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Modelling the Impact of Referral Guideline Changes for Mild Dyskaryosis on Colposcopy Services in England

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Abstract

Objectives. This model examines the effects of changing referral strategies within the established structure of NHS cervical screening driven colposcopy practice. It considers the effects of the new strategy on colposcopy workload, patient waiting times, and associated costs and health benefits.

Methods. By postal survey, the current operational strategies of colposcopy services were established by questionnaire with respect to referral practices and management protocols. After first-cut piloting, and utilising published and original research, a Markovian model was constructed, and the impact of the new strategy was determined on colposcopy workload and patient waiting times for three hypothetical clinic types. Expected costs and benefits of the new policy were assessed through the adaptation of a previous ScHARR cervical screening model.

Results. Clinic workload is expected to increase by between 21% and 35% within three years of the policy change, depending on clinic efficiency in other areas; the majority of this impact would be seen within the first year. It is predicted that particularly inefficient clinics would struggle to meet the existing waiting time requirements for women referred with low-grade disease, owing to the increased level of workload seen throughout the patient pathway as a result of the implementation of the new policy.

The impact of the new policy can, however, be mitigated through improving the efficiency of existing clinics, by altering policies relating to surveillance of low-grade disease, post-treatment follow-up, treatment policy (whether or not treatment

is performed at the initial colposcopy visit), and through adherence to national guidelines.

A cost-effectiveness analysis using the ScHARR liquid-based cytology model suggests that the policy change is likely to be have a cost per quality-adjusted life-year gained of between £1,400 and £5,500 per quality-adjusted life-year gained (exclusing the costs of follow-up), which would be deemed acceptable to organisations such as the National Institute for Health and Clinical Excellence.

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Abbreviations

Abbreviation	Explanation
ASCUS	Atypical Squamous Cells of Undetermined Significance
BNA	Borderline Nuclear Abnormality
BSCC	British Society for Clinical Cytology
BSCCP	British Society for Colposcopy and Cervical Patholoy
CIN	Cervical Intraepithelial Neoplasia
DNA	Did Not Attend
HPV	Human PapillomaVirus
HSIL	High Grade Squamous Intraepithelial Lesion
KC	Korner Community
LBC	Liquid Based Cytology
LLETZ	Large-loop excision of the transformation zone
LSIL	Low Grade Squamous Intraepithelial Lesion
LYG	Life Years Gained
NHS CSP	National Health Service Cervical Screening Programme
ONS	Office of National Statistics
QALY	Quality-Adjusted Life Year
ScHARR	School of Health and Related Research

1.0 Disclaimer

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2.0 Introduction

2.1 Background to disease

Cervical squamous carcinoma is now the eleventh most common cancer in women in the UK, and the eleventh largest cause of cancer deaths, with 1123 deaths attributable to the disease in 2002. [(1)] Caused by a sexually 'transmissable' virus, Human PapillomaVirus (HPV), the disease is characterised by a premalignant intraepithelial phase, Cervical Intraepithelial Neoplasia (CIN). [(2)] CIN is subdivided into histologically defined grades with different risks of progression to cervical cancer. High-grade disease (CIN 2 & 3) has a relatively high risk of progression, whereas low-grade disease (CIN 1) is recognised to have a much lower risk. The presence of pre-invasive disease is suggetsed by abnormal exfoliative cytology.

2.2 Current structure of services

Cervical cytology screening has been performed at a local level in the UK since the 1960s. In 1988, the Department of Health required each Health Authority in England to introduce a cervical screening programme "for all women aged 20 to 64 to have a smear at least every 5 years". [(3)] Through the NHS Cervical Screening Programme (NHS CSP) it also published guidelines to facilitate the implementation of this, most importantly the introduction of the repeat smear/referral patterns of patients in the target population, known as 'call and recall'. [(4)] Consequently, the incidence of cervical cancer in the UK has fallen more than that of any other cancer: 26% between 1992 and 1997.[(5)]

There has been much discussion of the relative benefits of changing the screening interval for women of different ages. Most notably, Sasieni et al [(6)] questioned the suitability of a uniform screening interval for all women aged 20 to 64 years, and instead demonstrated that a 3-year screening interval for younger women offers significantly improved disease outcomes, whilst outcomes from 5-yearly screening for women aged 55-69 is not significantly improved by more frequent screening.

The operational strategy of the cervical screening programme requires individual heatlh authorities or primary care trusts to be responsible for the 'call and recall' for cytology results. These are developed in liaison with commissioning primary care trusts, cytology laboratories and colposcopy services, under published guidance from the NHS CSP directorate.

The decrease in incidence of, and mortality from, cervical squamous carcinoma since the introduction of the NHS Cervical Screening Programme is attributed to good coverage of the at risk population followed by prompt and appropriate treatment of CIN. [9] Between 1995 and 1999 the number of newly diagnosed cases of carcinoma fell from 11.0 [10] to 9.6 [1] per 100,000 women. It is estimated that cervical screening saves approximately 1,300 lives per annum [11] It is now recommended that a cervical smear test be offered to all women between the ages of 25 and 64, and repeat cytology is performed every 3 years to the age of 50, and every 5 years thereafter. Women over the age of 65 who have had 3 consecutive normal smears are generally withdrawn from the recall system. [4] Women under 25 are now not invited for screening, as cervical cancer in this age group is rare and false positive results are high due to changes in the developing cervix. The proportion of eligible women screened within 5 years of their last test has increased from 22 percent in 1987-88 to just over 80 percent in 2003-04. [5,8] In 2003-4, a total of 3.5 million women were screened under the programme. [7] The annual cost of cervical screening in England, including treating cervical abnormalities, is estimated to be around £150 million, or £37.50 per woman screened. [12]

Recent research carried out by Peto et al [13] suggests that the introduction of the screening programme has prevented a cervical cancer epidemic, which might have led to one in sixty-five British women born since 1950 dying from the disease. The authors estimate that up to 80% of these deaths would be prevented by screening, but the estimates presented are subject to considerable uncertainty in relation to the effects of oral contraceptives and changes in sexual behaviour.

2.3 Pap screening

Cervical screening involves the patient having regular cervical cytology smears to check for pre-cancerous cells. For the majority of patients, this is currently carried out using a Papanicolaou smear, a generally quick and painless procedure which involves taking a small scraping of cells from an area of the cervix known as the Transformation Zone (TZ). This area is the point where the external (squamous) skin cells meet the internal (columnar) cells, and is where the majority of squamous cervical cancers originate. The sampled cells are "smeared" in a layer onto a glass slide and transferred to a laboratory for examination by a cytologist.

Analysis of each slide takes approximately six to eight minutes, with the cytologist examining for abnormalities known as nuclear dyskaryosis. [7] The results are classified according to the grade of changes seen: mild, moderate and severe, whichrelate to the risk of finding cervical disease on further assessment. Smears may also be classified: as showing borderline nuclear changes only, representing a lower risk of disease being present; as a smear where the cytologist is suspicious of invasive cancer being present; or where there is evidence of glandular neoplasia, which is intended to represent a different disease process. This method of screening also returns a significant proportion of "inadequate" results (9.1%), [8] in which insufficient cells are collected in order for a diagnosis to be made, or, more commonly, in which it is impossible to read the slide because of contamination with blood or infection.

