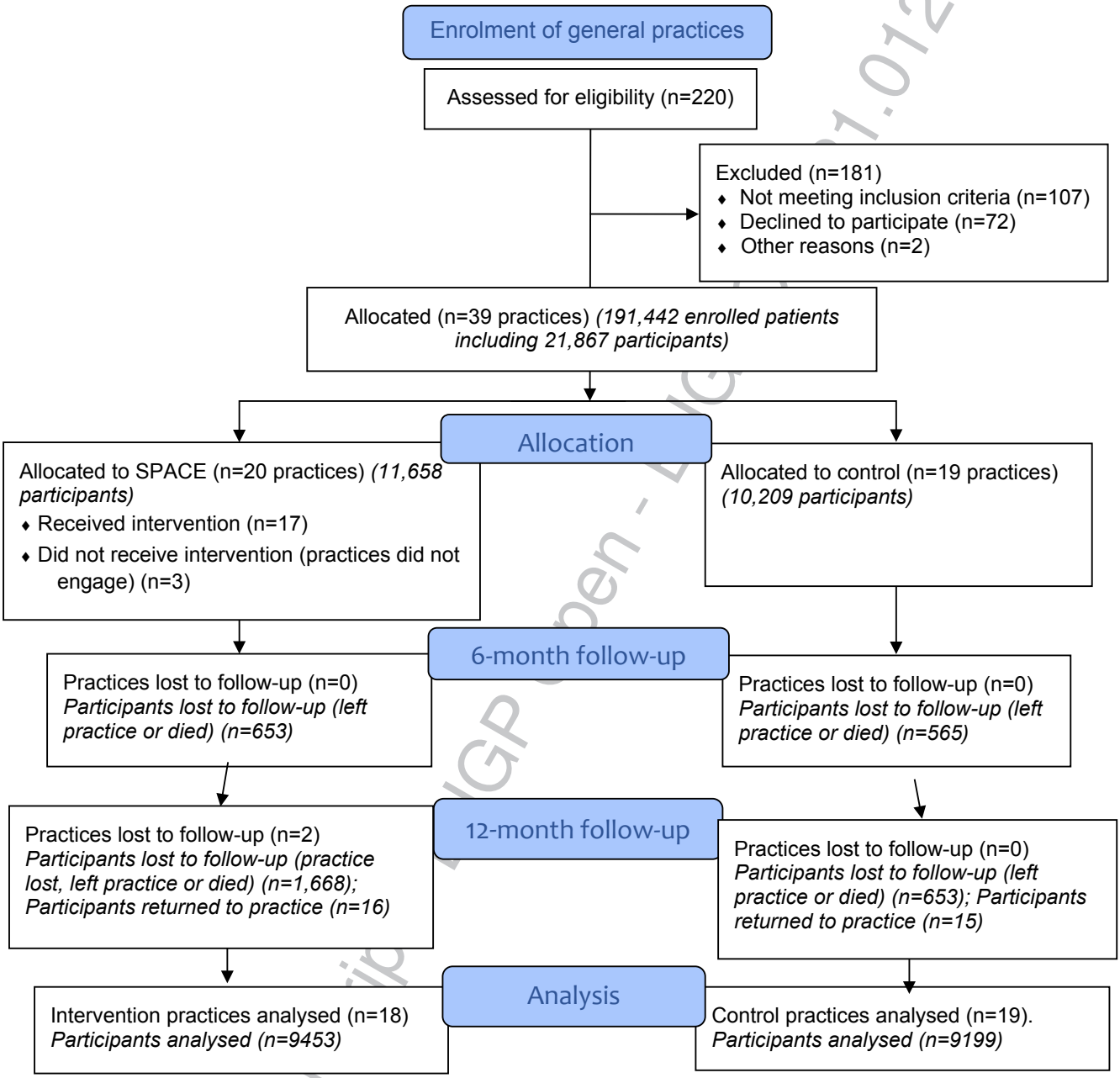

Figure 1. CONSORT diagram of SPACE cluster randomised controlled trial

Abstract

Background. Safer prescribing in general practice may help to decrease preventable adverse drug events (ADE) and related hospitalisations.

