

# Options for managing low grade cervical abnormalities detected at screening: cost effectiveness study

TOMBOLA Group

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## ABSTRACT

**Objective** To estimate the cost effectiveness of alternative methods of managing low grade cervical cytological abnormalities detected at routine screening.

**Design** Cost analysis within multicentre individually randomised controlled trial.

**Setting** Grampian, Tayside, and Nottingham.

**Participants** 4201 women with low grade abnormalities.

**Interventions** Cytological surveillance or referral to colposcopy for biopsy and recall if necessary or referral to colposcopy with immediate treatment based on colposcopic appearance.

**Main outcome measures** Data on resource use collected from participants throughout the duration of the trial (36 months), enabling the estimation of both the direct (health care) and indirect (time and travel) costs of management. Quality of life assessed at recruitment and at 12, 18, 24, and 30 months, using the EQ-5D instrument. Economic outcomes expressed as costs per case of cervical intraepithelial neoplasia (grade II or worse) detected, by trial arm, as confirmed at exit, and cost utility ratios (cost per quality adjusted life year (QALY) gained) for the three pairwise comparisons of trial arms.

**Results** The mean three year discounted costs of surveillance, immediate treatment, and biopsy and recall were £150.20 (€177, \$249), £240.30 (€283, \$415), and £241.10 (€284, \$400), respectively, viewed from the health service perspective. From the social perspective, mean discounted costs were £204.40 (€241, \$339), £339.90 (€440, \$563), and £327.50 (€386, \$543), respectively. Estimated at the means, the incremental cost effectiveness ratios indicated that immediate treatment was dominated by the other two management methods, although it did offer the lowest cost per case of cervical intraepithelial neoplasia detected and treated. The pronounced skews in the distributions indicated that probabilistic uncertainty analysis would offer more meaningful estimates of cost effectiveness. The observed differences in the cost effectiveness ratios between trial arms were not significant.

**Conclusion** Judged within the time frame of the TOMBOLA evaluation, there is no compelling economic reason to favour any one follow-up method over either of the others.

**Trial Registration** ISRCTN 34841617.

## INTRODUCTION

By enabling cervical intraepithelial neoplasia to be detected and treated, mass population screening using smear tests has contributed to reducing the incidence of cervical cancer throughout the United Kingdom.<sup>1,2</sup> Women with normal test results require no clinical management, other than routine recall for future screening, whereas those with high grade abnormalities should be referred for colposcopy. The optimal management of those with low grade abnormalities detected on screening (borderline nuclear abnormalities or mild dyskaryosis), however, has been the subject of debate.<sup>3-6</sup> Two alternatives have been advocated—namely, cytological surveillance (further smear tests at regular intervals) or immediate referral for colposcopic examination. When low grade abnormalities are viewed at colposcopy, some clinicians favour a policy of “see and treat,” whereby immediate excision, if indicated, is carried out in a single visit. Others prefer a more conservative approach, whereby one or more biopsies are taken at the initial colposcopy, with women returning for treatment at a later date as necessary.

To inform these management debates, a randomised controlled trial (TOMBOLA, trial of management of borderline and other low grade abnormal smears) was established in the late 1990s. The trial is now complete, and full details of its rationale, design, and conduct are available elsewhere.<sup>7</sup> We report on the economic evaluation conducted in parallel with the clinical trial. The primary function of cervical screening is to identify premalignant lesions and we therefore estimated the expected cost of detecting and treating a case of cervical intraepithelial neoplasia grade II or worse, for each of the three methods under investigation. The use of evaluation results in health policy formulation requires outcomes to be assessed with a common metric, and, in the UK, this metric is the quality adjusted life year (QALY). We present incremental cost effectiveness ratios for pairs of management options in terms of costs per QALY gained.

