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Cost-effectiveness of strategies to increase cervical screening uptake at first invitation (STRATEGIC)

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Abstract

Objective: To assess the cost-effectiveness of strategies to increase cervical cancer screening uptake at first invitation (STRATEGIC trial).

Methods: We performed an economic analysis alongside the STRATEGIC trial, comparing each of seven novel interventions for improving cervical screening uptake with control general practices in Greater Manchester and Grampian (United Kingdom). A template was developed to measure the intervention costs. Trial estimates of screening uptake were combined with data from the literature to estimate healthcare costs of each intervention. The added lifetime costs and quality adjusted life years (QALYs) of attending cervical screening were estimated by a systematic literature review, with relevant results pooled and weighted by study quality. Trial results and estimated lifetime costs and benefits of screening were then combined in a decision analytic model, giving an incremental cost per QALY gained for each intervention. Uncertainty was addressed in probabilistic and univariate sensitivity analyses.

Results: Intervention costs per screening round per woman attending varied from about £1.20 (2014 UK) for the nurse navigator intervention to £62 for the unrequested HPV self-sampler kit. The meta-analysis revealed a lifetime discounted benefit from screening of 0.043 QALYs per woman attending, at an additional lifetime discounted cost of £234. The incremental cost per QALY gained in all interventions was below £13,000. Probabilistic sensitivity analyses suggested that only unrequested self-sampling and timed appointments have a high probability of being cost-effective.

Conclusions: Unrequested self-sampling and timed appointments are likely to be cost-effective interventions. Further research is required on the duration of effects and on implementing combinations of interventions.

Keywords

Cost-effectiveness, screening uptake, cervical cancer, United Kingdom

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The United Kingdom (UK) has a lower than average incidence rate of cervical cancer among all European countries.[1] This is partly attributable to the National Health Service Cervical Screening Programme, which was established in 1988 throughout the country.[2] Coverage of the screening programme fell between 2003 and 2013 in England and Scotland,[3,4] most notably at initial cervical screening among young women, who already had lower coverage rates than older women. Similar trends have been reported in other developed countries.[5] This decline in coverage among young women is already reflected in the rising incidence of cervical cancer amongst this cohort.[6] Another concern is the great variation in coverage rates across local authorities, which implies unequal distribution of the screening programme benefits at national level, potentially disadvantaging socially deprived and ethnic minority groups.

The Strategies to Increase Cervical Screening Uptake at First Invitation (STRATEGIC) trial was designed to

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investigate whether a range of novel interventions, when embedded within routine cervical screening practice, improve young women's receptivity to and uptake of cervical screening.[7] As part of the trial, this study aimed to assess the cost-effectiveness of these interventions in terms of lifetime costs and quality adjusted life years (QALYs). Such information can support the redesign of cervical cancer screening services in the UK to reduce the future health and economic impact of cervical cancer.

Methods

An economic analysis was designed to be conducted alongside the STRATEGIC trial, a pragmatic, multicentre, cluster randomized controlled trial. The study included all women registered in general practices from three Greater Manchester (England) Primary Care Trusts and Grampian (Scotland), who were about to receive their initial cervical cancer screening invitation (aged 25 in Manchester and 20 in Grampian). The trial offered seven novel interventions in two consecutive phases, to increase screening attendance in those women. In phase 1, the trial offered a pre-invitation leaflet (pre-leaflet) six weeks prior to their first invitation that aimed to prepare young women to engage more fully, as well as an online booking system that enabled women to book their initial screening test at a date of their convenience (online booking). In phase two, the trial offered the following five interventions: a letter sent to the women offering them the opportunity to request a human papilloma virus (HPV) self-sampling kit (RSS), an unrequested HPV self-sampling kit (USS) sent directly to their home, a nurse navigator (NN) available to offer help and advice in attending a cervical screening test, a letter with a timed appointment for a cytology test with the option to be rearranged at a more convenient time if needed, and a letter offering women the choice of either having access to an NN or an RSS. A detailed description of how the interventions was operationalized is presented in Supplemental file 1.

In phase 1, 276 general practices (20,879 women) were randomized to the pre-leaflet group or a control group (i.e. women were not offered a pre-leaflet). Practices in Manchester Primary Care Trusts only were also randomized to the online booking group or a control group (i.e. online booking was not offered) and balanced for the pre-leaflet intervention. In phase 2, whilst also balanced for phase 1 interventions, 267 practices were randomized to one of the five phase 2 interventions (i.e. RSS, USS, NN, timed appointment, choice) or a control group (i.e. none of the phase 2 interventions was offered). The interventions in phase 2 were provided only to women who had not undergone screening by six months following their initial invitation and remained located in the same Primary Care Trust. The Consolidated Standards of Reporting Trials diagram for the STRATEGIC trial is presented in Figure 1. Further details of the study design and the provided interventions are provided in the trial protocol[8] and the accompanying paper.[9]

This economic analysis was designed alongside the STRATEGIC trial and aimed to provide reliable estimates of cost and cost-effectiveness, while adhering to the general approach of the trial, which maximized the use of routine data sources and minimized direct contact with participating women. The design and reporting follow the methodological guidelines issued by the National Institute of Health and Care Excellence (NICE) for economic evaluations[10] and the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement.[11]

All resources required to develop and implement each intervention were identified and recorded by two trial research team members, and intervention providers cross-checked these to ensure completeness and accuracy. The list included labour time, printing and distribution of information materials, laboratory kits, rent for meeting rooms, training of professionals, information and communications and programming. Labour time costs were based on total employer cost (including salary, superannuation, and national insurance) corresponding to the salary grade of the staff involved in an activity, and included 20% overhead costs to cover premises and utilities. A detailed list of the items for each intervention, and associated costs, is presented in Supplemental file 2. Data on cytology tests and HPV self-sampling tests were collected from the screening agencies in Greater Manchester and Grampian. The number of colposcopies was estimated using information from the National Screening Programme about the colposcopy referral rate for the relevant age group, the attendance rate, and the proportions of outpatient diagnostic procedures, outpatient diagnostic procedures with biopsy and therapeutic colposcopies. Based on this information, we estimated the total number of HPV tests, cytology tests and colposcopies for each intervention and control group. Unit costs of HPV tests and cytology tests were obtained from previous studies,[12,13] and included staff time in screening centres and laboratories, equipment and consumables. Unit costs of different types of colposcopy procedures were obtained from the NHS reference costs 2013–2014. All unit costs were inflated to 2014 prices using the Hospital and Community Health Services inflation index.

