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Supplementary webappendix

This webappendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

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PINCER trial and cost-effectiveness analysis: supplementary webappendices

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Further details of sample size calculations

Our sample size calculations were based on the assumption that for the proportion of patients fulfilling the criteria for any one of our primary outcome measures, there would be a maximum 11% reduction in the simple feedback arm and a 50% reduction in the pharmacist intervention arm.

The suggested 11% reduction in the simple feedback arm is the equivalent to the 75% centile for changes observed as a result of audit and feedback in a Cochrane systematic review available at the time that we did our sample size calculations.[1]

The suggested 50% reduction in the pharmacist intervention arm of the trial is based on extrapolation from our pilot studies[2,3] and findings from systematic reviews and other studies that, at the time of applying for funding for our study, showed that:

- Pharmacist-led interventions can lead to resolution of medication-related problems in 55-93% of patients.[4-8]
- Educational outreach is a moderately powerful tool for changing professional behaviour.[9]
- Multifaceted interventions aimed at different barriers to change are more effective than single interventions.[10]

Separate sample size calculations were performed for each of three primary outcome measures (see Web-table 1). Sample sizes unadjusted for clustering were calculated using the software package nQuery Advisor® version 6.0.[11] Sample sizes were inflated to adjust for clustering using ICCs and average cluster sizes estimated from QRESEARCH practices, as described below and shown in Web-table 1.

Data from 43 general practices contributing anonymous clinical data to the QRESEARCH research database (www.qresearch.org) were used to describe prevalence rates of asthma and peptic ulcer disease and to estimate the median proportions for each of our primary outcome measures. The intracluster correlation coefficients (ICCs) used in the calculation of the design effect (to inflate the sample sizes to adjust for the cluster design)[12] were as follows:

- 0.01082 for patients with a history of peptic ulcer who had been prescribed a non-selective NSAID (excluding those that were also in receipt of PPIs, which would protect against the risks from NSAIDs);
- 0.010657 for patients with asthma who had been prescribed a beta-blocker;
- 0.00952 for patients aged 75 years and older who have been prescribed an ACE inhibitor or a loop diuretic long-term who had not had a computer-recorded check of their renal function and electrolytes in the previous 15 months.

The calculation shown in Web-table 1 indicates that we needed at least 66 practices to detect a difference between an 11% reduction in error rate in the simple feedback arm and a 50% reduction in the intervention arm for each of our three primary outcome measures.

On the basis of these calculations, we decided to aim to recruit at least 68 practices. With 34 practices in each of the two intervention arms, we would have at least 80% power (two-tailed alpha of 0.05) to demonstrate a 50% reduction in rates of hazardous prescribing and medicines management in the pharmacist-led arm compared with 11% in the simple feedback arm.

References in relation to the sample size calculations

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Outcome measure	Patients with a history of peptic ulcer who have been prescribed a non-selective NSAID	Patients with asthma who have been prescribed a beta-blocker	Patients aged 75 years and older prescribed an ACEI or a loop diuretic long-term without a check of their renal function and electrolytes in the previous 15 months
Median error rate* (Interquartile range)	5·76% (3·76% - 7·85%)	1·90% (1·27% - 3·08%)	19·80% (15·13% - 32·69%)
Error rate in control group (assuming 11% reduction)	5·13%	1·69%	17·62%
Error rate in intervention group (assuming 50% reduction)	2·88%	0·95%	9·90%
Intraclass Correlation Coefficient (ICC)*	0·01082	0·00657	0·00952
Cluster size*	63	439	105
Inflation factor	1·7	3·9	2·0
Total number of practices required	64	66	12

*Estimated using data obtained from 43 general practices contributing to the QRESEARCH database (www·qresearch.org)

Web-table 1: Sample size calculations for the three primary outcome measures assuming an 11% reduction in error rates for the simple feedback group and a 50% reduction in error rates for the intervention group

Characteristics of general practices

Web-table 2, below, shows the characteristics of participating and non-participating general practice invited to take part in the PINCER trial.