## METHODS

### Resource use

Cervical screening in the UK is provided by the state funded National Health Services (NHS) and is

available to eligible women free of charge. We collected data on use of resources at the level of individual participants throughout the three year observation period (initial recruitment to exit). To facilitate cost discounting, we recorded the specific timing of every management event relative to the recruitment baseline. The principal resource using events contributing to NHS screening costs were smear tests and colposcopy examinations. The nature of the management methods, however, meant that the colposcopies themselves were often accompanied by additional, contemporaneous interventions—for example, further smear tests, biopsies, large loop excisions of the transformation zone, or cold coagulation. Resource use due to after effects of management during the weeks after the first surveillance smear or the first colposcopy appointment was captured in questionnaires returned by a subsample of trial participants.

In addition to the costs of cervical screening and treatment borne by the NHS, we calculated costs borne by others. Firstly, the opportunity costs of the actual time consumed during consultations and treatments were borne by women privately, their employers, or society as a whole. Secondly, women incurred direct costs of travel to appointments and some needed to finance a substitute carer for their dependants. Thirdly, many women were accompanied to their appointments, resulting in additional opportunity costs and travel expenses for companions. The data on resource use required to estimate the costs of time and travel were obtained from a questionnaire survey of a large subsample (n=2269) of participants.<sup>8</sup>

#### Unit costs

The chosen evaluation baseline was 2004, the year in or around which most of the resource use actually occurred. Accordingly, all unit costs were translated to 2004 prices using the hospital and community health services pay and price index.<sup>9</sup>

As routine smear taking in the UK has always been organised locally in primary care, the NHS cost of testing varies across the countries. Accordingly, we took the unit cost of a smear test to be the average of smear test costs derived from three independent micro-costing studies. Firstly, a specific cost audit was undertaken in Nottingham. This study used data obtained from a survey of resource use among local general practitioners and cost records from the local cytology laboratory.<sup>10</sup> The second study had collected data at one of the Tayside centres before the start of the trial.<sup>11</sup> The third had been conducted independently as part of the evaluation of human papillomavirus testing at pilot sites in Bristol, Norwich, and Newcastle.<sup>12</sup> The three independent estimates of the cost of a smear test were, respectively, £24.30, £26.80, and £36.90 at 2004 prices, yielding a mean unit cost of £29.30 (€34.5, \$48.5 at current conversion rates).

The unit cost of colposcopy was derived from the 2003 NHS reference cost of outpatient colposcopy, based on a national sample of about 250 000 events.<sup>13</sup> The published reference cost included that of the

colposcopic examination itself, plus the costs of biopsy, excision, or ablation if carried out. To identify the cost of the procedure alone, we adjusted the published average cost on the basis of the proportion of colposcopies known to have been followed by each of these other procedures in the English programme<sup>14</sup> and the unit costs of histopathology,<sup>13</sup> excision,<sup>15</sup> and ablation.<sup>16</sup> The unit costs associated with the various procedures related to colposcopy ranged from £111.40 for an examination only to £210.00 for a combined examination, smear test, and large loop excision. A small number of smear tests and colposcopies occurred either outside the trial areas or in private practice, although these were all costed as for the corresponding procedures within the trial.

For patients who needed hospital treatment as part of their management, the costs apportioned were specific to both the condition being treated and the type of visit—for example, outpatient, inpatient (the product of the cost per day and length of stay), or accident and emergency.<sup>17</sup> A hospital outpatient attendance cost £70.40, inpatient care cost £341.70 per day, and an emergency admission cost £135.40. When the costs of condition specific procedures performed were unavailable, we applied day reference costs for gynaecology patients. All additional prescribed medication was costed with *British National Formulary* (BNF) prices.

The questionnaire study<sup>8</sup> estimated time and travel costs at £10.10 per attendance for a smear test and £30.00 per attendance for colposcopy. Time costs were calculated by combining the reported duration of an event with the prevailing average wage.<sup>18</sup> Using these estimates, we estimated the costs of time and travel for all formal contacts with care providers for each participant. The estimate for attending a colposcopy appointment without treatment was applied also to investigations in the private sector and to hospital procedures, as a measure of entailed cost. In all cases, we adjusted the time costs applied by the length of visit. Absences from work due to complications and after effects were costed at the prevailing average wage. Reported contacts with specific health services (general practitioner, nurse, NHS or trial help lines) were costed according to the type of service consulted and the mode of contact, either by telephone or in person.<sup>9</sup> These were apportioned as costs borne by the NHS or the participant, as appropriate.