The within-trial outcome measure for all interventions was completion of a cervical cancer test at the age of initial screening, measured at three and six months post-invitation for phase 1 interventions (i.e. pre-leaflet and online booking) and at 12 and 18 months post-invitation for phase 2 interventions. The primary endpoint for phase 1 interventions was uptake of screening at three months, and for phase 2 interventions at 12 months post-invitation.

Information about the incremental lifetime costs and benefits (quality adjusted survival) of attending cervical cancer screening was obtained through a systematic literature review (see Supplemental file 3). We searched for all economic evaluations of cervical cancer screening strategies which included no screening as a comparator and

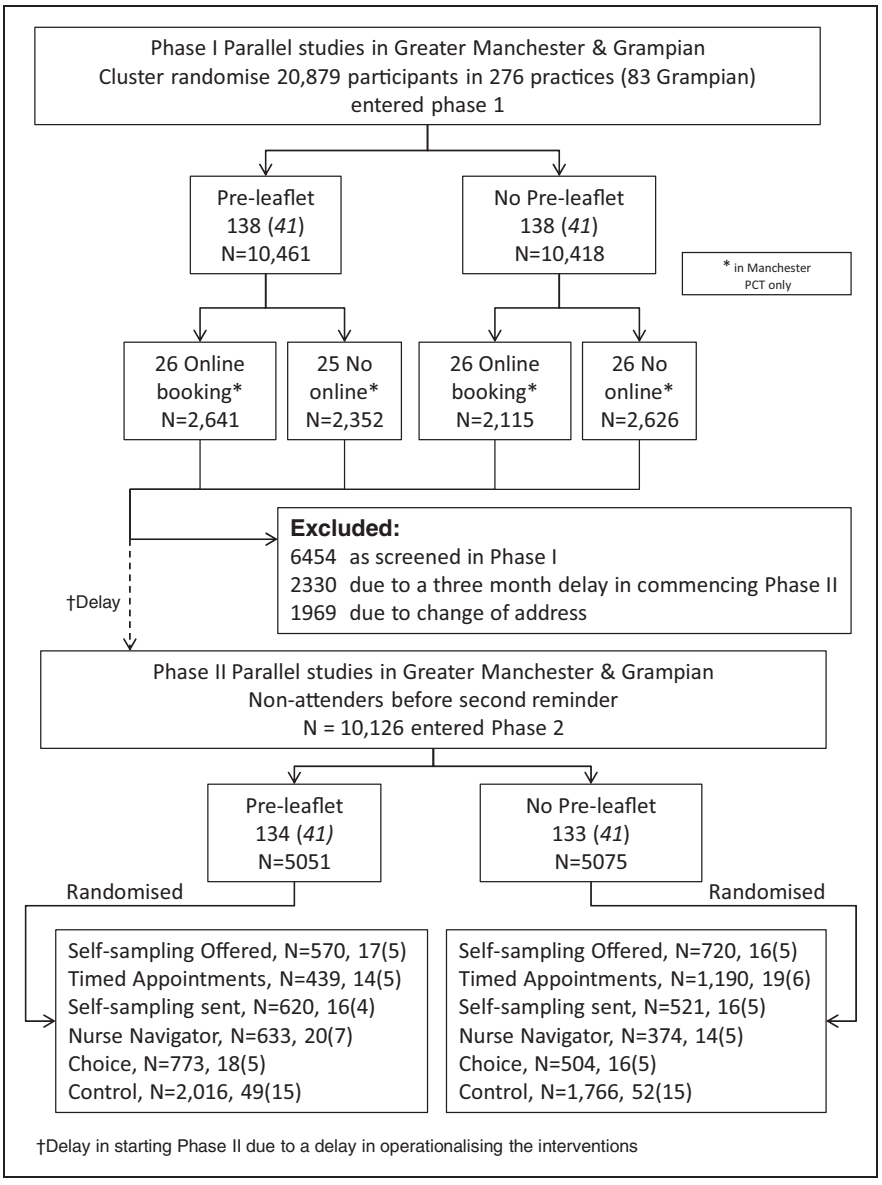

Figure 1. CONSORT diagram for the STRATEGIC trial.

reported lifetime costs and outcomes in the form of life years and/or QALYs, and followed the recommendations of the Centre for Reviews and Dissemination[14] and Cochrane Central Register of Controlled Trials[15] in searching MEDLINE, MEDLINE In-Process, EMBASE, EconLit, and NHS Economic Evaluation Database (NHS EED). Letters, editorials, animal studies, studies published before 1995 and non-English language studies were excluded. Titles and abstracts of retrieved studies were scanned for relevance and full text accessed if the paper was judged to meet the inclusion criteria. Full texts were then assessed for eligibility against the PICOS criteria. The process was documented in MS Excel, and reasons for inclusion and exclusion were detailed to facilitate updates of the review. The websites of agencies including NICE, MRC, and national cancer screening programmes were also scanned for relevant reports. A template was developed and used to extract the information from the studies most relevant to the STRATEGIC trial. In this process, the next more costly strategies to no screening, as well as strategies that had similar population (i.e. age groups), interval of screening, and discount rates (i.e. 3.5%) to UK were preferred. Where results from cancer screening in several countries were reported, we selected the UK-based estimates. The review was performed in May 2015. The quality of identified studies was assessed by two assessors using checklists of good practice for modelling and reporting,[11,16] with mean assessment score assigned in cases of disagreement.