The number of unstatisfactory smears will be reduced in the near future following the replacement of Pap screening with liquid-based cytology (LBC), a test in which the cells collected from the cervix are rinsed in a preservative fluid to form a suspension from which a layer of cells can be prepared and analysed on a slide. This method improves the quality of the slide preparation, allowing faster and possibly more reliable screening by laboratory staff, and is associated with a lower inadequate rate - 1.6% in the NHS LBC pilot studies. [7] A further advantage of this test is that the suspension can be retained and

used for further investigations such as testing for HPV-DNA and infections such as Chlamydia Trachomatis.

2.4 Colposcopy and referral criteria

Women whose smear shows abnormalities necessitating further investigation are referred by their primary care team to a colposcopy service, of which there are 178 in England. A colposcopy involves a detailed visual assessment of the cervix, with the application of indicator solutions. This process may also incorporate a biopsy of any abnormal area, to facilitate accurate diagnosis. For any significantly abnormal area, treatment may offered, either at the initial diagnostic visit (so-called 'see & treat'), or at a deferred appointment. Although national guidelines exist on the referral of women with abnormal smears, local policy tends to dictate the manner and speed with which this happens. Table (1) summarises the national referral recommendations for each smear state.

Table (1): Recall/referral strategies based on smear result [4]

Smear result	**Recommendations for care**
Inadequate	• Repeat smear in 3 months • If 3 consecutive smears inadequate, Refer for colposcopy
Negative	• Patient recalled routinely
Borderline nuclear Changes	• Repeat smear in 6 months • If 3 smears show borderline changes, refer for colposcopy • If 3 consecutive smears negative, Patient recalled routinely
Mild dyskaryosis	• Minimum standard – 2 consecutive mild smears triggers referral to colposcopy • Best practice – refer after 1 mild smear

Moderate dyskaryosis	• Immediate referral for colposcopy
Severe dyskaryosis	• Immediate referral for colposcopy
Suspected Invasive cancer	• Target referral colposcopy/gynaecology Oncology
Suspected Glandular neoplasia	• Immediate referral for colposcopy

Previous advice to practitioners and cytologists had stated that referral of patients should be made following the return of two mild dyskaryosis smears. [(14)] It has been recognised from clinical trials that a relatively high proportion of women returning a single mild dyskaryosis smear have significant cervical disease. The current published guidelines acknowledge this evidence, recommending that 'best practice' would include the referral to colposcopy of all women with single smears returned in this group. Significant concern has been expressed as to the ability of colposcopy services to accommodate this increased workload. The guideline reflects this concern in recommending that referral after two mild smears is acceptable as a 'minimum standard'.

Other changes new to the current guidelines are the recommendation that patients with normal smears, but clinical concerns regarding disease of the cervix, such as post-coital bleeding, are not referred for colposcopy assessment from primary care, but rather to general gynaecology or genito-urniary medicine.

The new guidelines also include recommendations concerning the age at which women are invited to attend screening, and the frequency of repeat cytology.[(4)] Together these are known as "call-recall". Previous advice recommended that the first smear, or "call" smear, should be performed between the ages of 20 to 24 years old. This has been altered to the invitation for screening being made at the woman's 25th birthday. "Recall" smears are then recommended at 3 year intervals till the age of 49, and then the interval should extend to 5 years. Screening finishes at 65 years old in the presence of 3 previous negative adequate smears. Previous advice was screening to 65 years, but no intervals were recommended.[(8)]

2.5 Waiting times

The impact on the patients themselves is an important consideration in making policy changes, particularly with regard to the time each patient must wait for their initial (and subsequent) appointment(s). Current guidelines recommend that women requiring referral to the colposcopy service should wait no longer than two weeks for an appointment if the smear is reported as representing suspected cancer or glandular neoplasia, four weeks for an appointment if their smear shows high-grade disease (moderate or severe dyskaryosis), and not longer than eight weeks if the referral smear shows low-grade disease (mild dyskaryosis or borderline changes). [(4)]

3.0 Aims & Objectives

The project constructs a computer model of current colposcopy practice in the NHS, and considers the impact of recommended changes in referral practice with respect to single mild dyskaryosis, current and possible changes in recommended colposcopy practice, and new "call-recall" strategies. In particular, the model is intended to:

1. Quantify the current number of clinic sessions required in a 'typical' colposcopy service;
2. Model the flow of patients through such a 'typical' clinic service;
3. Assess the implications of policy changes on colposcopy workload and waiting times in this service, and in the two clinics likely to experience the highest and lowest impact of new policy;
4. Aid national policy analysis and decision-making.

The first model is referred to within this report as the "pathway model". A second model, derived through an adaptation of the ScHARR liquid-based cytology model, is used to

assess the impact of the new mild smear policy on the expected costs and health benefits associated with the screening programme

4.0 Literature Review

Literature on cervical pre-invasive disease is extensive and many sources were utilised in the construction of the model. Cytological and histological nomenclature systems have changed dramatically since Papanicalaou's original description of vaginal lavage, and Richart's work into the natural history of cervical 'carcinoma-in-situ'. [15,16] There are variations in cytology classification systems between countries, with the UK retaining its own British Society for Clinical Cytology (BSCC) classification, and the rest of the world using the Bethesda classification of cytology. [17,18] Colposcopy practice also differs significantly between countries. Contained within this review is data predominantly from UK studies, where results are directly applicable to the modelling work. Data from other countries is included where it is thought to be significant and directly translatable, and when data from the UK is not available on a particular outcome. Data sources are reviewed in chronological order, in the sections to which they contributed information for the model construction. Some data sources provided information for several areas of modelling.
Studies are classfiied (A), where the work was directly used in the Markov state transition models, or (B) where the data was used to support modelling, but not directly used.

4.1 Previous modelling work

A number of relevant modelling studies were indentified to inform the modelling process and to identify methodologies which may be appropriate.

Johnson et al [19] carried out decision analysis regarding the change in policy from referral to colposcopy after a single mild dyskaryosis smear to the referral after two mild smears.

This work uses a decision tree analysis to establish the likelihood of a patient with mild dyskaryosis developing cervical cancer under the two colposcopy service access policies. Published work is used to establish the probabilities that disease subsequently occurs in each group. It highlights there is a risk that women in both groups will develop cervical cancer despite appropriate surveillance. A distinction is made between three year versus five year recall policies. Results are presented in terms of cervical cancer incidence. With a 5-year recall policy the predicted cancer incidence is 2.0 per 1000 for the repeat cytology group compared with 1.6 per 1000 under an immediate colposcopy policy. Under the 3-year recall policy, the decision analysis predicts an identical rate of cancer incidence under both management strategies. With a repeat cytology policy, economic calculations suggest that to save a single referral to colposcopy a total of six smears would be taken from four women.

A key paper on modelling of cervical screening is that of Sherlaw-Johnson et al [(20)], in which a stochastic model is used to describe the development and progression of pre-invasive disease in a cohort of screened women under two referral policies for single borderline/mild dyskaryosis: immediate colposcopy and repeat cytology (see also Section 4.3). The greatest reduction in incidence of cancer presented is effected by increasing coverage of the target population. Open colposcopy referral for all grades of cytological abnormality, or reducing screening intervals are expected to have a much smaller effect on disease incidence.

A US study by Myers et al [(21)] used a 19-state Markov model to follow a simulated cohort of women from 15 to 85 years old moving from normal to HPV infection states over a 1 year Markov cycle. The study presents prevalence rates of HPV infection by age, and progression/regression rates for HPV infection to varying degress of Squamous Intraepithelial Lesions (SIL), equivalent to CIN.