Aim. To test effect of SPACE on high-risk prescribing of non-steroidal anti-inflammatory drugs (NSAIDs) and/or antiplatelet medicines and related hospitalisations.

Design and setting. Pragmatic cluster randomised controlled trial in general practice. Participants were patients at increased risk of ADEs from NSAIDs and/or antiplatelet medicines at baseline. SPACE comprises automated search to generate for each general practitioner (GP)a list of patients with high-risk prescribing; pharmacist outreach to provide education and one-on-one review of list with GP; and automated letter inviting patients to seek medication review with their GP.

Methods. Primary outcome was difference in high-risk prescribing of NSAIDs and/or antiplatelet medicines at 6 months; secondary outcomes included high-risk prescribing for gastrointestinal, renal or cardiac ADEs separately; 12-month outcomes; and related ADE hospitalisations.

Results. We recruited 39 practices with 205 GPs and 191,593 patients including 21,877 (11.4%) participants, 1479 (6.8%) with high-risk prescribing. High-risk prescribing improved in both groups at 6 and 12 months compared with baseline. At 6 months, there was no significant difference between groups (OR: 0.99 (0.87, 1.13)) although SPACE improved more for gastrointestinal ADEs (0.81 (0.68, 0.96)). At 12 months, the control group improved more (OR: 1.29 (1.11, 1.49)). There was no significant difference for related hospitalisations.

Conclusion: Further work is needed to identify scalable interventions that support safer prescribing in general practice. The use of automated search and feedback plus letter to patient warrants further exploration.

Background

"Medication without harm" is a Global Patient Safety Challenge theme and top priority for the World Health Organisation which aims to reduce severe avoidable medication-related harm by 50% globally between 2017 and 2022.[1] Most prescribing of on-going medication occurs in general practice, making safer prescribing in this context important for protecting patient safety. Adverse drug events (ADEs) in primary care are common causing distress and burdening health systems.[2-7] About one-fifth of ADEs in primary care may be preventable through safer prescribing.[2]

Cardiovascular medications (including anti-platelet medicines) and non-steroidal anti-inflammatory drugs (NSAIDs) account for up to a third of serious ADEs in older age-groups, including upper gastrointestinal bleeding, kidney injury and exacerbation of heart failure, so are an important target for improvement.[2,7,8] High-risk prescribing places patients at increased risk of ADEs although may be justified by the individual circumstances of the patient. People taking multiple medications are particularly at risk. Ethnic disparities for prescribing and ADEs exist. In New Zealand, Māori and Pasifika are more likely to be prescribed NSAIDs than other ethnic groups and have higher rates of associated ADEs and at younger age.[9,10]

Trials of interventions to decrease high-risk prescribing in general practice have demonstrated improvements although the quality of evidence is mixed with many studies having short-term follow-up or interventions that are not readily scalable.[11-16] One cluster-randomised stepped-

wedge trial of a pharmacist-led intervention plus financial incentives found decreased high-risk prescribing of NSAIDs and related ADE hospital admissions, but this trial did not have a true control group.[17] Two recent systematic reviews found no high-quality evidence of interventions in general practice decreasing ADEs or related hospitalisations despite short-term improvements in prescribing.[15,18]

We developed an intervention to support safer prescribing in general practice that can be applied to any prescribing topic (SPACE). A pilot of SPACE showed promising results and good GP and patient acceptability.[13,19] We then sought to test the effectiveness of SPACE on high-risk prescribing in general practice for NSAIDs and/or anti-platelet medicines, and related ADE hospitalisations.[20]