Costs were inflated from each study's price reference year to 2014 using consumer price inflation rates for each study's country of origin, as reported by OECD,[17] and converted to UK Sterling using average exchange rates for the year 2014 (see Supplemental file 3).[18]

Life-years and QALYs retrieved from the included studies were adjusted to make them comparable and relevant to the UK context, by applying the ratio of discounted life expectancy between the screening and control cohorts in the selected studies to the discounted life expectancy at the mean age of women in the trial. Mean EQ5D utility weights from women in the UK general population at each year of the discounted life expectancy were then applied to calculate discounted QALYs. These modelling studies included screening coverage at different age groups to allow for different non-attendance patterns over a woman's life, and these patterns are therefore included in our pooled lifetime estimates for outcomes and costs.

A meta-analysis was then performed, using a random effects model to pool the estimated lifetime discounted costs and outcomes reported in the identified studies, assuming real differences in treatment effects because of heterogeneity in screening strategies, population, and other factors.[19] Study quality scores were used to weight each study's contributed information to the pooled estimate (i.e. a study with high quality score contributed more to the pooled estimate than a lower quality study).

A decision model was constructed in Excel to calculate the lifetime costs and outcomes of each intervention. In the baseline analysis, we treated all interventions as independent. The accompanying paper reports no significant interaction between the phase 1 interventions, or between the phase 1 and phase 2 interventions. Consequently, each of the seven interventions was compared with the respective control group. However, some of the phase 2 interventions could be considered mutually exclusive, and so we also report an analysis comparing them against each other. The basic approach of the model was to combine the within-trial cost and effectiveness results for each intervention and control group with the estimated lifetime discounted outcomes and costs of screening attendance, derived from the results of the meta-analysis. The probabilities of attendance in each intervention and control group were informed by the trial results. Intervention costs were obtained from the trial and lifetime QALYs and lifetime costs from the meta-analysis. Incremental cost-effectiveness ratios (ICERs) were expressed as incremental costs per woman attending a screening test, and incremental costs per QALY gained.

Probabilistic sensitivity analysis was performed to address uncertainty in the ICERs by performing 5000 draws of all cost and effect parameters using pre-specified distributions, recording incremental costs and incremental QALYs from each draw, and plotting the results on cost-effectiveness planes and acceptability curves. The latter display the probability that each intervention is cost-effective, as the ceiling ratio for the maximum acceptable incremental cost-effectiveness ratio varies from £0 to £75,000 per QALY gained. Distributions for within-trial costs, outcomes and attendance rates were derived from reported means and standard errors. Distributions for lifetime screening costs and QALYs were estimated from means and standard errors from the meta-analysis. The intervention costs per attendee, unit costs and probabilities of having an HPV test, cytology test and colposcopy were also included in the probabilistic sensitivity analysis.

Seven univariate sensitivity analyses were also performed. One examined the impact of using secondary endpoints (six months instead of three for phase 1, 18 months instead of 12 in phase 2) of the trial on the results of the economic evaluation (Supplemental file 4). In a second sensitivity analysis, study quality scores based on Phillips et al.[16] to weight the pooled estimates in the meta-analysis were replaced with study quality scores based on the CHEERS statement. In a third sensitivity analysis, only the lifetime costs and lifetime QALYs reported in the most recent UK study were used in the meta-analysis. The fourth, fifth and sixth sensitivity analyses explored the effect of changing the baseline assumption that the intervention is a one-time behavioural "nudge", i.e. that a non-attender is a never attender and that once the intervention achieves screening adherence, the woman becomes an always attender. These analyses assessed the impact on the results if the interventions had to be provided 3, 6 or 12 times, respectively, in a woman's lifetime to obtain lifetime participation in cervical screening. The seventh sensitivity analysis assessed the impact on the results of the economic evaluation of treating phase 2 interventions as mutually exclusive.

Finally, a scenario analysis was performed to explore the adoption of these interventions for a population of 365,087 women in phase 1 interventions, which is approximately the total number of women annually invited for cervical screening for the first time in England, Scotland, and Wales. A similar scenario analysis was performed for phase 2 interventions applied to a population of 255,561 women, assuming that only 30% of women were screened during phase 1. In these analyses, intervention costs were categorized into fixed one-off costs, semi-fixed scalable costs which are incurred in steps as scale increases and variable costs. In this analysis, it was assumed that large-scale purchasing of materials and equipment would allow a cost discount – set at 20% – to be obtained. Therefore, only the components of total cost that are not variable will affect the cost per woman and the ICERs.

Results

Table 1 reports the probability of attending cervical cancer screening by intervention and trial arm, at three months follow-up for phase 1 and 12 months for phase 2, with accompanying standard errors, alphas and betas as used in the probabilistic analysis. The probabilities of attending cervical screening at follow-up for each arm are reported with adjustment for clustering. The table shows that, for example, probability of attendance was 15.8% in the control group for timed appointments, compared with 20.8% in the group receiving that intervention. The highest probability of attending cervical cancer

Table 1. Probability of attendance (at three months follow-up for phase 1, 12 months for phase 2), and probability of being tested, by arm and intervention: mean (se), distribution and source.