A second US study by Birch et al [(22)] concerned a unique prospective utility measurement of the management policies of mild dyskaryosis in a family planning clinic environment. One hundred and seventy patients underwent one of six scenarios of care, three

dedicated to repeat cytology (so-called observation) and three to early colposcopy, and completed questionnaires to establish utility scores using standard gamble techniques. In these groups a comparison is also made between cryotherapy and cone biopsy as treatment for CIN. Patients found to be normal following completion of care showed a statistical difference in utilities in preference of observational versus early referral. Where pathology requiring cryotherapy was discovered, patients preferred immediate diagnosis over surveillance. There was no statistical difference in the cone biopsy group.
The study presents data previously published by the same lead author in the Journal of Family Practice, which draws attention for the need to individualise access policies in line with patient needs. [23]

Canfell et al [24] reported a modelling exercise of the effects of changing recall intervals in UK cervical screening programme: 3 years in women aged 25-49 and 5 years in those aged 50-64, with women under 25 years no longer being invited for screening. Based on a mathematical model of cervical HPV infection, cervical intraepithelial neoplasia and invasive cervical cancer, and published UK age-specific screening coverage rates, screening intervals and treatment efficacy. The predicted cumulative lifetime incidence of invasive cervical cancer in the UK stated as 1.70% in the absence of screening, and 0.77% under the previous "recall" policies. A reduction in lifetime incidence to 0.63% is predicted following implementation of the new recommendations. Screening women aged 20-25 years would have minimal impact, with the cumulative lifetime incidence decreasing from 0.63 to 0.61%.

Flannelly et al [25] conducted a cost-effectiveness analysis to compare a policy of immediate colposcopy versus cytological surveillance, using data from the Aberdeen Birthright randomised trial, in which 145 women were allocated to the immediate colposcopy group and 158 women were allocated to the two-year surveillance group. In the immediate colposcopy group, 66 women (46%) were found to have CIN 3, whilst in the surveillance group, 82 women were referred for a colposcopy, of which 43 had CIN 3 (or 27% of the 158 women in this group). The analysis reported a cost per extra case of CIN 3 detected and treated under a change from a surveillance policy to an immediate

diagnosis of £148.22. This study did not take into account the eventual cost of treating the women who defaulted during the study and the associated utility loss for these women upon their progression to invasive cancer.

4.2 Cytology state transition

The need for two Markov chains is explained in Section 5: one for smear transitions, as this determines how and when women get referred to colposcopy, and one for transitions in the true underlying histological state.

Giles et al [26] present the results of a UK-based prospective study of colposcopy in 200 women referred with mild dyskaryosis. Repeat cytology and colposcopy performed at a mean time interval of 8.2 months. In the 143 with a single previous mild dyskaryosis smear, the repeat cytology is shown in Table (2) below.

Table (2): repeat cytology in women referred with a single mild dyskaryosis smear (mean time 8.2 months from index smear)

Smear result	*Number*	*Percentage*
Negative	51	39.8
Mild dyskaryosis	23	18.0
Moderate dyskaryosis	28	21.9
Severe dyskaryosis	10	7.8
Indequate	16	12.5

Borderline results were not reported in this study, making this data difficult to interpret for the model transitions.

The results of a UK-based retrospective and prospective study of the outcome for 225 and 762 women respectively, with first mild dysaryosis on cytology was reported by Fletcher et al [27]. Three smear states recorded: borderline with inflammatory changes; borderline

without evidence of inflammation; mild; and moderate dyskaryosis. Repeat cytology for borderline changes was requested at six months, and three months for mild dyskaryosis, Table (3) shows the results of repeat cytology for 356 women with mild dyskaryosis: -

Table (3): outcome in patients with initial mild dyskaryosis by classification of dyskaryosis in first repeat smear

Repeat cytology	*Number*	*Percentage*
Negative	156	43.8
Borderline or inflammatory	42	11.8
Persistent mild	129	36.2
Moderate	23	6.4
Severe	6	1.7

The 3-month screening interval for mild dyskaryosis for these women makes this data difficult to incorporate within the cytology transition matrix, as does the inclusion of the 'inflammatory' group in the borderline category.

Anderson et al [(28)] performed a cross-sectional analysis of a UK-based randomised prospective study (the Aberdeen Birthright), which examined the cytological behaviour of women with mild and moderate dyskaryosis. Repeat cytology and colposcopy was performed on these patients, (Table (4) shows the cytology results); however, the mean time from referral to colposcopy and repeat cytology is not stated, and this study is therefore of limited use.

Table(4): results of repeat cytology following mild/moderate dyskaryosis

Smear result	*Number (%)*
Less severe	88 (40)
Mild dyskaryosis	67 (31)
More severe	62 (29)

Inadequate	11 (N/A)

The paper does not present a breakdown of these results by the index smears, although it is noted that these results are similar between the two groups of women.

Cooper et al [29] report a UK-based retrospective review of one year's atypical cytology, with comparison made of the results of repeat cytology for 127 women with those of the index smear. The results of the last two smears are shown in Table (5).

Table (5): smear results transitions over 6 months

Last-but-one smear	*Last smear (percentage)*				
	Inadequate	Negative	Borderline/ Mild	Moderate/ Severe	Total
Negative	1 (1.7%)	55 (91.7%)	4 (6.7%)	0 (0%)	60
Borderline/Mild	5 (8.9%)	27 (48.2%)	22 (36.7%)	2 (3.6%)	56

The median time interval from last-but-one to last smear is six months. No breakdown of smear results in the low and high-grade groups is given, and results are of limited use for the modelling exercise.

Hirschowitz et al [30] report the results of a UK-based case-control retrospective study of 437 women who underwent routine cervical screening and were found to have their first borderline cytological change. The cytology records of these women were examined with a mean follow-up period of 73 months, with 22.4% progressing to high grade disease on cytology.

Flannelly et al [31] describe the results of the Harris Birthright Research Centre study, a prospective randomised trial with 902 patients recruited to four management strategies following mild or moderate dyskaryosis. 793 women completed the study. The first group were given immediate colposcopy, the second had cytology followed by colposcopy at six months, the third had cytology at six and 12 months with colposcopy at 12 months,

while the fourth group had cytology at 6, 12 and 24 months with colposcopy at the final visit. Results are given below for the immediate diagnosis group and the six month surveillance groups in Table (6).

Table (6): cytological appearance of final smear in women who completed study period and whose final cytology was adequate

Final smear	*Immediate diagnosis (%)*	*Six months' surveillance (%)*
No dyskaryosis	67 (31.3)	58 (29.1)
Mild/moderate dyskaryosis	109 (50.9)	84 (42.2)
Severe dyskaryosis	38 (17.8)	57 (28.6)

No inadequate cytology rates are given, and no distinction is made between mild and moderate groups, although histological outcome is noted to be different between the two groups.

The ALTS trial is a US-based prospective trial of management of Atypical Squamous Cells of Undetermined Significance (ASCUS) and cytology suggesting Low-grade Squamous Intraepithelial Lesion (LSIL), , provides data for low-grade cytology transition. Results appropriate for this study are reported by Solomon et al [(32)]. 3,488 patients were randomised to receive immediate colposcopy, repeat cytology and HPV testing or cytology alone following a single ASCUS or LSIL smear. Enrollment cytology was performed at an average of 2 months, while 3,470 cytology results of the enrolment cytology were available and are shown in Table (7).