Methods

Study design and participants: A pragmatic cluster randomised controlled trial design was used with the practice as the unit of randomisation (Figure 1).[20] All GP practices in two regions of New Zealand were identified and eligible practices invited to participate via email and telephone. Practices were not told of the trial high-risk prescribing topic. Eligibility was restricted to practices using compatible electronic practice management systems and where all GPs consented to participate. Practices were excluded if they had participated in the SPACE pilot study or were participating in a non-trial initiative focussing on NSAID prescribing. Patients were included as participants if, at baseline, they were identified as at increased risk of gastrointestinal, renal or cardiac ADEs from NSAIDs or anti-platelet medications (Table 1).[20] Written consent for participation was obtained from all GPs, or practice manager on behalf of GPs. Written consent was not required from patients as all data were anonymised and linked by encrypted national health identifier (NHI) prior to extraction. The study was approved by

the University of Auckland Human Participants Ethics Committee: UAHPEC 020092. Trial registration: ANZCTR 12618000034235.

Randomisation and masking: Enrolled practices were stratified by region and practice size (small (0-2999 enrolled patients), medium (3000-7999) and large (8000-14,999)) and randomly assigned within strata to receive intervention or control in randomly occurring blocks of two and four. The random sequence was generated by a statistician not involved in recruitment or baseline data extraction. All outcomes and anonymised data extraction procedures were pre-specified and automated. Data at each time-point were electronically extracted, de-identified and sent by secure file to analysts (SM, CRE and AL), all of whom were masked to allocation until after trial completion.

SPACE intervention: comprised (i) automated search of practice records using pre-defined algorithms to identify and generate for each GP a list of patients with high-risk prescribing for NSAIDs and/or anti-platelet medications; (ii) outreach visit from the trial clinical advisory pharmacist to provide a one hour group educational session with GPs on the prescribing topic, and to (iii) meet one-on-one with each GP to support GPs to review their list of patients and select for each patient an intended action from a tick-box in the computer software ('Letter'; 'No letter but review'; 'No action'); and (iv) automated letter from GP to selected patients prompting patients to discuss their medicines at their next scheduled appointment.[13,19,20] GPs were recompensed for their time with a $100 gift voucher. All prescribing decisions were made as usual by GP and patient together. Control practices provided usual care.

Outcome measures: Practice prescribing data were extracted using automated pre-defined algorithms at baseline, 6 months and 12 months after allocation. The primary outcome was the difference between SPACE and control practices in the proportion of participants with high-risk prescribing of NSAID and/or antiplatelet medicines at 6 months after adjusting for baseline and clustering by practice (Table 2). Secondary outcomes included proportions of participants

at 6 months with high-risk prescribing of NSAID and/or antiplatelet medicines for gastro-intestinal, renal and cardiac ADEs separately, all outcomes at 12 months, and related hospitalisations for the 12 months following baseline compared with the 12 months prior (Table S7). Diagnostic codes and lab results were obtained from general practice electronic patient management systems. Prescribed medication was defined as any prescription for this category of medication in the practice electronic prescribing database in the previous 14 weeks. This time-period was used because in New Zealand patients must obtain repeat prescriptions for on-going medications every 12 weeks. Anonymised patient-level demographic and clinical data were extracted and linked over time by encrypted NHI. National level hospitalisation and mortality data were also linked by encrypted NHI to identify hospitalisation outcomes.

Sample size calculations and statistical analysis: The sample size calculation was based on previous trials demonstrating a clinically relevant 25-45% relative risk reduction in the proportion of high-risk NSAID or antiplatelet prescribing.[12,17] We estimated an average of 200 participants per practice, and an intracluster correlation coefficient (ICC) of 4.68×10^{-7} for the primary outcome.[12] We assumed an 8% high-risk prescribing rate based on local feasibility study data. Assuming approximately 12% of patients would be lost to follow-up over the 12-month study period, data from 8000 patients from 40 practices (20 practices in each group) with an average of 200 participants per practice were required to detect as statistically significant a difference of 6% in the intervention group and 8% in the control group of high-risk prescribing at follow-up (p=0.9, alpha=0.05).