	Mean	Standard error	Distribution	Alpha	Beta	Source
Probability of attendance – control:						
Pre-leaflet	0.196	0.006	Beta	987.33	4064.74	Trial
Booking	0.176	0.009	Beta	296.71	1395.73	Trial
Requested self-sampler	0.158	0.007	Beta	405.13	2165.97	Trial
Unrequested self-sampler)	0.158	0.007	Beta	405.13	2165.97	Trial
Nurse navigator	0.158	0.007	Beta	405.13	2165.97	Trial
Timed appointment	0.158	0.007	Beta	405.13	2165.97	Trial
Choice requested self-sampler or Nurse navigator	0.158	0.007	Beta	405.13	2165.97	Trial
Probability of attendance – treatment						
Pre-leaflet	0.190	0.005	Beta	1106.31	4719.09	Trial
Booking	0.179	0.007	Beta	495.64	2282.54	Trial
Requested self-sampler	0.168	0.013	Beta	143.74	718.86	Trial
Unrequested self-sampler	0.220	0.018	Beta	119.68	428.12	Trial
Nurse navigator	0.143	0.016	Beta	67.71	412.45	Trial
Timed appointment	0.208	0.015	Beta	152.64	584.67	Trial
Choice requested self-sampler or nurse navigator	0.170	0.015	Beta	109.80	542.14	Trial
Probability of having a test by phase 2 trial arm:						
HPV test: Control	0.002		Beta	1.00	612.00	Trial
Requested self-sampler	0.091		Beta	19.00	190.00	Trial
Unrequested self-sampler	0.350		Beta	85.00	158.00	Trial
Nurse navigator	0.007		Beta	1.00	145.00	Trial
Timed	0.000		Beta	0.00	323.00	Trial
Choice	0.029		Beta	7.00	233.00	Trial
Cytology: Control	0.998		Beta	612.00	1.00	Trial
Requested self-sampler	0.943		Beta	197.00	12.00	Trial
Unrequested self-sampler	0.786		Beta	191.00	52.00	Trial
Nurse navigator	1.000		Beta	146.00	0.00	Trial
Timed	1.000		Beta	323.00	0.00	Trial
Choice	0.979		Beta	235.00	5.00	Trial
Follow-up tests:						
Proportion of HPV triage after cytology (age: 20–24)	0.096		Beta	1231.00	11,561.00	PHE HPV Pilot
Colposcopy referral rate (cytology only and after HPV triage; age: 20–24)	0.117		Beta	1503.00	11,289.00	PHE HPV Pilot
Colposcopy attendance rate	0.767		Beta	188775.57	57,346.43	Health and Social Care Information Centre[3]
Colposcopy, outpatient procedure	0.387		Beta	73072.18	11,5744.82	Health and Social Care Information Centre[3]
Colposcopy with biopsy, outpatient procedure	0.482		Beta	91009.79	97,807.21	Health and Social Care Information Centre[3]
Therapeutic colposcopy, outpatient	0.131		Beta	24735.03	164,081.97	Health and Social Care Information Centre[3]

screening was in the group randomized to USS (22%) and timed-appointment (20.8%) interventions.

Table 2 reports the mean cost of each phase 1 and phase 2 intervention per woman attending, for one screening cycle. In phase 1, the pre-leaflet cost was £4.62 per woman attending, and the online booking was £3.88 per woman attending. In phase 2, intervention costs per woman attending varied from £1.22 for the NN to £62 for

Table 2. Costs of each intervention for one screening cycle (at three months follow-up for phase 1, 12 months for phase 2), and unit costs for tests and procedures: mean (se), distribution and source (£s 2014).

	Mean	Standard error	Distribution	Alpha	Beta	Source
Intervention costs per woman attending						
Pre-leaflet	4.62	0.22	Gamma	436	0.01	Trial
Booking	3.88	0.34	Gamma	130.18	0.03	Trial
Requested self-sampler	2.03	0.21	Gamma	89.62	0.02	Trial
Unrequested self-sampler	62.00	6.40	Gamma	93.90	0.66	Trial
Nurse navigator	1.22	0.17	Gamma	51.45	0.02	Trial
Timed appointment	24.85	2.48	Gamma	100.15	0.25	Trial
Choice of RSS or nurse navigator	6.24	0.68	Gamma	84.87	0.07	Trial
Unit costs						
Cytology test	36.37	1.66	Gamma	478.97	0.08	Kim[12]
HPV test	29.01	8.56	Gamma	11.48	2.53	
HPV (only lab costs)	8.00					Department of Health[20]
Colposcopy, outpatient procedure	169.56					Department of Health[20]
Colposcopy with biopsy, outpatient procedure	219.51					Department of Health[20]
Therapeutic colposcopy, outpatient	229.86					Department of Health[20]

Table 3. Pooled estimates from meta-analysis of lifetime discounted costs and outcomes for screened and unscreened populations.

	Coefficient	Standard error	p	95% CIs		Alpha	Beta
Lifetime costs, no screening	125.72	39.87	0.002	47.58	203.86	9.94	12.64
Lifetime costs, screening	359.43	102.05	0.000	159.41	559.45	12.40	28.98
Lifetime QALYs, no screening	22.564	0.003	0.000	22.346	22.853		
Lifetime QALYs, screening	22.607	0.016	0.000	22.575	22.639		

QALY: quality adjusted life year.

the USS kit, the relatively high cost of the latter being because those attending are bearing the costs of sending self-sampler kits to all women. Further details of the intervention costs are provided in Supplemental file 2.

From 3766 studies screened by title and abstract, and 30 screened by full-text, eight studies met the inclusion criteria and were included in the final review. Table 3 reports the results of the random effects model used to obtain pooled estimates of lifetime discounted costs and QALYs for screened and unscreened populations, with each study's contribution weighted by study quality score. These results indicated that participation in a screening programme increased lifetime discounted quality adjusted life expectancy by 0.043 QALYs (= 22.607–22.564), at an additional lifetime discounted cost of £233.71 (= £359.43–£125.72).

Table 4 reports the summary results of the cost-effectiveness analysis, combining the within-study intervention and test costs with lifetime costs and QALYs from participating in screening. Full details of each analysis are given in Supplemental file 5. The pre-leaflet and NN interventions appear as cost-saving (lower costs per woman in the intervention arm), due to the probability of attending being slightly higher in the control group than the intervention group, resulting in lower long-term screening costs, but also lower lifetime quality adjusted life expectancy. The remaining interventions led to higher costs and more QALYs. However, only the USS and timed-appointment interventions had statistically significantly higher incremental costs and incremental QALYs. These interventions had the highest incremental costs (£29.90 and £19.90, respectively) and the highest QALY gains (0.00271 and 0.00219, respectively). All ICERs were below £13,000.