Characteristic	Participating practices n=72	Non-participating practices n=168	Test statistic, P value
Median list size (IQR)	6 332·5 (3 566·0, 9 389·5)	4 557·5 (3 040·0, 7 777·5)	Z=2·03, P=0·04
Median number of GPs (IQR)	3 (2, 5)	3 (1, 4) [9]*	Z=1·97, P=0·05
Median percentage of practice population aged 75 years and over (IQR)	7·8 (6·0, 9·0) [3]*	7·4 (6·1, 8·9) [3]*	Z=0·72, P=0·47
Training practice (%)	23 (31·9)	29 (17·3)	χ^2=6·40, P=0·01
Median IMD score (IQR)	28·4 (18·5, 39·0)	27·2 (17·5, 36·6)	Z=0·77, P=0·44
Median QOF total points (IQR)	99·0 (95·5, 99·9)	98·0 (94·7, 99·5)	Z=2·14, P=0·03

Web-table 2: Characteristics of participating and non-participating practices
*Figures in square brackets are missing values

IMD =Index of Multiple Deprivations
IQR =inter-quartile range
QOF =Quality and Outcomes Framework. This is a voluntary incentive scheme for GP practices in the UK, rewarding them for how well they care for patients. It was introduced in 2004 as part of the General Medical Services Contract, and contains groups of indicators, against which practices score points according to their level of achievement (http://www.qof.ic.nhs.uk).

Web-table 3, below, shows the characteristics of practices participating in the PINCER trial by allocation arm.

Practice characteristics	Simple feedback (%)	PINCER (%)
Number of practices	36 (50·0)	36 (50·0)
Study center		
Nottingham	22 (61·1)	21 (58·3)
Manchester	14 (38·9)	15 (41·7)
Median list size (IQR)	6 438 (3834, 9707)	6 295 (2911, 9390)
Age of practice population		
0-14	38 804 (16·3)	39 818 (17·4)
15-64	159 277 (67·1)	152 156 (66·5)
65-74	20 683 (8·7)	19 151 (8·4)
>=75	18 648 (7·9)	17 623 (7·7)
Total	237 412 (100·0)	228 748 (100·0)
Sex of practice population		
Male	118 469 (49·9)	113 284 (49·5)
Female	118 943 (50·1)	115 464 (50·5)
Median Index of Multiple Deprivation 2004 score (IQR)	26·3 (18·8, 36·5)	30·3 (18·2, 39·6)
GP training practices (%)	10 (27·8)	13 (36·1)
Median Quality and Outcomes Framework medicines management points (IQR)	42 (38,42)	42 (38,42)
Median total Quality and Outcomes Framework points (IQR)	1 041 (1 004, 1 049)	1 036 (993, 1 048)

Web-table 3: Characteristics of practices at baseline by allocation arm

Additional information on the cost-effectiveness analysis

Methods

Interventions
As noted in the main paper, 36 practices were randomly allocated to the Simple feedback arm and 36 to the PINCER intervention. Web-figure 1 illustrates the comparators and the probabilistic events associated with each strategy.

Outcome measures
The primary and secondary outcome measures were the proportion of patients in each practice at six- and 12-months post-intervention with a specified set of prescribing or monitoring errors (see Table 1 in the main paper). The outcome for the economic analysis was the number of errors detected by the report generation process in both PINCER and Simple feedback arms at six months and 12 months after the intervention. For the economic analysis we used outcome measures 1, 2, 3, 5(a and b), 7 and 8 (see Table 1 in the main paper). We did not include outcome measure 4 because the number of patients with errors was very small; we did not include outcome measures 6, 9 and 10 because there were difficulties obtaining full data in all practices, as described in our trial protocol.[1]

Costs
Costs were obtained from the perspective of the English NHS in terms of the direct costs of providing an intervention to reduce prescribing errors in general practice. The study was not powered to detect differences in costs because there is no prior study upon which to base a power calculation. The time horizon was six months in the base case. All costs were incurred at practice level, so correction for clustering was not required.

Resource use
The only cost associated with the Simple feedback arm required the researchers to go back into the practices at set time periods to generate error reports from general practitioner (GP) systems. These costs were retained in the model to reflect the equivalent resource that would be consumed in practice to generate these error reports. The PINCER intervention comprised these report generation costs, plus a training session; facilitated meetings; monthly meetings; practice feedback meetings; time spent in each practice outside meetings following up errors. Web-table **4** provides a summary of the cost components for the Simple feedback and PINCER arms.

Error report generation
Researchers involved with the study estimated that running computer queries took two hours and report printing took 15 minutes. These times were not recorded but considered to vary between practices, independently of practice size. Key reasons included the speed of the system in the practice, how many people were using the system at the time the computer query was run and whether the system crashed before completion. If the system crashed before finishing the query, then the query would have to be run again from the start. The time taken to run the computer queries was based on the time it should take without any problems occurring.