#### Outcomes

Although changes in health state utilities that arise as a result of cervical screening have been modelled,<sup>19</sup> we collected health state utility data in real time. Participants were invited to complete the EQ-5D<sup>20</sup> immediately before initial randomisation and at intervals throughout the trial, specifically at 12, 18, 24, and 30 months after recruitment. In addition, a subsample of women completed an EQ-5D questionnaire six weeks after their first surveillance smear test or colposcopy appointment. Using the established algorithms for the UK,<sup>21,22</sup> we translated EQ-5D classifications directly into index scores. We were therefore able to

**Table 1** | Smear tests and colposcopies by trial arm. Figures are numbers (percentage) of participants

	Cytological surveillance	Immediate treatment	Biopsy and recall	$\chi^2$	P value
Participants receiving:					
Smear tests:					
≤2	451 (20.3)	564 (57.4)	524 (52.4)	662.5	<0.001
3-4	1302 (58.7)	390 (39.7)	437 (43.7)	—	—
>4	466 (21.0)	28 (2.9)	39 (3.9)	—	—
Colposcopies without treatment	307 (13.8)	670 (68.2)	994 (99.4)	2260.2	<0.001
Colposcopies with treatment	291 (13.1)	498 (50.7)	198 (19.8)	545.4	<0.001
Both types of colposcopy	207 (9.3)	188 (19.1)	193 (19.3)	85.2	<0.001
CIN grade II or higher	269 (12.1)	220 (22.4)	192 (19.2)	61.8	<0.001
Mean No received/participant:					
Smear tests	3.39	2.30	2.40	—	—
Colposcopies without treatment	0.24	0.75	1.21	—	—
Colposcopies with treatment	0.13	0.55	0.21	—	—

CIN=cervical intraepithelial neoplasia.

plot index scores against time for each participant, with the area under the curve representing the total number of QALYs experienced by the participant between recruitment and 30 months thereafter. By implication, the maximum outcome within the trial for each participant was 2.5 undiscounted QALYs.

We did not expect all women to complete all EQ-5D questionnaires, and many women failed to complete at least one. We excluded from the analysis any woman whose initial or final questionnaire was uncompleted and also any whose questionnaires at two or more adjacent time points were missing. When a single utility value was missing within the individual's EQ-5D sequence, we used linear interpolation between the two known values on either side.

### Cost effectiveness

The accounting conventions for economic evaluation differ between countries. In England, the National Institute for Health and Clinical Excellence (NICE) stipulates an NHS perspective for costs, a validated generic measure of individual health outcomes, and an annual discount rate of 3.5% for both costs and outcomes.<sup>23</sup> In most other countries, evaluations adopt a social perspective, whereby costs incurred outside the confines of formal health care are also included.<sup>24,25</sup> Debate continues over the rate at which health outcomes should be discounted, including whether they should be discounted at all.<sup>26-28</sup> Unlike England, Scotland does not place a priori restraints on accounting conventions.<sup>29</sup> Given different conventions, we evaluated under different assumptions with respect to perspective and discount rate, and we present two sets of results. For the first, we followed the NICE approach, including only NHS costs and discounting both costs and benefits at 3.5% a year. For the second, we adopted a social perspective on costs (NHS costs plus costs of time and travel) with costs discounted at 3.5%, but benefits undiscounted.

In all cases we refer to cervical intraepithelial neoplasia grade II or higher. The mean costs of detection and

management for each arm comprised the costs of management of all women in the arm, divided by the number of cases detected at any point during follow-up.