The results from the probabilistic sensitivity analysis are presented in Figure 2, in the form of cost-effectiveness acceptability curves, which display the probability of each intervention being cost-effective at different willingness-to-pay values for one QALY. The probabilities do not add up to 1 because the interventions are treated as

Table 4. Cost-effectiveness of each intervention compared with control, assuming each intervention is offered only at initial screening round.

	Mean difference in discounted cost per woman (95% CI)	Mean difference in discounted QALYs per woman (95% CI)	Incremental cost per QALY gained[a]
Pre-leaflet	−£0.65 (−5.58; 3.77)	−0.00023 (−0.0010; 0.0004)	[a]
Internet booking	£1.57 (−5.33; 9.78)	0.00013 (−0.0009; 0.0014)	£12,121
Requested self-sampler	£2.75 (−5.15; 13.14)	0.00042 (−0.0008; 0.0021)	£6565
Unrequested self-sampler	£29.90 (17.78; 48.63)	0.00271 (0.0013; 0.0131)	£11,033
Nurse navigator	−£4.23 (−14.81; 7.39)	−0.00066 (−0.0005; 0.0060)	[a]
Timed appointment	£19.90 (9.59; 35.95)	0.00219 (0.0025; 0.0011)	£9070
Choice of requested self-sampler or nurse navigator	£4.34 (−4.39; 15.65)	0.00051 (−0.0004; 0.0049)	£8484

QALY: quality adjusted life year.
[a]Difference in costs divided by difference in outcomes.
[b]Lower costs and lower outcomes.

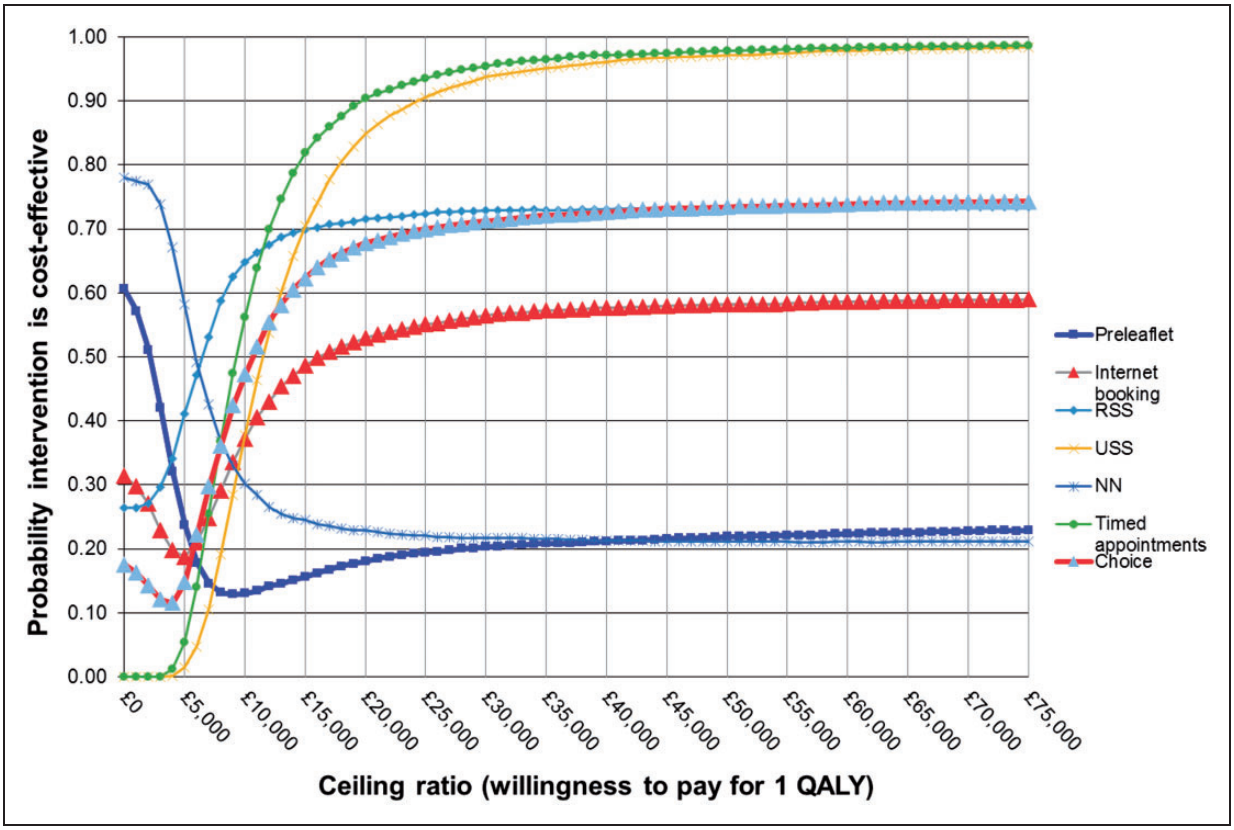

Figure 2. Cost-effectiveness acceptability curves for each intervention (baseline analysis: interventions offered over 1 cycle; outcomes assessed at three months for phase 1 interventions and 12 months for phase 2).

independent. The pre-leaflet intervention is characterized by high uncertainty surrounding costs and effectiveness; hence, the probability of this intervention being cost-effective is very low. A similar pattern is displayed by the NN intervention. Internet booking similarly has no clear evidence of effectiveness, and so the probability that this intervention is cost-effective at conventional ceiling ratios (i.e. NICE uses a range between £20,000 and £30,000 as an explicit threshold) of willingness-to-pay for one QALY never rises above 60%. RSS has a slightly higher probability of being cost-effective, but this rises no higher than 73% at any level of willingness to pay; a similar pattern is displayed by the Choice intervention, which includes RSS. For timed appointments, the probability that the intervention is cost-effective at a ceiling ratio of £20,000 per QALY gained is 90% rising to 95% at a ceiling ratio of £30,000. USS, the most expensive intervention, has 85% and 94% probability of being cost-

effective at £20,000 and £30,000 ceiling ratio per QALY, respectively. Both interventions are clearly more effective than control, and both are also almost certain to cost more than control. This is illustrated clearly in the cost-effectiveness planes for each intervention, reported in Supplemental file 6, in which 5000 cost–effect pairs are derived with all parameters varying.