Table(7): repeat cytology results following LSIL/ASCUS

Repeat cytology	*Number (%)*
Negative	1460 (41.9)
ASCUS	1134 (32.5)
LSIL	630 (18.1)
HSIL	246 (7.0)

*HSIL = Cytology suggesting High-grade Squamous Intraepithelial Lesion

The study group includes 45% of women whose index cytology was reviewed and found to be of a higher or lower grade. Definitions of ASCUS do not correlate exactly with borderline nuclear abnormalities, and as such the results are not directly transposable to this project.

A study by Rawal et al [33] report the results of a UK-based prospective cytological and histological study conducted in 627 women with first abnormal smear showing borderline nuclear abnormality. Data from 534 women were available for study and results from repeat cytology in 491 at six months are represented in *Table (8)*.

Table (8): persistence of borderline smears

Smear result	*Number*
Normal	268 (50.2)
Borderline	121 (22.7)
Mild dyskaryosis	41 (7.6)
Moderate dyskaryosis	13 (2.4)
Severe dyskaryosis	5 (0.9)
Inadequate	43 (8.0)

Key data on the persistence of mildly dyskaryotic smears was extracted from work by Woodward et al [34] on a five-year retrospective study of 269 women returning a mildly dyskaryotic smear with no previous cytological abnormality. Included in the data is a breakdown of the next smear result, which was performed at 6 months following the initial smear. This data is summarised in *Table (9).*

Table (9): persistence of mild smears

Smear result	*Number of women (%)*
Negative	113 (42)
Borderline	36 (13.4)

Mild	85 (31.6)
Moderate	22 (8.2)
Severe	12 (4.5)
Inadequate	1 (0.4)

4.3 CIN state transition

Literature searches identified a number of studies which report the natural history of pre-invasive cervical disease (i.e. the progression of the true underlying tissue state, as opposed to the transitions between smear states). These data are important in following disease in patients undergoing surveillance by colposcopy.

Campion et al [35] carried out a UK-based study designed to gain an improved understanding of the natural history of CIN 1. This prospective study of 100 women under 30 years old, with a mildly dyskaryotic smear, followed patients for between 19 and 30 months, during which time each patient was reviewed at 4-monthly intervals with both cytology and colposcopy to check for disease progression or regression. Seven women showed no signs of cervical disease after a minimum of 19 month's follow-up, while 26 showed evidence of progression to CIN 3 over the same period. However, to avoid interfering with disease biology, no biopsies were taken until progression was detected, and so the diagnosis relied on the visual inspection at colposcopy of the lead author alone.

Oster et al [36] carried out a meta-analysis of published research from 1950 on, into the natural history of CIN broken down by disease category. It includes only data where a minimal disturbance of the lesion has occurred, excluding studies that have used postconisation outcomes. The summary table from this review is shown in Table (10).

Table(10): Results of meta-analysis of disease progression data

CIN Grade	*Regress*	*Persist*	*Progress to CIN 3*	*Progress to invasive cancer*

CIN 1	57%	32%	11%	1%
CIN 2	43%	35%	22%	5%
CIN 3	32%	<56%	-	>12%

There is no weighting of the studies for reliablility of evidence, and no time interval for changes is incuded in the summary of results.

Sherlaw-Johnson et al [20] describe the development and progression of pre-invasive disease in a cohort of screened women. This includes data regarding transitions between histological states: normal, CIN 1, CIN 2, CIN 3 and invasive cancer, which is shown in the Table (11).

Table (11): Histological disease progression [18]

	To				
From	*Negative*	*CIN 1*	*CIN 2*	*CIN 3*	*Inv Ca*
Negative	99.88	0.12	0	0	0
CIN 1	2	89.5	6	2.5	0
CIN 2	0	0	85	15	0
CIN 3	0	0	0	99	1
Invasive cancer	0	0	0	0	100

Two clinical strategies are compared, colposocpy referral after single mild dyskaryosis versus repeat cytology at six months with referral for persistent abnormality. The model assumes the screening of women over 18 years old, and predicts the incidence of cervical cancer. Modelling is performed with varying screening interval (one to 10 year “recall”); varying population coverage (50 to 90%); and varying specificity and sensitivity of cytology. At 70% coverage with 3 yearly cytology the incidence of cervical cancer is predicted to be 2.00 per 10,000 women over 18 years old with immediate single mild referral, compared to 2.10 with repeat cytology. This is significantly reduced by

increasing coverage to 90%, but there was little effect of changing screening interval or cytology sensitivity/specificity.

A Finnish study by Väyrynen et al [37] is the first in an impressive series of articles on a group of patients identified with cervical HPV lesions and reviewed by cytology and colposcopy +/- biopsy on a six-month basis. At this stage 286 women had been recruited and followed at a mean time of 16.0 months. The basis of the paper is the identification of OKT-6^+ cells, but data is presented on the overall rate of progression to CIN (19.0%), persistence of the HPV lesion (52.1%) or regression to normal (28.8%) over the stated time interval.

A Canadian meta-analysis by Melnikow et al [37] used data from 15 studies post-1970, relating cervical cytology to outcome following a minimum of six months cytology or colposcopy/pathology follow up without treatment. For this analysis, non-Bethesda classification systems were adapted. Studies are scored on data quality. Random effect models were used to estimate the pooled rates of disease regression to normal, and progression to high-grade SIL and cancer. Regression was defined as return to normal cytology or biopsy results. Progression was defined as cytology or biopsy showing a higher-grade lesion than that at referral. No relation was found between regression rates and follow-up intervals. Six-month progression rates are included in the results, which are summarised in Table (12).

Table(12): Results of regression/progression rates for cervical cytology/biopsy in meta-analysis

Tissue state	*Regression (no time interval)*	*Progression to higher-grade (at 6 months)*	*Progression to invasive CA (at 6 months)*
ASCUS	68.19%	1.97%	0.06%
LSIL	47.39%	6.56%	0.04%
HSIL	35.03%	-	0.15%

4.4 Colposcopy outcome by referral indication

Data for this part of the model were provided by the Office of National Statistics, derived from the national annual cytology service Korner Community returns (KC61) 2003-4.[39] Original research was not included in the model as this KC61 constitutes a 'real world' assessment of the outcome of referral by indication. Research that was considered prior to the availability of national data for this year, has been previously extensively analysed and presented in systematic reviews and meta-analyses. These summary studies are presented below.

Fahey et al [40] conducted a meta-analysis using a MEDLINE keyword search to identify over 500 citations published in English, combining data from 59 to estimate the accuracyof the Pap test. The study used a positive/negative dichotomy derived from ordinal study results, for both cytologic and histologic thresholds for construction of a Standard Receiver Operating Curves (SROC) curve. At the high specificity (90-95%) desirable for cervical screening, sensitivity is appreciated to be low (20-35% range). The critical appraisal identified "significant deficiencies" in the studies used.

A meta-analysis by Nanda et al [41] utilised MEDLINE, EMBASE, HealthStar, CancerLit and CINAHL to identify 94 studies of conventional cytology which allowed construction of 2 x 2 tables where colposcopy/histology was performed within three months of the referral smear. Other classification systems are integrated into the Bethesda system and results for the sensitivity and specificity are shown in Table (13).