Having ranked the comparators by increasing cost, we estimated the incremental cost effectiveness ratios (the ratios of the mean incremental costs to the mean incremental benefits) for the three pairwise comparisons. In view of the skew typical of trial data (positive skew for costs, negative skew for outcomes), arithmetically calculated means and confidence intervals are generally misleading. We therefore fitted distributions to the individual cost and outcome data for each arm and thereafter used these to estimate the means and distributions of the incremental cost effectiveness ratios. We adopted the standard Monte Carlo approach to uncertainty analysis,<sup>30</sup> using Palisade @RISK version 4.5 with 10 000 iterations for each comparison.

Further details of the data collection and cost effectiveness calculations are provided in the appendix on [bmj.com](http://bmj.com).

### RESULTS

The economic evaluation sample comprised 4201 women, of whom 2219 had been randomised to cytological surveillance, 982 to colposcopy with immediate treatment, and 1000 to colposcopy with biopsy and recall. Table 1 shows the numbers and proportions of women in each of the three trial arms receiving different numbers of smear tests and different types of colposcopies. The category “colposcopies without treatment” includes cases of colposcopic examination only, or examination coupled with further smear tests or with biopsies. For “colposcopies with treatment,” the treatment concerned was large loop excision or cold coagulation. Table 1 also shows the women in each arm in whom cervical intraepithelial neoplasia grade II or higher was detected before the exit colposcopies. Differences between the mean numbers of the three different types of procedure by trial arm were significant for all pairwise comparisons, with the

**Table 2** | Costs and outcomes per woman by trial arm

	Cytological surveillance	Immediate treatment	Biopsy and recall
Mean cost (£) by expenditure category:			
Smear tests	101.9	68.7	71.5
Colposcopy without treatment	30.7	87.7	149.5
Colposcopy with treatment	25.1	106.3	40.7
Hospital visits	7.3	6.8	8.5
Complications	1.5	2.5	2.5
Time and travel (non-NHS)	59.1	107.1	94.2
NHS costs (£):			
Mean	166.5	272.1	272.4
Median	89.5	231.4	220.7
IQR	89.5-148.2	172.7-313.5	172.6-319.5
Mean, discounted	150.2	240.3	241.1
Skew coefficient	2.80	3.64	2.88
Social costs (£):			
Mean	225.6	379.1	366.6
Median	130.6	343.5	305.9
IQR	130.6-209.4	264.7-428.0	247.7-424.7
Mean, discounted	204.4	339.9	327.5
Skew coefficient	2.62	3.37	2.77
Outcomes (QALYs):			
Mean	2.225	2.243	2.277
Median	2.348	2.348	2.383
IQR	2.120-2.500	2.120-2.500	2.165-2.500
Mean, discounted	2.129	2.149	2.181
Skew coefficient	-2.83	-2.22	-2.92
Mean discounted costs (£) per CIN case detected:			
NHS perspective	1241	1073	1256
Social perspective	1689	1517	1706

QALY=quality adjusted life year.

exception of the mean number of smear tests received by the women in the two colposcopy arms (one way analysis of variance, with Bonferroni correction, at 5%). While each woman in the two colposcopy arms underwent at least one colposcopy, most of those randomised to surveillance (1824, 82.2%) were not subjected to colposcopic investigation.

We had data on after effects from the intervention, such as pain, bleeding, or discharge, from 1646 women (53.9% from the surveillance arm). In the surveillance arm 1238 women (55.8%) reported no after effects with colposcopy compared with 667 (33.6%) in the colposcopy arms ( $z=8.90$ ,  $P<0.01$ ); and 87 (3.9%) and 412 (20.8%) women, respectively, reported taking medication for after effects ( $z=10.51$ ,  $P<0.01$ ). Within the whole trial sample, 82 women (2.0%) made a total of 96 visits to hospital as a result of their management. These visits were a combination of 32 outpatient appointments, 27 day case appointments, 17 inpatient admissions, and 20 emergency visits, which resulted in six further admissions.

Table 2 presents average costs for the major categories of undiscounted costs, plus descriptive statistics of total costs and outcomes, both undiscounted and discounted at 3.5% a year. Of the three management options, colposcopy with immediate treatment had the

lowest cost for detection per case of cervical intraepithelial neoplasia. This result arose because the higher costs per woman in comparison with surveillance and, to a much lesser extent, with biopsy and recall, were more than offset by the increased yield of cervical intraepithelial neoplasia (table 1). The considerable skews of the distributions of cost and outcome indicate the need for uncertainty analysis.