The results from the univariate sensitivity analyses are presented in separate panels in Table 5, along with the results from the main analysis to facilitate comparison. When using the secondary endpoints in the analysis (Panel A), the results remain similar to the results of the main analysis for most interventions. Only the cost-effectiveness of the pre-leaflet intervention changes markedly, reflecting the odds ratio changing from 0.967 at three months to 1.014 at six months, and suggesting that the intervention may have a small effect in increasing attendance, resulting in better health outcomes but increased lifetime costs per woman. The cost-effectiveness acceptability curves for each intervention using the secondary endpoints are reported in Supplemental file 6. The main differences with the primary analysis are that the probability that timed appointments are cost-effective at a £20,000 ceiling has fallen from 90% to 79%, while the probability that the pre-leaflet or online booking interventions are cost-effective has increased.

Panel B of Table 5 reports the results for each intervention when the studies used to derive estimates of lifetime benefits and costs of screening are given quality weights using the CHEERS study criteria. This change makes each intervention slightly more cost-effective. Panel C shows the results when using only the most recent UK study for estimates of the lifetime costs and outcomes of screening; lifetime costs and outcomes are both lower than in the pooled meta-analysis results, but particularly outcomes, with the result that the cost-effectiveness ratios all increase compared with the baseline analysis while uncertainty increases. Panels D, E and F and Supplementary Figures 6.5, 6.6, and 6.7 show the results when assuming that the interventions are provided for three, six and 12 rounds, respectively, over a woman's lifetime, compared with a single round in the baseline analysis. As expected, the ICERs increase substantially and the corresponding probability that any of the interventions are cost-effective at a £20,000 ceiling ratio decreases markedly. Panel G reports cost-effectiveness results if the phase 2 interventions were to be treated as mutually exclusive, ranked in ascending order of effectiveness and compared with the next best intervention. The two phase 1 interventions – pre-leaflet and internet booking – are omitted from this comparison. The choice intervention is shown as being extended dominated. Results for the RSS intervention are unchanged, control being the next best alternative; timed appointments have an ICER of £9660 compared with RSS, and USS has an ICER of £19,380 when compared with timed appointments. These results are also shown graphically in Supplementary Figure 7.1.

Panel H in Table 5 reports the results of the scenario analysis in which it is assumed that the relevant population is all women eligible for cervical screening in England (365,087 in 2014). Effectiveness is unchanged in this analysis, but the per person costs of each intervention are lower due to economies of scale in the fixed costs of these interventions, which could be spread over a much larger population. We have also assumed that some variable costs, such as printing and postage, could be reduced via bulk contracts if these interventions were scaled up to the national level, and have assumed a reduction of 20%. As a result, the cost-effectiveness of all interventions improves.

Discussion

In this study, we have estimated the within-trial costs and lifetime cost-effectiveness of each of the interventions considered in the STRATEGIC trial, in comparison with the relevant control group as in the trial design, and also in comparison with each other in a sensitivity analysis.

Using information collected in the trial, we found that the costs of each intervention varied widely, from £1.22 per woman attending for the NN to £62 for USS per woman attending. These costs could be lower if the interventions were rolled out nationally and realized economies of scale, but the reductions were not dramatic.

The effectiveness of the interventions in our study is informed by the observed impact in the trial of the interventions on screening attendance. It was clear from the attendance probabilities of different interventions that the USS intervention had the largest statistically significant effect, followed by the timed-appointment intervention. The trial provided less guidance on how the different interventions examined in phase 1 and phase 2 of the evaluation might be offered in routine practice, and in particular, whether they can be considered mutually exclusive, or might be combined in various ways. Statistical tests suggested no interaction between the two phase 1 interventions, or between the phase 1 and the phase 2 interventions, but it is not clear whether phase 2 interventions could be offered simultaneously, or whether, for example, timed appointments could be offered to all, and USS to those who did not attend. The full range of such implementation scenarios goes beyond the remit of this study and would require further attention. However, whether the interventions are independent or mutually exclusive affects the economic evaluation directly, and given the ambiguities, we have provided results under both assumptions, which show that the ICERs remain below the £20,000 threshold.

Neither does the STRATEGIC trial provide clear guidance on the duration of the effects observed for some interventions. In our baseline analysis, we simulate a continuing effect from the initial intervention. However, in sensitivity analyses, we vary this assumption between a

Table 5. Cost-effectiveness results from the univariate sensitivity and scenario analysis.