Table (13): Summary statistics from meta-analysis of conventional Papanicolaou testing

Smear/Histology Correlation	*Number of studies included*	*Sensitivity (mean)*	*Specificity (mean)*
ASCUS/CIN 1	37	0.74	0.68
LSIL/CIN 1	71	0.69	0.81
LSIL/CIN 2-3	54	0.83	0.66
HSIL/CIN 2-3	43	0.58	0.92

Walker et al [42], a study of women with mild atypia on a cervical smear. Women with such an abnormality were classified into one of five categories: normal, atypical, abnormal, highly suspicious and conclusive, and had a subsequent colposcopy directed biopsy to determine the grade of underlying disease existed. Table (14) shows the outcome at colposcopy of these women, divided by the grade of the referral smear.

Table (14): Correlation of smear result with subsequent histology

	Referral smear				
Histology	*Normal*	*Atypical*	*Abnormal*	*Highly suspicious*	*Conclusive*
No CIN	17 (22.8%)	14 (16.7%)	1 (1.8)	-	-
CIN 1	22 (37.3%)	16 (19.3%)	13 (22.8%)	-	-
CIN 2	15 (25.4%)	28 (33.7%)	17 (29.8%)	3 (25%)	-
CIN 3	5 (8.5%)	25 (30.1%)	26 (45.6%)	9 (75%)	3 (100%)
Total (%)	59 (27.6%)	83 (38.8%)	57 (26.6%)	12 (5.6%)	3 (1.4%)

HPV-NCIN infection was not considered as part of this study, and the interpretation of the data is hindered by the uncertainty in the correlation between the smear states used and the current classification system.

Robertson et al [43] studied the cytology, histology and clinical records of 1,781 women returning a mild dyskaryosis smear between 1965 and 1984, followed until mid-1987. The study reported a poor correlation between a single mildly dyskaryotic smear and the subsequent biopsy result, although this relationship became more reliable following persistence of cytological abnormality. Table (15) shows the main results of the study by smear and biopsy result.

Table (15): Results of serial smears and biopsies during first two years of follow-up

	Biopsy result (%)						
Smear result	***Normal***	***Condyloma (HPV infection)***	***CIN 1/2***	***CIN 3***	***Invasive carcinoma***	***Unknown***	***Total***
Mild dyskaryosis in 1 or 2 smears with biopsy	101 (32%)	2 (0.06%)	173 (55%)	38 (12%)	1 (0.3%)	0	315 (100%)
Persisting mild dyskaryosis with biopsy at 18-24 months	19 (13%)	2 (1.4%)	67 (46%)	39 (27%)	0	18 (12%)	145 (100%)
More severe dyskaryosis in second or later smear with biopsy	20 (8%)	0	115 (44%)	124 (47%)	3 (1.1%)	0	262 (100%)
Smear regressed to normal	-	-	-	-	-	-	625 (100%)

Unfortunately, the biopsy results do not distinguish between CIN 1 and CIN 2, nor is it clear exactly when repeat smears were taken, making it difficult to determine the exact timing of disease "progression".

A UK-based prospective study reported by Jones et al,[(44)] compared two strategies for management of mild dyskarosis: cytological surveillance and immediate referral. The study was performed retrospectively in units with the different management strategies. In one unit, 278 women had cytology surveillance for two to three years if subsequent cytology had been normal or borderline, with colposcopy if repeat cytology was abnomal (75 patients). Patients not previously seen for colposcopy were asked to attend for definitive diagnosis; 144 attended. In the other unit, 191 patients had colposcopy

immediately at the first mild smear, 137 had further colposcopy at a mean of 32 months. All patients with disease at colposcopy had biopsies to confirm histological grade. Results are shown in Table (16), numbers are for patients completing the study in each unit.

Table (16): Colposcopy outcome for two different mild dyskarysosis policies

	Cytological surveillance			Early colposcopy	
	At referral colposcopy (n=70)	On study colposocpy (n=144)	Total (n = 214)	On initial colposcopy (n=191)	On study follow-up (n=137)
No disease	9 (13%)	54 (38%)	63 (29%)	31 (17%)	87 (63%)
HPV/CIN	10 (13%)	64 (44%)	74 (35%)	83 (43%)	45 (33%)
CIN 2	19 (27%)	8 (6%)	27 (13%)	39 (20%)	5 (4%)
CIN 3	32 (46%)	18 (12%)	50 (23%)	38 (20%)	0 (0%)

Because results are given for surveillance in line with previous two mild dyskaryosis smear referral advice, and single mild dyskaryosis colposcopy referral, these results are integral to the model design.

4.5 Treatment outcome

Most UK studies of the last ten years examine outcome following LLETZ. These were reviewed and papers used as modelling data are presented below. One unit in the UK has published extensive data on the outcome following destructive treatment of the cervix. This is included in this review to demonstrate the similar success rates from treatment by these modalities. Overall, treatment success rate is generally assumed to be 90% for negative cytology follow-up, and 95% for absence of high-grade disease following treatment. This forms the basis of the minimum standards in colposcopy practice, and this source was used for direct data entry to the model.[4]

Luesley et al [45] carried out a retrospective review of cervical LLETZ. Six hundred and sixteen treated women had abnormal smears and treatment by loop diathermy excision, of whom 557 subsequently attended for review with cytology and colposcopy at six months. Six month outcome data are recorded in terms of potential failure (cytology abnormal) and confirmed failure (histology abnormal), and is summarised in Table (17).

Table (17): Cytological and histological findings following cervical LLETZ

Histological state	*Cytology findings*		*Histological failure (%)*
	Normal	*Abnormal*	
CIN 1	84	13	4 (4.1)
CIN 2	71	7	4 (5.1)
CIN 3	208	20	9 (4.3)
Invasive cancer	9	1	1 (10.0)

Gordon et al [46] reported the findings of a UK-based study of the oucome of destructive treatment in 1,661 women with two mild dyskaryosis smears or a single moderate/severe smear. Follow-up was performed with cytology, with colposcopy only used if smears were abnormal. Follow-up protocols are affected by pre-treatment CIN grade. The majority underwent diagnosis and treatment at a single visist ('see & treat'). Studu end points included persistent or recurrent histological abnormality (≥CIN 1) in follow-up. Ninety-eight percent completed follow-up at four months, falling to 87% at five years. Overall a single treatment resulted in restoring normal cytology in 1518 (93%) patients, with primary success rates falling from 96% at four months, to 91% at six years plus. There was a positive association between age and failure rates.

Murdoch et al [47] presents a study of 721 women who had abnormal or inadequate cytology, treated by LLETZ with the intention of complete excision. Women were reviewed at three months with cytology and colposcopy where primary incomplete excision at the endocervical margin was observed, at three months. The paper reported excision margin status, which is reproduced in Table (18).

Table (18): Excision margin status in women undergoing LLETZ with intent to treat

	Excision complete	*Excision incomplete*				*Not Stated*
		Endo	*Ecto*	*Both*	*Not stated*[*]	
Total	405	106	26	28	96	60
Percentage	56.2	14.7	3.6	3.8	13.3	8.3

[*]*Margins incomplete – incomplete margins where the histology does not record which are involved*

.

The finding of residual CIN at three months is then reported by grade of CIN at treatment, and is shown in Table (19) below, by grade of CIN treated.