Training session
The initial pharmacist training session costs reflect set-up costs of the intervention and would be incurred if the intervention were rolled out into clinical practice.

Facilitated meetings
Five quarterly facilitated meetings were held for the pharmacists running the interventions across the 36 intervention practices to provide a strategic overview of the initiative and to maximise homogeneity of the intervention. In clinical practice, a facilitated meeting would equate to a strategic practice meeting.

Monthly meetings
The aim of the monthly meeting between practice pharmacists and the Trial Manager was to deal with operational issues within individual practices. Twelve monthly meetings were held. These meetings would equate to operational meetings and, in practice, would be added onto other Primary Care Trust (PCT) team pharmacist meetings with general practices.

Practice feedback sessions
The aim of the feedback session was to provide each practice with feedback and support on management of errors, using root cause analysis to identify how systems could be improved. Between one and three practice

feedback sessions were held for each of the 36 intervention practices. The length of time spent per practice was not recorded, but was estimated by the pharmacists to be about one hour.

Time spent dealing with errors
PINCER pharmacists also spent time working on the intervention outside the meetings listed above to deal with errors identified. On the basis of information recorded by the pharmacists, the mean time spent dealing with each error was 23·3 minutes (median 18·4 minutes, range 0 – 180 minutes). The time spent on dealing with these errors was calculated for each practice. Where data were missing for time spent dealing with an error, it was assumed that time taken equated to the mean time taken for that error. The mean time spent in a PINCER intervention practice on the errors included in the economic analysis was 1 106 minutes (median 873 minutes, range 155 – 3 585 minutes). The mean cost per practice was £406·7 (median £320·9, range £57·0 – £1 318·8).

The general practices involved in the Simple feedback arm and the PINCER intervention arm may have spent time correcting errors and improving safety systems, but these data were not collected in either arm.

Construction of total costs associated with Simple feedback and PINCER intervention delivery
Three reports were run in each practice (baseline, six months and 12 months), costing £92·84 per practice at six months follow-up, and £139·26 per practice at 12 months follow-up. In total, report generation cost £3 342·24 and £5 013·36 for 36 Simple feedback and 36 PINCER intervention practices at six months and 12 months, respectively. This was the only cost attached to the Simple feedback arm.

The PINCER arm also generated £9 933·26 training costs, £102·89 preparation costs, £6 976·81 facilitated meeting costs, £1 996·30 monthly meeting costs, £794·52 practice meeting costs and £14 641·20 error management costs.

The cost components were summed together to give the total mean cost per practice in each arm of the trial (see Web-table 5).

Economic analysis
Prior to incremental cost effectiveness analysis, costs and outcomes were adjusted for specific characteristics. Regression analysis was planned to assess the effect of base list-size and at-risk list-size, as well as the following: i) number of GPs, in order to capture scale effects (this included the square of base list-size and at-risk list-size to also capture non-linear economies of scale); ii) Quality and Outcomes Framework (QOF - http://www.qof.ic.nhs.uk) and medicine-related QOF score (both were tested but QOF score was more informative), in order to capture efficiency; iii) Strategic Health Authority, in order to capture any potential regional fixed effects, and iv) demographic information on area-level deprivation, average ages and gender proportions.

The negative binomial model was used for regression analysis of errors.[2] The negative binomial model is used to estimate count data when over-dispersion means that the Poisson regression model would be inappropriate. Variance is greater than the mean for errors per practice in both groups, and the relative variation differs between groups. As a result Poisson regression would underestimate the standard errors of the coefficients. Costs were estimated via generalised linear modelling (GLM) assuming a gamma distribution.

Incremental cost-effectiveness ratios (ICERs) were calculated for differences in error rates between the Simple feedback and PINCER interventions.

Bootstrapping with replacement was employed, to identify the magnitude of uncertainty around the ICERs, utilising Microsoft Excel, using a minimum of 10 000 iterations to obtain 2·5% and 97·5% percentiles of the ICER distribution.[3]

A cost-effectiveness acceptability curve was constructed to express the probability that the cost per extra unit of outcome (error avoided in this study) gained from within the trial (y-axis) is cost-effective as a function of the decision-maker's ceiling cost effectiveness ratio (λ) (x-axis).[4]

Findings

Adjustment of outcomes

Negative binomial regression determined that only intervention and list-size were important predictors of error rates. An interaction term was also included between intervention and scale variables. It was not significant, however, and was subsequently removed. The model was estimated using the robust sandwich-estimator of the variance-covariance matrix.[5] Marginal effects from the final model are in Web-table 6.