Statistical analyses were performed according to the intention-to-treat (ITT) principle, with the use of mixed-effect models to account for clustering in the data. Primary analysis was by practice allocation. The proportions of participants with high-risk prescribing were analysed using random-effects logistic regression with the individual as the unit of analysis and the practice included as the random effect to control for the effects of clustering. GLIMMIX with

Group*Time interaction were used to assess the overall difference between intervention and control at 6 and 12 months. The model adjusted for the stratification factors including practice location (region A or B) and practice size (small, medium and large).

An inadvertent transcription error inverted the random group assignment of six practices prior to allocation (I,C,I,C,I,C instead of C,I,C,I,C,I where 'I' is intervention and 'C' control) which was not apparent until trial end. Analysis by allocation is presented in the Results section below. Per protocol analysis and analysis by original random group assignment are provided in the on-line Supplementary Appendix.

Results

Practices and participants: Of the 220 general practices identified, 110 fulfilled inclusion criteria, of whom 39 (35%) agreed to participate and were enrolled between April 2018 and July 2019 (Figure 1). There were 14 small, 18 medium, and seven large practices. Most practices not fulfilling inclusion criteria were either participating in the non-trial NSAID prescribing initiative, did not use compatible practice management systems, or had participated in the SPACE pilot study. The main reason eligible practices declined was that they were too busy.

There were 191,442 patients registered in the 39 trial practices. Of these, 21,867 (11.4%) were identified as participants (at increased risk of ADEs from NSAIDs or antiplatelet medications), of whom 1479 (6.8%) had high-risk prescribing over the previous 14 weeks (Figure 1). Demographic and clinical characteristics of participants were similar (Table 3), although high-risk prescribing rates at baseline were higher in SPACE (7.1%) than control practices (6.4%) (Table 4). By 6 months, 1218/21,867 (5.6%) participants were lost to follow-up (Figure 1). By

12 months, two large intervention practices had changed data management systems resulting in a loss to follow-up of 3215/21,867 (14.7%) participants.

Intervention delivery: There were often delays between baseline measures, group education, and one-on-one list review, ranging from one week to six months, mostly because GPs were "too busy". Often, the automated search was re-run to generate an up-to-date list of patients with high-risk prescribing for one-on-one review. In three intervention practices (two large and one medium), there was minimal or no engagement with the intervention (Table S1); one practice did not receive the group education, and only one of 15 GPs agreed to meet with the pharmacist for the one-on-one list review. These three intervention practices included 254/828 (31%) participants with high-risk prescribing at baseline. Poor engagement resulted in the trial pharmacist having one-on-one sessions with only 70% of GPs and reviewing only 416 of the 683 participants (68%) identified at intervention delivery as having high-risk prescribing (Table S1).

GP tick-box selection (intended action): The GP tick-box selections for the 416 participants reviewed were 'Letter' 97 (23%); 'No letter but review' 151 (36%); and 'No action' 168 (40%). The reasons for 'No letter but review' included GP concern about upsetting the patient, or the patient not understanding written English; patient due to be seen soon; or GP preference to leave themselves a note. The reasons for 'No action' were mostly that the high-risk prescribing had already ceased (short-course or topical NSAIDs, proton pump inhibitors had been initiated, renal function had returned to normal); or occasionally the patient had moved practice, the GP considered the individual circumstances of the patient justified the high-risk prescribing, or the GP did not agree that the prescribing was high-risk (Table S1).

Prescribing outcomes: High-risk prescribing decreased in both SPACE and control practices at 6 and 12 months compared to baseline as shown in Table 4. At 6 months, there was no significant difference in high-risk prescribing between groups (OR: 0.99 (0.87, 1.13)), although

high-risk prescribing for gastrointestinal ADEs had improved significantly more in SPACE practices (OR: 0.81 (0.68, 0.96)) (Table 4). At 12 months, high-risk prescribing had improved more in the control than the SPACE group overall (OR: 1.29 (1.11, 1.49)) and for renal ADEs (OR: 1.35 (1.10, 1.65)). There was no significant difference in the outcomes between ethnic groups.