Table (19):Grade of CIN and finding of residual disease at follow-up

Histology	*Excision Complete*	*Excision incomplete*				*Not stated*	*Total (CIN)*	*Residual Disease*
		Endo	*Ecto*	*Both*	*NS*			
CIN 1	63	2	1	0	10	11	87	1(1.1%)
CIN 2	69	8	1	2	21	11	112	6 (5.4%)
CIN 3	273	96	24	26	65	38	522	26 (4.7%)
Total	405	106	26	28	96	60	721	33 (4.6%)

Finally, the rates of residual disease by excision margin status are reported and are shown in the Table (20).

Table (20): Excision margin status and finding of residual disease at follow-up

Histology report	*Number*	*Residual(%)*
Complete	405	7 (1.7)
Incomplete endocervix	106	10 (9.4)
Incomplete ectocervix	26	2 (7.7)
Incomplete endocervix and ectocervix	28	10 (35.7)

Incomplete NS	96	4 (4.2)
Not stated	60	-

A UK-based retrospective case-control study described by Shafi et al [48] was designed to determine factors predicting cytological outcome. Fifty eight women with abnormal follow up cytology formed the study group, and were compared to a control group of 116 women treated immediately before or after the study patient. Stepwise logistic regression analysis was used to show excision margin status as an independent prognostic indicator of cytological outcome. The results for excision margin status are shown in Table (21).

Table (21): univariate analysis of prognosis in cytological outcome by excision margin status (at 3 months)

Excision margin status	*Cytological follow up*		*Odds ratio*
	Normal (n=116)	*Abnormal (n=58)*	
Complete	88	33	3.02
Incomplete	15	17	

The second of two publications from a cohort of 1000 women with abnormal cytology treated by LLETZ in Bristol, UK [49]. If excision was complete, patients were followed by cervical cytology for over two years: 94% attending for follow up at 10 or more months, and 86% at 22 or more months. If cytology was abnormal patients were seen for colposcopy. If excision was initially incomplete patients were additionally seen at 4 months for cytology and colposocpy. The recurrence/residual CIN rates were 5.0% in the first year (median 11 months) and 0.6% in the second year (median 22 months).

Flannelly et al [50] reported a retrospective review of cytology following treatment with LLETZ for 1,000 women, 977 of whom attended for at least one interval cytology review following treatment. Dyskaryosis was present in the smears of 80 (8.2%) women at some time in follow-up. Treatment failure is then defined as histological evidence of CIN within four years of follow-up. A number of time intervals are presented; the overall

outcome by excision margin status of the 466 women for whom results were available are summarised in Table (22).

Table (22): Characteristics of LLETZ treatment failures

Excision margin status	*Number*	*Number with no CIN on follow up (%)*	*Number with CIN on follow up (%)*
Complete	390	367 (94)	23 (6)
Incomplete	76	65 (86)	11 (14)

Dobbs et al [51] report the results of a retrospective study of 394 consecutive LLETZ treatments for CIN. Patients were followed up with cytology at six and 12 months, and then annually for a further four years. Patients with abnormal cytology were referred back to the service for colposcopy. Outcome data by grade of CIN and excision margin status are shown in Table (23).

Table (23): Success of LLETZ for women with CIN

Histology	*Number*	*Complete excision (%)*	*Incomplete excision*		
			Ectocervix	*Endocervix*	*Total (%)*
CIN 1	56	46 (82)	3	7	10 (18)
CIN 2	97	78 (80)	7	12	19 (20)
CIN 3	168	122 (73)	27	19	46 (27)
Total	321	246 (77)	37	38	75 (23)

Excision status is related to abnormal histology in follow-up (women with both ectocervical and endocervical margins involved were re-treated); two women had cervical carcinoma in follow-up.

A retrospective review of 3,426 women undergoing cervical LLETZ and a minmum of one further colposcopy assessment with cytology was reported by Flannelly et al [52]. 3,386 women had at least one adequate smear in follow-up; the total follow-up period comprised 9,765 women years, with a mean duration of 35 months. Four hundred and

seventeen (12.2%) women had dyskaryosis on the cytology follow-up: 256 (61%) at the first smear, 68 (16%) at the second and 43 (10%) at the third. Univariate analysis demonstrated that age ≥50, involved excision margins and incomplete excision at the internal margin were associated with increased risk of dyskaryosis. Histological evidence of recurrent/residual disease was shown in 298 women. Six were found to have invasive cancer, 146 (49%) had CIN 2 or 3, and 119 (40%) had CIN 1. The same risk factors were associated with recurrent or residual disease by univariate analysis.

5.0 Methodology

The analyses for this project were carried out using two connected models: -

- A service pathway model, incorporating a waiting time model
- A health economic model.

The first model focuses on the referral of patients to colposcopy services (including women referred from the screening programme and those presenting with symptomatic disease), their subsequent treatment, surveillance and follow-up in terms of workload and time to access colposcopy. The primary aim was to provide estimates of the impact of changing referral and screening policies in terms of colposcopy service workload and patient waiting times. The second model was constructed to consider the economic impact of the new policies, along with the expected health benefits.

5.1 Colposcopy service pathway model

5.1.1 Modelling theory

The primary model in the analysis is the service pathway model, which predicts the flow of patients from the screening programme into the colposcopy service when referred from community-based screening. It incorporates disease diagnosis, surveillance, treatment and post-treatment care, both within the service and in the community setting.

Consideration is also given to the impact on colposcopy services of women who present with symptoms of cervical disease, thereby including those women whose involvement is not specifically a result of cytology screening. The model quantifies the impact on the number of clinic sessions required in each six month period following the implementation of the new guideline on mildly dyskaryotic smears in the three years following the introduction of the new policy. This is followed by modelling of the impact of other recent changes in screening policy. Three modelled service scenarios are presented, representing the breadth of the likely experience of colposcopy services nationwide.

The model uses state transition (Markov) theory to simulate the natural history of the disease, from normal cervical epithelium, through the pre-invasive cervical intra-epithelial neoplasia (CIN) stages and eventually to invasive cancer. The Markov methodology allows a finite number of discrete health states to be modelled, with patients regression and progression between these states determined by transition probabilities which apply to a pre-determined time horizon. In this case, transitions are modelled at six monthly intervals, a time horizon within which it is feasible for such transitions to occur, and which is amenable to the available published data on disease progression.

Markov theory states that a patient's health state in the next time period depends only on their current health state, and not on health states in previous time periods. This approach is particularly useful in the modelling of diseases in which the risk is ongoing, where events may occur more than once, and in which the timing of events is important. The model uses these transitions to predict the number of women in each health state at any given point in time, thus enabling predictions to be made regarding the number of women being referred to a colposcopy service following an abnormal smear result. The model was developed through a series of interviews with clinicians from which an extensive set of conceptual patient pathways were constructed. An excerpt from these sessions is given in Appendix 1. The parameters and data used within the service pathway model are described in Section 6.

5.1.2 Colposcopy questionnaire

In order to establish the current protocols of English services on a number of management issues, and of regional variances in community-based smear practice, the 2004 National Colposcopy Questionnaire was circulated under the auspices of the British Society for Colposcopy and Cervical Pathology (BSCCP) and the NHS Cancer Screening Programme to all 178 colposcopy services in England. The questionnaire included questions on individual policies relating to: -

- Community policies on referral of women with inadequate, borderline and mild smears;
- Service / community follow-up following normal assessment at colposcopy;
- Policy regarding management of low grade disease (HPV-NCIN and CIN1), that is discharge, repeat colposcopy or treatment;
- Timing and nature of treatment (i.e. at initial colposcopy visit or at a later visit);
- Service and community-based follow-up policy after treatment;
- Clinic appointment strategy.