Base list-size was scaled downwards for regression; the coefficient reflects the marginal increase in errors from a predicted mean of 33·69 per practice of an additional 100 patients. The variables for number of GPs and at-risk list-size were not statistically significant when base list-size was included, suggesting that they are all representing the overall catchment of the practice. Neither area-level deprivation nor QOF scores were statistically significant.

Besides using information criteria to select specifications and to choose between Poisson and negative binomial regression models, standard approaches to testing for independence in the errors were used, including fitting covariates to the residuals and fitting residuals to the fitted values. This supported the models above as appropriate approaches.

Adjustment of costs

Adjusted costs were estimated via GLM assuming a gamma distribution. Only the PINCER group was used in this analysis, since intervention costs in the Simple feedback group were constant (see Web-table 7). Only base list-size was significant.

Probabilistic incremental economic analysis

A probabilistic incremental cost-effectiveness analysis was completed using the adjusted cost and outcome data outlined above (see Table 4 in the main paper). The predicted errors and costs following the negative binomial regression for errors and the GLM regression for cost were used to characterise the distributions of incremental cost and effect. This allowed for bootstrapping with broader probabilistic sensitivity analysis since the values of the covariates were allowed to vary in the sample.

Web-figure 2 illustrates the ICER distribution at six and 12 months.

Discussion

To our knowledge, this is the first study of this kind to present the cost-effectiveness of an intervention to reduce medicines-related errors in primary care. The PINCER intervention reduced error rates, with increased cost, at both six and 12 months post-intervention.

Limitations

The costs of the Simple feedback and PINCER intervention arms were assumed to reflect how the interventions would be implemented in practice. It is possible that, once the trial environment is not present, the interventions may consume resources differently, although a qualitative study that was done alongside the trial does not suggest that this would be the case (publication forthcoming). There are also different potential models of this type of service provision, which may affect costs.

This economic analysis did not include any costs other than those incurred as a direct result of the intervention. In particular, the costs did not take account of any time spent by the general practices dealing with errors or improving safety systems. It is not clear whether Simple feedback or the PINCER intervention would be most costly in terms of general practice time, but in either case the costs presented here underestimate the real cost to practices.

This economic analysis of "cost per error avoided" carries the assumption that reducing errors is a desired objective. The analysis did not include any costs or outcomes that may have been incurred as a result of the error. It is not clear how cost per error avoided translates into actual health lost, and therefore whether the ICER for the PINCER intervention will represent good value for money; the true clinical and economic impact of the intervention cannot be assessed on the basis of this analysis. This is reflected in the lack of a net benefit statistic. While there is an assumption running through this study that reducing errors is a good thing to do, it could be argued that for some outcomes the PINCER intervention is using resources to be overly cautious with few benefits for patients. This assumption can only be disproved when we know more about the links between avoiding errors and patient benefit. Some outcomes in this study have clear probabilistic events, such as gastrointestinal bleeds from non-selective non-steroidal anti-inflammatory drugs in patients with a history of peptic ulcer, but others have less clear future morbidity and resource use.

Discussion of other studies

Cost per error avoided has not been widely generated by other studies. There has been no systematic review of economic evaluations of interventions to reduce medication errors in primary or secondary care. A review of economic effects of 17 clinical pharmacy interventions demonstrated that studies had serious limitations in their methodological quality and applicability to current practice; did not use a comparative study design, or include incremental cost-effectiveness analysis.[6] None were based in primary care or reported cost per error avoided. The poor quality of economic studies of pharmacy-based interventions has led to calls for improved research in the future.[7]

One modelling study was found that aimed to detect the economic impact of a pharmacy-based intervention to reduce medication errors.[8] No cost per error was reported so we cannot compare their results directly with our study. Using a range of assumptions, however, this UK study estimated from the error rate, what was the potential to cause harm. Utility weights were attached to harm from undetected errors divided into significant, serious, severe, life-threatening or fatal. These were hypothetical estimates as there are no relevant data available to describe the utility effects of the broadly defined severity categories. This pharmacist-led reconciliation intervention was demonstrated to have a probability of being cost-effective of over 60% by a QALY value of £10 000. This suggests that pharmacist-led interventions to reduce error rates may have the potential to be cost-effective according to currently employed cost-effectiveness thresholds.