The per-protocol analysis showed that at 6 months there was no significant difference in high-risk prescribing overall (OR: 0.94 (0.82, 1.08)), although high-risk prescribing for gastrointestinal ADEs had improved significantly more in the SPACE group (OR: 0.76 (0.64, 0.92)), which was sustained at 12 months (OR: 0.75 (0.64, 0.92)) (Table S2).

Analysis by original random group assignment showed the SPACE group was significantly more likely to have high-risk prescribing than the control group at 6 months (OR: 1.21 (1.06, 1.38)) (Table S3).

Hospitalisations: There was no significant difference between the groups for total hospitalisations or for related gastrointestinal, renal or cardiac ADE hospitalisations in the 12 months following baseline adjusting for the 12 months prior to baseline (Table 5 and Tables S4-6).

Discussion

Summary: In this pragmatic trial in general practice, high-risk prescribing of NSAIDs and/or antiplatelet medicines improved in both groups at 6 and 12 months compared with baseline. This may have been due to general increase in awareness of the prescribing topic in the GP community. There was no significant difference between groups at 6 months in high-risk prescribing overall although the SPACE group improved more for gastrointestinal ADEs. This improvement was not sustained at 12 months when high-risk prescribing had improved more

in the control group. There was no significant difference between groups in related ADE hospitalisations. The CONSORT-Equity extension of 2017 encourages the investigation of intervention effects in people experiencing social disadvantage.[21] We found no ethnic differences in outcomes although the trial was not powered to detect this.

A possible explanation for the partial, short-term effect of SPACE may be that improving prescribing for gastrointestinal ADEs involves starting medication (proton pump inhibitor) while improving prescribing for renal and cardiac ADEs requires stopping medication, which GPs can find more challenging.[22] Given the time pressures and multiple competing demands in general practice it is not easy for interventions to produce lasting improvement. Brief interventions likely need repeating at regular intervals to achieve sustained improvement, balancing affordability and scalability.

Strengths and limitations: The strengths of this study include pragmatic trial design, and a scalable intervention for use in general practice that may be applied to any prescribing topic that includes novel elements of pharmacist supporting GPs to review a list of patients and for GPs to select patients for an automated letter prompting patients to seek medicines review. Important limitations include lower than expected engagement and uptake of the intervention. For one-third of SPACE participants, practices did not engage or there was minimal engagement making it difficult to show an effect. For practices that did engage, it was often difficult for the trial pharmacist to secure time with GPs delaying intervention delivery. Unlike in the SPACE pilot study, the trial pharmacist was not known to practices and GPs which may explain the difficulties.[13] A further limitation was that some practices enrolled in the contemporaneous prescribing initiative during follow-up which confounded our results but reflects the real-world conditions in which the study was conducted. A further limitation was the transcription error, where one block of six practices were allocated to the inverse of the random group assignment generated. We present ITT analysis by original random group

assignment in the appendices although this analysis risks a type 2 error, introducing bias towards the null hypothesis.

Comparison with existing literature: Our findings are consistent with previous research investigating ways to improve prescribing in general practice with limited success.[15,18,23-29] Complex interventions combining educational outreach visits, audit and feedback can work,[30,31] as can interventions involving pharmacists in general practices,[12,28,32,33] especially when combined with financial incentives.[17] Interventions that include empowering patients have also shown promise.[34] An intervention that included seven prescribing audits, seven face-to-face or group sessions, then four-monthly sessions showed a lasting effect on high-risk prescribing.[11]

Implications for research and/or practice: Further work is needed to identify scalable interventions that support safer prescribing in general practice in the longer term. The role of practice-based clinical advisory pharmacists and the use of automated searches to generate lists of at-risk patients for each GP and letter to patients to prompt medication review warrant further exploration.

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