Table 3 presents the uncertainty analysis results for the three pairwise comparisons. For each comparison, the table shows the estimated mean incremental cost effectiveness ratio, plus the likelihood of the nominated management option generating higher costs, higher benefits, or acceptable cost effectiveness in relation to its nominated comparator. An “acceptable incremental cost effectiveness ratio” is a cost per QALY gained of up to and including £30 000 (€65 319, \$49 706), the maximum threshold amount suggested by NICE.<sup>31</sup>

## DISCUSSION

In this study of management of low grade cervical abnormalities our results indicate that different approaches to follow-up had different cost and outcome implications. Of the three approaches, cytological surveillance was the cheapest, colposcopy with biopsy and recall was associated with the most average QALYs per person, and immediate treatment offered the lowest costs per case of cervical intraepithelial neoplasia detected. The size of the confidence intervals for the cost and outcome distributions, however, indicate that none of the three approaches could be shown to be significantly more cost effective than the other two. Thus, our economic evaluation of managing women with low grade abnormalities detected at screening has provided no scientific basis for choosing immediate referral to colposcopy in preference to continued cytological surveillance, or vice versa.

### Comparison with other studies

A recent review observed that immediate treatment after an abnormal smear result has become “accepted internationally.” The authors claimed that immediate treatment “decreased patient anxiety” and offered “low costs.”<sup>32</sup> Moreover, it has been taken to represent a “safer option” than surveillance in the current medico-legal climate.<sup>33</sup> Our results suggest that the higher costs of immediate treatment were more than outweighed by its higher yield of neoplasia, making it a lower cost method of detection of cervical intraepithelial neoplasia than cytological surveillance. This finding echoes earlier predictions both from models<sup>34,35</sup> and from a previous empirical study,<sup>36</sup> although some researchers have found exactly the opposite.<sup>37</sup>

Nevertheless, the cost argument might be less clear cut than has previously been thought. Different studies can have different protocols in terms of, for example, the number of smear tests before referral to colposcopy and the nature and extent of follow-up after colposcopy. Different protocols imply different resource

**Table 3** | Cost effectiveness by accounting convention

	NICE convention	Social costs, undiscounted benefits
<b>Immediate treatment v surveillance:</b>		
Nominal ICER (£ per QALY)	4546	7378
Uncertainty analysis:		
Higher costs (%)	81.0	83.7
Higher benefits (%)	51.9	52.1
Acceptable ICER (%)	51.1	50.5
95% CIs for ICER (£)	-11 375 to 11 109	-22 977 to 23 262
<b>Biopsy and recall v immediate treatment:</b>		
Nominal ICER (£ per QALY)	26	-370
Uncertainty analysis:		
Higher costs (%)	47.9	44.1
Higher benefits (%)	53.9	56.2
Acceptable ICER (%)	53.4	55.4
95% CIs for ICER (£)	-9390 to 9858	-18 698 to 21 344
<b>Biopsy and recall v surveillance:</b>		
Nominal ICER (£ per QALY)	1764	2373
Uncertainty analysis:		
Higher costs (%)	80.5	80.9
Higher benefits (%)	55.1	59.1
Acceptable ICER (%)	54.3	57.4
95% CIs for ICER (£)	-12 989 to 11 196	-24 651 to 25 770

ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year.

use and, therefore, different costs and different yields. The unit costs of the principal procedures depend on accounting conventions and are likely to vary between settings and between countries.<sup>38</sup> For example, were the costs of smear tests to be lower relative to those of excision, then the mean cost per case of cervical intraepithelial neoplasia with surveillance would be lower relative to that with referral to colposcopy. In our study, an £80 increase in the unit cost for colposcopy with treatment would be sufficient to make the cost per case of cervical intraepithelial neoplasia with surveillance cheaper than that with immediate treatment. Interestingly enough, a recent UK study found a higher cost differential.<sup>39</sup>