A draft version of the questionnaire was circulated to a clinician from each of the English health regions, from whom feedback and advice was obtained. A number of revisions were made based on this pilot to produce the final version of the questionnaire which was distributed to the named lead clinicians of all NHS colposcopy services. Responses from 158 out of the 176 NHS services (89.7%) were processed for the model construction (note - two services had merged with other clinics since commencing the modelling work). Section 6 describes this data and how it was used to produce example services for the main analysis.

5.1.3 Modelled clinic services

The model was designed to allow the impact of any community or clinic guidelines to be assessed in any service, in addition to an estimation of the impact at a national level. To this end, three example services were modelled in the main analysis: -

- High ‘intensity’ service;
- Low ‘intensity’ service;

- National ‘typical’ service.

The characteristics of the “high-intensity” colposcopy service were identified from the colposcopy questionnaire returns. This type of service is modelled under the stated local policy that patients are seen in colposcopy before returning the nationally recommended number of borderline smears. This type of service organises colposcopy based surveillance for patients following a normal colposcopy assessment, performs treatment at a separate visit from the diagnostic colposcopy, manages low-grade disease conservatively, and arranges colposcopy follow-up for all patients following treatment. It receives referrals from an area recommending “recall” cytology at 3 year intervals. This service would be generating a high clinical workload, due to the higher volume of patients being referred to the service from the community, and the intensive surveillance and follow-up policies.

The opposite of this type of service was also identified and modelled. The “low-intensity” service has clinical and community policies which minimise both the number of patients being referred to the service, and the time which they spend under clinical review. This is achieved by adhering to national guidelines regarding patients accessing the service, and adopting clinical policies including immediate treatment of disease of all grades at the diagnostic visit (‘see & treat’) and the discharge of patients with negative colposcopy and following treatment back to their primary care provider. It receives referrals from an area recommending “recall” cytology every 5 years. These policies would be expected to generate a much lower workload than the high-intensity service.

Both service types are assumed to adhere to the previous recommended policy of referral of women with mild dyskaryosis after two mildly abnormal smears to allow examination of the impact of changing guideline policies. Table (24) summarises the characteristics of the low and high-intensity services.

Table (24): Management policies of colposcopy services: High & Low intensity services

Policy	**Options**	**High intensity service**	**Low intensity service**
Access policy (borderline)	2 smears	P	O
	3 smears	O	P
Normal colposcopy follow-up	Yes	P	O
	No	O	P
Treatment timing (low-grade disease)	See and treat	P	O
	Defer treatment	O	P
Treatment timing (high-grade disease)	See and treat	P	O
	Defer treatment	O	P
Post-treatment follow-up	See in clinic	P	O
	Discharge	O	P

The national 'typical' service incorporates all combinations of clinic and community policies from the questionnaire returns, and applies weights to each policy based on the questionnaire responses (e.g. the questionnaire results show that 62% of all colposcopy services see patients following two borderline abnormal smears, so the modelled service sees 62% of women following two borderline smears, with the remaining 38% being referred only after a third borderline smear). The national "typical" policies are shown for comparison in Table (25). A more detailed description of how the policies were established is given in section 6.5.

Table (25): Management policies of colposcopy services - National 'typical' service policies

Policy	Options	National weighted average
Access policy (borderline)	1 smear	3%
	2 smears	60%
	3 smears	37%
Access policy (mild)	1 smear	20%
	2 smears	79%
	3 smears	1%
Normal colposcopy follow-up	Yes	35%
	No	65%
Treatment timing (low-grade disease)	See and treat	16%
	Defer treatment	84%
Treatment timing (high-grade disease)	See and treat	61%
	Defer treatment	39%
Post-treatment follow-up	See in clinic	55%
	Discharge	45%

Source: 2004 NHSCSP/BSCCP questionnaire

5.1.4 Model phases.

The model is divided up into two distinct phases: a warm-up phase and a model phase; the model results quoted in section 7 of this report refer only to data from the model phase. In order to assess the impact of policy changes, it was necessary to simulate a scenario which reflected the current workload of each of the three types of colposcopy service in terms of the expected number of patients currently in the colposcopy service at any time. Since the existing number of women in the system (and at what stage of the

diagnosis/treatment pathway they are) cannot be known exactly at any one point in time, the model assumed an empty service at the outset i.e. no patients in the service. By assuming a constant arrival rate of new patients into the screening programme (based on the current national screening statistics), the flow of patients over time was built up to reflect current service capacities. This "warm-up" modelling phase was simulated until a point was reached at which the number of colposcopy clinic sessions required per 6 months remained almost constant (known as "steady state").

With the model having been built up in the warm-up phase to a point which reflected current clinic activity and patient flow, the impact of changes to referral guidelines could be assessed from that time point onwards. The analysis was conducted in such a way that a direct comparison could be made between services continuing with current policies and the effects expected if they adopt the new policies. The differences in the number of clinic sessions which would be required could be compared between the policies, in addition to an assessment of the impact on waiting times of the extra referrals which would be induced by the new policy.

5.1.5 Pathway model assumptions

Given the potential complexity of the flow of patients through the pathway model, a number of simplifying assumptions were made regarding timing of treatment, repeat treatment for cervical lesions, referral policies from surveillance and post-treatment smears, and patient compliance between subsequent appointments. These are outlined below: -

- Women who have a negative initial colposcopy followed by a repeat smear 6 months later are assumed to be referred back to the clinic for any abnormality on this smear (excluding inadequate smears)
- All post-treatment smears and surveillance smears following negative colposcopy are assumed to be performed in the community and not in the hospital clinic.

- Only women treated for high-grade disease are eligible for annual surveillance smears. Those treated for low-grade disease are followed up in accordance with their health authority's guidelines.
- Women undergoing annual smears following treatment are assumed to be referred back to the colposcopy clinic if any such smear returns an abnormal result (excluding an indequate result).
- Women under surveillance for CIN 1 are assumed to be treated following persistence of disease at 24 months following the initial colposcopy.
- DNA rates are assumed to be equivalent for both low- and high-grade referrals.
- Patient compliance with both screening and clinic appointments is assumed to be independent from one visit to the next.
- Women who do not attend a clinic appointment are automatically offered a further appointment. If this appointment is not attended, and no previous contact was made by the patient, they are discharged back to the smear taker.

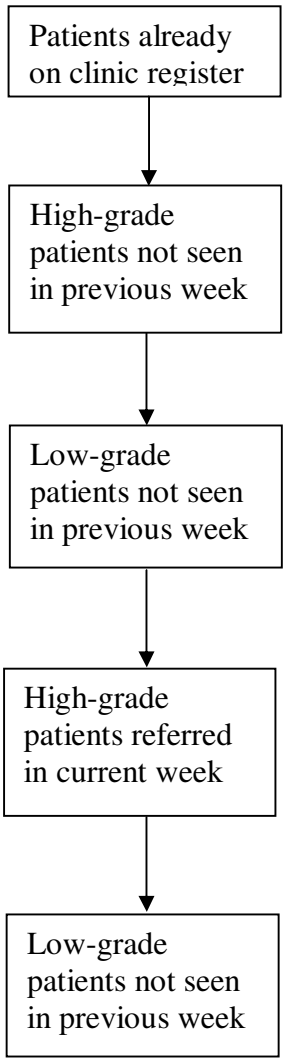
5.2 Waiting time model

One of the key outcomes of any policy change of this nature is the impact which it has on the patients themselves. An increase in the volume of patients being referred to colposcopy services due to abnormal smears has a direct effect upon the length of time each patient could expect to wait for a clinic appointment. A waiting time model was therefore constructed to use the estimates of the number of clinic-based appointments (calculated in the service pathway model) to provide insight into expected waiting times for newly-referred patients.