Policy implications and further research

In considering the possibility of rolling-out the PINCER intervention to the English NHS it is important to recognise that there would be opportunity costs. Currently general practices in England have access to a variable amount of support from pharmacists employed by primary care organisations, with much of their time taken up with helping practices to control prescribing costs. For the outcomes included in the economic evaluation, the PINCER intervention took around 18 hours of pharmacist time per practice. Such an amount of time would probably be manageable for pharmacists currently working with English general practices, but without the addition of more resource, it may mean less time spent on other activities.

The economic analysis of "cost per error avoided" carries the assumption that reducing errors is a desired objective. The analysis did not quantify the clinical effects on patients of avoiding errors, nor the subsequent economic effects of managing the effects of those errors. Therefore, "cost per quality-adjusted life year (QALY) gained" could not be generated for the intervention. This means that it is not possible to assess whether the ICER generated for this intervention would be considered cost-effective according to current policy decision rules in England, such as a £20 000 to £30 000 per QALY threshold, as used by National Institute for Health and Clinical Excellence (NICE). The current convention is that interventions need to demonstrate an incremental cost per quality adjusted life year of £20 000 - £30 000 or less to be considered a cost-effective use of NHS resources. However, it may be argued that interventions to improve safety have a wider objective than to increase the health gain in the population. It is likely that increasing safety of health services increases public trust in that system. In a privately funded system, this may lead to increased utilisation of that system, and in a publicly funded system, this may lead to increased support from the electorate and their representatives. Therefore, the aim of the intervention may be broader than health gain, rendering the application of the current convention for cost effectiveness questionable. Nevertheless, further research is needed on the costs and benefits of avoiding different types of medication error so that future interventions can be designed to be as cost-effective as possible.

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Cost component	Method of cost allocation
Error report generation	Flat rate per practice
Pharmacist training Preparation for meetings Pharmacist facilitated meetings Monthly meetings	Allocated to intervention practices according to list-size, calculated by deriving the total cost for the 36 practices, and then allocating a portion of that cost to a practice based on the list-size.
Practice feedback meetings	Allocated to the PINCER intervention practices according to how many were carried out
Time spent dealing with errors	Costs of time spent per error detected were calculated and added to the cost for each practice

Web-table 4: Summary of cost components for Simple feedback and PINCER intervention arms

Cost category	Mean cost per practice (£) in Simple feedback arm	Mean cost per practice (£) in PINCER intervention arm (median, range)
Report generation 6 months: 12 months:	 92·84 (n/a) 139·26 (n/a)	 92·84 (n/a) 139·26 (n/a)
Pharmacist training costs	0	275·92 (267·76, 79·54 – 591·23)
Facilitated meetings	0	195·23 (189·45, 56·28 – 418·33)
Monthly meetings	0	56·88 (55·20, 16·40 – 121·88)
Practice feedback	0	22·07 (21·42, 6·36 – 47·29)
Management of errors	0	406·70 (320·93, 57·04 – 1 318·68)
Total 6 months: 12 months:	 92·84 139·26	 1 049·67 (967·86, 329·22– 2 086·78) 1 096·09 (1 014·28, 375·64– 2 133·20)

Web-table 5: Costs and outcomes associated with Simple feedback and PINCER intervention

Variable	Six months coefficient (standard error)	12 months coefficient (standard error)
Intervention	-11·2520* (4·0502)	-10·0475* (3·7493)
Base list-size/100	1·3031* (0·4406)	1·8265* (0·5146)
Base list-size squared/100	-0·0043† (0·0025)	-0·0068† (0·0029)
At-risk list-size	-0·0092 (0·0157)	-0·0069 (0·0194)
At-risk list-size squared	0·0000 (0·0000)	0·0000 (0·0000)
Number of general practitioners	-4·7186 (5·7827)	-11·0905 (6·6207)
Number of general practitioners squared	0·3857 (0·5549)	0·9626 (0·6664)
Index of Multiple Deprivation score	0·0528 (0·1607)	-0·1744 (0·1384)
Quality and Outcome Framework score 2005/2006	-0·1452 (0·3566)	-0·2679 (0·3859)