	Mean difference in cost per woman		Mean difference in QALYs per woman		Incremental cost per QALY gained	
	Sensitivity/scenario analysis	Main analysis	Sensitivity/scenario analysis	Main analysis	Sensitivity/scenario analysis	Main analysis
Panel A: Cost-effectiveness results when using secondary endpoints (six months for phase 1 and 18 months for phase 2)						
Pre-leaflet	£1.80	−£0.65	0.00014	−0.00023	£13,266	[a]
Internet	£6.16	£1.57	0.00081	0.00013	£7623	£12,121
Requested self-sampler	£2.77	£2.75	0.00046	0.00042	£6041	£6565
Unrequested self-sampler	£25.74	£29.90	0.00221	0.00271	£11,649	£11,033
Nurse navigator	−£11.60	−£4.23	−0.00176	−0.00066	[a]	[a]
Timed appointment	£15.33	£19.90	0.00151	0.00219	£10,143	£9070
Choice	£4.02	£4.34	0.00048	0.00051	£8431	£8484
Panel B: Cost-effectiveness results when using the CHEERS study quality weights						
Pre-leaflet	−£0.75	−£0.65	−0.00028	−0.00023	[a]	[a]
Internet	£1.63	£1.57	0.00016	0.00013	£10,325	£12,121
Requested self-sampler	£2.94	£2.75	0.00051	0.00042	£5764	£6565
Unrequested self-sampler	£31.13	£29.90	0.00330	0.00271	£9433	£11,033
Nurse navigator	−£4.53	−£4.23	−0.00080	−0.00066	[a]	[a]
Timed appointment	£20.89	£19.90	0.00267	0.00219	£7820	£9070
Choice	£4.57	£4.34	0.00062	0.00051	£7340	£8484
Panel C: Cost-effectiveness results when using only most recent UK study for lifetime costs and outcomes						
Pre-leaflet	£0.04	−£0.65	−0.00011	−0.00023	[b]	[a]
Internet	£1.17	£1.57	0.00006	0.00013	£18,194	£12,121
Requested self-sampler	£1.46	£2.75	0.00021	0.00042	£7031	£6565
Unrequested self-sampler	£21.59	£29.90	0.00135	0.00271	£16,010	£11,033
Nurse navigator	−£2.21	−£4.23	−0.00033	−0.00066	[a]	[a]
Timed appointment	£13.17	£19.90	0.00109	0.00219	£12,064	£9070
Choice	£2.77	£4.34	0.00025	0.00051	£10,887	£8484
Panel D: Cost-effectiveness results when providing the interventions at three screening rounds of a woman's lifetime						
Pre-leaflet	−£0.86	−£0.65	−0.00023	−0.00023	[b]	[a]
Internet	£2.76	£1.57	0.00013	0.00013	£21,308	£12,121
Requested self-sampler	£3.33	£2.75	0.00042	0.00042	£7958	£6565
Unrequested self-sampler	£53.39	£29.90	0.00271	0.00271	£19,703	£11,033
Nurse navigator	−£3.93	−£4.23	−0.00066	−0.00066	[a]	[a]
Timed appointment	£28.80	£19.90	0.00219	0.00219	£13,129	£9070
Choice	£6.16	£4.34	0.00051	0.00051	£12,036	£8484
Panel E: Cost-effectiveness results when providing the interventions at 6 screening rounds of a woman's lifetime						
Pre-leaflet	£2.61	−£0.65	−0.00023	−0.00023	−£11,564	[a]
Internet	£4.14	£1.57	0.00013	0.00013	£31,979	£12,121
Requested self-sampler	£4.01	£2.75	0.00042	0.00042	£9575	£6565
Unrequested self-sampler	£80.68	£29.90	0.00271	0.00271	£29,773	£11,033
Nurse navigator	−£3.58	−£4.23	−0.00066	−0.00066	£5433	[a]
Timed appointment	£39.14	£19.90	0.00219	0.00219	£17,845	£9070
Choice	£8.26	£4.34	0.00051	0.00051	£16,162	£8484
Panel F: Cost-effectiveness results when providing the interventions at 12 screening rounds of a woman's lifetime						
Pre-leaflet	£4.73	−£0.65	−0.00023	−0.00023	−£20,918	[a]
Internet	£5.80	£1.57	0.00013	0.00013	£44,846	£12,121
Requested self-sampler	£4.82	£2.75	0.00042	0.00042	£11,526	£6565
Unrequested self-sampler	£113.58	£29.90	0.00271	0.00271	£41,915	£11,033
Nurse navigator	−£3.16	−£4.23	−0.00066	−0.00066	£4797	[a]
Timed appointment	£51.62	£19.90	0.00219	0.00219	£23,530	£9070
Choice	£10.81	£4.34	0.00051	0.00051	£21,137	£8484

(continued)

Table 5. Continued

	Mean difference in cost per woman		Mean difference in QALYs per woman		Incremental cost per QALY gained	
	Sensitivity/scenario analysis	Main analysis	Sensitivity/scenario analysis	Main analysis	Sensitivity/scenario analysis	Main analysis
Panel G: Cost-effectiveness results when treating the phase 2 interventions as mutually exclusive (in increasing order of effectiveness, the struck out intervention (choice) being extended dominated)						
Nurse navigator	−£4.23	−£4.23	−0.00066	−0.00066	[a]	[a]
Control	£0.00	NA	0.00000	NA	£0	NA
Requested self-sampler	£2.75	£2.75	0.00042	0.00042	£6565	£6565
Choice	£1.59	£4.34	0.00009	0.00051	ED	£8484
Timed appointment[c]	£17.15	£19.90	0.00178	0.00219	£9660	£9070
Unrequested self-sampler[b]	£10.00	£29.90	0.00052	0.00271	£19,380	£11,033
Panel H: Cost-effectiveness results if interventions offered to entire eligible population of England at first screening invitation						
Pre-leaflet	−£0.90	−£0.65	−0.00023	−0.00023	[d]	
Internet	£1.29	£1.57	0.00013	0.00013	£10,007	£12,121 [a]
Requested self-sampler	£2.68	£2.75	0.00042	0.00042	£6402	£6565
Unrequested self-sampler	£27.16	£29.90	0.00271	0.00271	£10,023	£11,033
Nurse navigator	−£4.23	−£4.23	−0.00066	−0.00066	[a]	[a]
Timed appointment	£18.86	£19.90	0.00219	0.00219	£8596	£9070
Choice	£4.06	£4.34	0.00051	0.00051	£7949	£8484

NA: not applicable; ED: subject to extended dominance; QALY: quality adjusted life year.
Note: each STRATEGIC intervention is compared with control in all Panels except Panel G, where they are compared with the next most effective STRATEGIC intervention.
[a]Lower costs and lower outcomes.
[b]USS compared with timed appointment.
[c]Timed appointment is compared with RSS after deleting extendedly dominated option (Choice).
[d]Higher costs lower outcomes.

single round and offering the intervention for all 12 rounds of the current screening programme, making the intervention less cost-effective. Studies with longer follow-up could provide valuable evidence on this question.