Measuring outcomes as QALYs allowed us to account for any consequences of management for health state utility in terms of, for example, anxiety, pain, or restrictions in activities over a period of 2.5 years. Our results thus contrast with those of earlier studies, which concerned themselves with health impacts judged only within a short time frame of weeks or months at most.<sup>40</sup>

#### Limitations

Our results pertain to an economic evaluation within a trial and concern the economics of options for management of follow-up rather than of cancer prevention. Judgments about long term cost effectiveness would require modelling to be undertaken, although such models would require information as yet unavailable. By way of example, the exit colposcopies showed that significantly more cases of cervical intraepithelial neoplasia were reported in the colposcopy arms than in the

surveillance arm. On the one hand, it is possible to conclude that a higher level of detection of invasive disease must eventually result from using surveillance rather than colposcopic management. On the other, it is conceivable that many such cases would regress.<sup>41 42</sup> Women who did not might well be identified at future routine screening attendances, entailing neither adverse health consequences from non-detection at present nor any additional costs. In fact, the higher level of cervical intraepithelial neoplasia detected in the colposcopy arms attests to the probability of over-detection and overtreatment, although the extent of this remains unclear. It has been shown that excision might adversely affect future fertility and pregnancy outcomes,<sup>43 44</sup> implying the existence of further costs of colposcopic management, as yet unaccounted for.

#### Policy implications

As the trial progressed, the UK screening programmes began to replace conventional cytology with liquid based cytology. A modelling exercise<sup>45</sup> had suggested that liquid based cytology would prove more cost effective than conventional cytology, and implementation was guided by feasibility studies conducted at various sites throughout the UK, including Scottish TOM-BOLA centres. A proportion of women in our trial, therefore, would have been screened with liquid based cytology, although their resource use was evaluated as if they had undergone conventional cytology. From the evaluation point of view, it follows that our surveillance arm does not represent current practice in the UK.

How the incremental cost effectiveness ratios of colposcopy relative to liquid based cytology surveillance, as opposed to that with conventional cytology, will differ from those estimated in the present analysis depends on one's interpretation of the current evidence. The unit costs of smear tests are expected to be higher as a result of liquid based cytology.<sup>12</sup> Trials in France<sup>46 47</sup> and South Africa<sup>48</sup> have concluded that, despite the additional cost, liquid based cytology could offer test parameters (sensitivity and specificity) inferior to those of conventional cytology. An Italian trial has reported a fall in the positive predictive value of screening as a result of using liquid based cytology.<sup>49</sup> Meta-analysis of earlier research results has failed to confirm the belief that liquid based cytology was associated with a reduction in the rate of unsatisfactory smear tests,<sup>50</sup> although recent case studies<sup>51 52</sup> and trials<sup>49</sup> have reported such a reduction. It therefore remains unclear whether, on balance, liquid based cytology does actually out perform conventional cytology.<sup>53</sup> With respect to our trial, if the unit cost and the false positive rate of liquid based cytology did prove to be higher than that of conventional cytology, the mean cost of management by surveillance would increase, although the effect might possibly be ameliorated by a reduced need to repeat unsatisfactory smear tests. Clearly, in the event of the surveillance method becoming less efficient, the relative economic advantage of the colposcopy options would increase correspondingly.

## WHAT IS ALREADY KNOWN ON THIS TOPIC

There has been uncertainty about how best to follow up women with mild or borderline changes in cervical smears

More intensive follow-up by colposcopy might be better for detecting progression to higher grade lesions but might cause more anxiety and side effects and impact on quality of life

## WHAT THIS STUDY ADDS

Taking into account costs, outcomes, and quality of life, follow-up by immediate colposcopy is no more and no less cost effective than follow-up by cytological surveillance

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**Ethical approval:** This study was approved by the joint research ethics committee of NHS Grampian and the University of Aberdeen, the Tayside committee on medical research ethics, and the Nottingham research ethics committee. All participants provided informed consent.

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