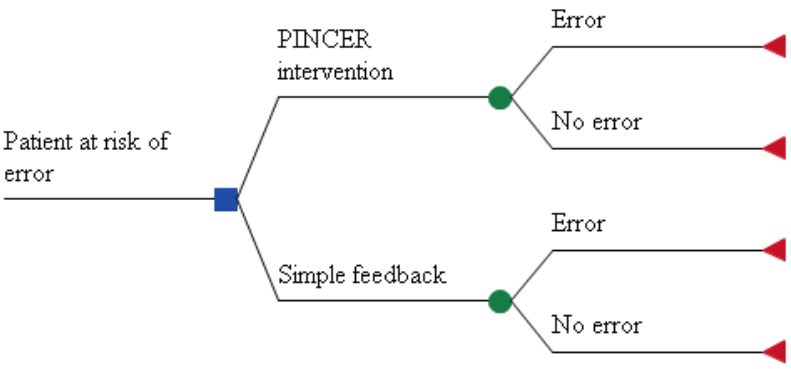
* Significant at 1% level, † Significant at 10% level

Web-table 6: Marginal effects coefficients from negative binomial regression of errors per practice

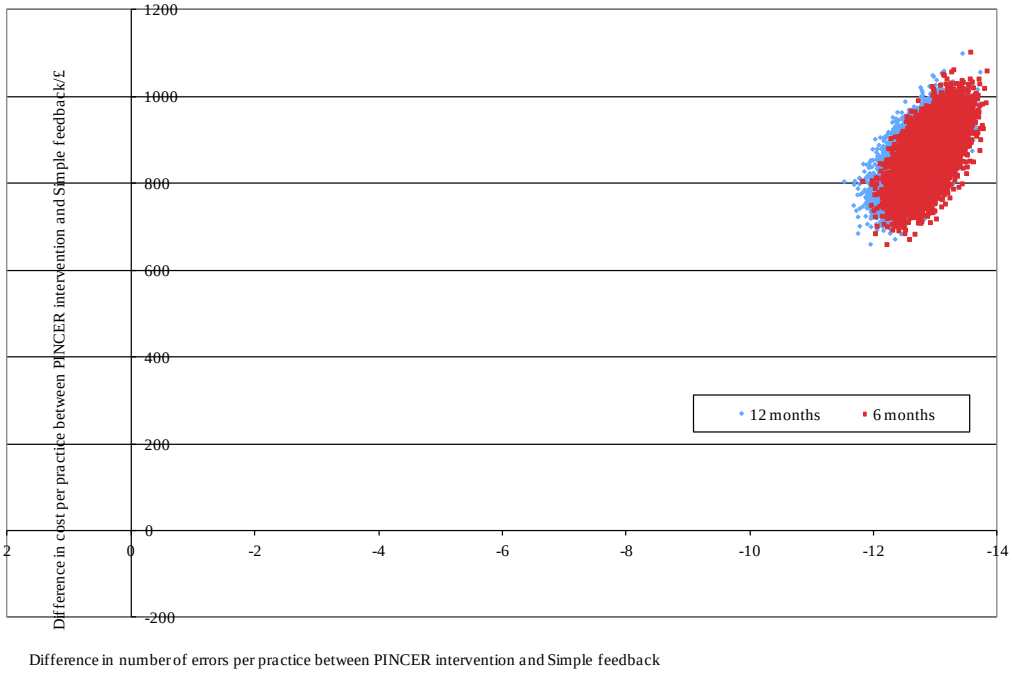
Variable	Six months coefficient (standard error)	12 months coefficient (standard error)
Base list-size/100	39·5040* (20·4400)	-0·0179 (16·8212)
Base list-size squared/100	-0·1855 (0·1388)	-0·0066 (0·0982)
At-risk list-size	-0·3738 (0·6852)	-0·1374 (0·5488)
At-risk list-size squared	0·0003 (0·0004)	0·0001 (0·0003)
Number of general practitioners	-63·5842 (227·5400)	64·9077 (211·6131)
Number of general practitioners squared	6·9328 (27·0750)	-4·6072 (19·0732)
Index of Multiple Deprivation score	0·6389 (5·4158)	0·0729 (5·3311)
Quality and Outcome Framework score 2005/2006	2·6424 (9·9520)	-3·1226 (10·1581)

* Significant at 10% level

Web-table 7: Coefficients (standard errors) from regression of intervention cost per PINCER intervention practice



Web-figure 1: A decision analytic model of pharmacist intervention versus simple feedback in patients at risk of error



Web-figure 2: Cost effectiveness plane (cost per error avoided at six and 12 months)