Previous economic evaluations of interventions aimed at increasing (mainly breast) cancer screening uptake are relatively few and have methodological limitations such as short time-horizons.[21–23] A recent economic evaluation of strategies to increase uptake of cervical cancer screening in Spain had a 3.5-year time-horizon, and reported ICERs in terms of costs per 1% increase in screening coverage.[24] To translate participation in the screening programme into the lifetime cost-effectiveness perspective that decision makers require, we extracted and pooled information on the lifetime costs and benefits of participating in cervical cancer screening from a systematic literature review and meta-analysis of lifetime models of cervical cancer screening. Our baseline analysis uses the pooled results across all eligible studies, but we also report an analysis using only the most recent UK-based modelling study, which results in poorer cost-effectiveness estimates combined with more uncertainty. Further work would be helpful in understanding the sources of heterogeneity between such models. Existing models also typically simulate lifetime participation or non-participation in screening, and further research is required to explore changes in participation rates over the life-cycle and their effects.

The STRATEGIC study found that two of the interventions examined – USS and timed appointments – were associated with small but statistically significant increases in screening uptake.[7] In this analysis, which also takes the intervention costs and possible long-term costs and benefits into account, we find that both interventions offer a reasonable probability of being cost-effective at conventional UK thresholds. The results of our analysis can also be used to estimate the cost reductions (such as lower kit prices) that would be required to increase the likelihood of USS being cost-effective at a £20,000 ceiling ratio, if its effectiveness made it an attractive option to decision makers or to women in the target age-groups.

The economic analysis has not replicated the subgroup analyses performed in the main trial results, comparing vaccinated and unvaccinated women and comparing Grampian and Greater Manchester, because it is unclear how any cost-effectiveness differences arising from these comparisons could be interpreted or used by decision makers. However, it is likely that vaccination will have an increasing impact on the future operation and cost-effectiveness of the cervical cancer screening programme.

Conclusion

Using new evidence from this large cluster randomized controlled trial, we conclude that USS and timed appointments offer a reasonable probability of being cost-effective at conventional UK thresholds. Further research is required on the duration of effects and on implementing combinations of interventions.

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References

1. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. *Eur J Cancer* 2013; 49: 1374–1403.
2. Peto J, Gilham C, Fletcher O, et al. The cervical cancer epidemic that screening has prevented in the UK. *Lancet* 2004; 364: 249–256.
3. Health and Social Care Information Centre. *Cervical screening programme, England, statistics for 2013–14*. England, 2014.
4. NHS Scotland. *Scottish cervical screening programme statistics 2013–14*. Edinburgh: NHS Scotland, 2014.
5. Lancucki L, Fender M, Koukari A, et al. A fall-off in cervical screening coverage of younger women in developed countries. *J Med Screen* 2010; 17: 91–96.
6. Network NCI. *Profile of cervical cancer in England: Incidence, mortality and survival*. London: National Cancer Intelligence Network, 2012.
7. Kitchener HC, Gittins M, Rivero-Arias O, et al. A cluster randomised trial of strategies to increase cervical screening uptake at first invitation (STRATEGIC). *Health Technol Assess* 2016; 20: 1–138.
8. Kitchener HC, Cruickshank M, Roberts C, et al. Strategies to Increase Cervical Screening Uptake at First Invitation (STRATEGIC): protocol version 8. National Institute for Health Research, www.nets.nihr.ac.uk/projects/hta/0916401 (2013, 31 March 2017).
9. Kitchener HC, Gittins M, Cruickshank M, et al. A cluster randomised trial of strategies to increase uptake amongst young women invited for their first cervical screen; the STRATEGIC trial. *J Med Screen* 2017. DOI: 10.1177/0969141317696518.
10. National Institute for Health and Care Excellence. *Guide to the methods of technology appraisal 2013*. London: NICE, 2013.
11. Husereau D, Drummond M, Petrou S, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. *Bmj* 2013; 346: f1049.
12. Kim EJ. *Modelling the cost-effectiveness of human pappilomavirus (HPV) testing for triage of women with low-grade abnormal cervical smears: a study within the TOMBOLA trial*. Sheffield: The School of Health and related Research, University of Sheffield, 2010.
13. Sherlaw-Johnson C and Philips Z. An evaluation of liquid-based cytology and human papillomavirus testing within the UK cervical cancer screening programme. *Br J Cancer* 2004; 91: 84–91.
14. Centre for Reviews and Dissemination. *CRD's guidance for undertaking reviews in health care*. York: Centre for Reviews and Dissemination, 2009.
15. CochraneLibrary. Cochrane Central Register of Controlled Trials (CENTRAL). http://www.cochranelibrary.com/about/central-landing-page.html (2015, accessed 7 April 2017).
16. Philips Z, Ginnelly L, Sculpher M, et al. Review of guidelines for good practice in decision-analytic modelling in health technology assessment. *Health Technol Assess* 2004; 8: iii–iv, ix–xi, 1–158.
17. Organization for Economic Cooperation and Development. *OECD health statistics 2015*. Paris: OECD, 2015.
18. HM Revenue and Customs. *Foreign exchange rates: Yearly average and spot rates*. London: HMRC. https://www.gov.uk/government/publications/exchange-rates-for-customs-and-vat-yearly (2015, accessed 7 April 2017).
19. Riley RD, Higgins JPT and Deeks JJ. Interpretation of random effects meta-analyses. *BMJ* 2011; 342: d549.
20. Department of Health. *NHS reference costs 2013–2014*. London: Department of Health, 2015.
21. Thompson B, Thompson LA, Andersen MR, et al. Costs and cost-effectiveness of a clinical intervention to increase mammography utilization in an inner city public health hospital. *Prev Med* 2002; 35: 87–96.
22. Ishikawa Y, Hirai K, Saito H, et al. Cost-effectiveness of a tailored intervention designed to increase breast cancer screening among a non-adherent population: a randomized controlled trial. *BMC Public Health* 2012; 12: 760.
23. Saywell RM Jr, Champion VL, Skinner CS, et al. Cost-effectiveness comparison of five interventions to increase mammography screening. *Prev Med* 1999; 29: 374–382.
24. Trapero-Bertran M, Acera Perez A, de Sanjose S, et al. Cost-effectiveness of strategies to increase screening coverage for cervical cancer in Spain: the CRIVERVA study. *BMC Public Health* 2017; 17: 194.