Since clinic appointments are typically made on a regular basis, the model reflects this and considers the weekly flow of patients through the service, based on whether the referral smear was low- or high-grade. In each 6-month time period, the number of clinic-based appointments for colposcopy and treatment is taken from the service pathway model, and used to calculate a total clinic time available for that period. This value was then compared with the expected number of clinics required to meet the demand to assess how quickly newly-referred patients would be seen for their first clinic appointment.

Patients within the model who have already attended the service for their initial colposcopy and are thus already on the service register are assumed to have 'priority' over new patients, since these appointments would for example, be made six months in advance in the case of patients entering surveillance or follow-up in the service. New patients with a high-grade abnormality on the referral smear would be prioritised next, followed by new patients with a low-grade abnormality. New patients who do not get a clinic appointment in the week of their referral are pushed forward into the following week. At this point, such patients take 'priority'over patients who are newly-referred in that week; as the appointment would be made in the preceding week. The structure of these priorities are shown in Figure (1) below.

Figure (1): Prioritisation of patients in colposcopy service



This prioritisation sequence indicates that in services which are 'inefficient' and clinic time is limited, the time which new patients with low-grade disease wait is likely to be higher than is the case in more 'efficient' services (in some scenarios it is possible that because of intensive surveillance and follow-up policies, the services become overloaded with patients who are already on the service register, leading to a situation whereby newly-referred patients with low-grade disease cannot be seen at any time, unless additional clinics are run to accommodate these patients). It is also assumed that appointments within the service are made on a weekly basis, with the prioritisation of patients made as in Figure (1).

No differentiation is made between the relative importance of different visit types, so for example, a diagnostic colposcopy is considered equally important as a treatment visit. The model takes account of the difference types of appointment (e.g. diagnostic colposcopy appointment, see and treat appointment, and treatment-only appointment) and the expected time required for each type of appointment. Based upon consultations with clinicians working within colposcopy units, a diagnostic colposcopy is assumed to take 15 minutes per patient (including a biopsy), a colposcopy appointment combinied with treatment (at the same visit) is assumed to require 30 minutes (also including a biopsy), and the time required for a treatment visit is taken to be 20 minutes.

The BSCCP questionnaire results showed that, on average, a typical colposcopy unit would run 4.5 clinic sessions per week, each lasting for three hours i.e. a total of 13.5 hours of clinic time would be available per week. All subsequent analyses are based on this assumption. The model assumes that patients being referred to the colposcopy service during any given 6 month period do so at a constant rate per week. This is implemented simply by dividing the number of referrals by 26 weeks.

Once patients are discharged from the service, it is likely that a proportion will require further investigation at a later date within the service, having tested positive at a subsequent annual screen. Given that such patients have been discharged from the service, they are assumed to be new patients when they are re-referred.

A similar prioritisation system was applied to women who are treated at a separate visit from their initial colposcopy. Those with high-grade disease (CIN 2/3) are modelled to have priority over those with low-grade disease (HPV/CIN1).

5.3 Health economic model

The second part of the analysis focused on the expected impact of the new mild smear policy on the costs and health benefits associated with the screening programme. This was achieved through an adaptation of the ScHARR model used in the recently-updated rapid review of liquid-based cytology (LBC) for cervical screening, commissioned by the National Co-ordinating Centre for Health Technology Assessment (NCCHTA).[7]

The model provides a macro-simulation of the life experience of women followed from the age of 15 to 95 years, and uses state transition methodology to simulate the natural history of the disease, the screening programme, adjusted for all-cause mortality. The model was originally designed to compare the health economics of LBC compared to conventional Pap screening and a policy of no screening, and generates a number of health and economic outcomes under a set of screening policy comparisons. The key health outcomes are the annual incidence of invasive cancer,the percentage of women having invasive cancer at some point in their life, and the life-years gained, with health economic outcomes being generated relating to the cost per invasive cancer avoided and cost per quality-adjusted life year (QALY) gained.

Two policies were considered in HTA review regarding referral policies for women with abnormal cervical smears. The first such policy assumed that all women with any grade of abnormality (i.e. everything but inadequate or negative) would get referred for immediate colposcopy. The second policy assumed that only high-grade smears would trigger a referral to colposcopy, whilst women whose smear showed borderline changes or mild dyskaryosis would be re-screened 6 months later, at which point a second abnormality would trigger a referral to colposcopy. The cost aspect of the analysis considered the costs of conventional Pap screening, costs of LBC techniques, colposcopy costs, along with direct treatment costs (which would vary according to whether the treatment was for pre-invasive lesions or for invasive cancer).

In order to utilise this model within the context of this project, a number of modifications needed to be made to the LBC model. This process included: -

- Updating of costs of Pap smears, colposcopies and treatment;
- Assessment of the impact for low / high "intensity" clinics (in terms of screening interval and mild referral policy);
- A revised discounting scheme which is in line with new NICE guidelines (both costs and QALYs discounted at 3.5%);
- Updating of inadequate rate on Pap smears; [8]
- Age at first screen changed to 25 years.

A detailed description of these changes is given in Section 6.7.

There are a number of features of the original LBC model which do not make it entirely compatible with the pathway and capacity model. For example, the LBC model assumed that all women are treated on a see and treat basis rather than at a separate visit, which contradicts the results of the BSCCP questionnaire. Neither does it incorporate the costs associated with follow-up appointments for women treated for CIN or invasive cancer, or surveillance colposcopies for women with CIN or HPV. This suggests that the costs of the screening programme will have been underestimated, although this is offset somewhat in the LBC model by the assumption that all women who have a colposcopy require treatment. The referral policies within the LBC model assume that, under the new policy, all women with either a mild or a borderline smear would be referred immediately, meaning that the model is likely to overestimate the number of referrals. Because of these inconsistencies between the two models, the health economic results discussed in Section 7 should be interpreted only as broad estimates of cost-effectiveness.

6.0 Model Data

The following descriptions summarise the parameters and their values which are used in the pathway and waiting time models.

6.1 Population & population growth

Data on a number of demographic parameters were collected to provide inputs for the model. Population data from the 2002-03 National Korner Community (KC 53) returns reports that the number of women eligible for cervical screening in England was 12,804,400 – this population encompasses all screen-eligible women aged 25-64.[8] Figures from the KC53 returns were used to provide estimates of coverage of routine community screening: 80.6% of women had been screened within the last five years, and 70% within the last three and a half years. In order to model a typical service, the entire eligible population was broken down into 176 equally sized groups, to give an estimate of the average population covered by each colposcopy service (71,272 per clinic). The model is presented in the context of an increasing population, using estimates of annual population increase from the Office of National Statistics (ONS). [53]

6.2 Screening Interval

Policies on the screening interval vary nationwide, and are dictated by the local health authorities and primary care trusts in discussion with cytology services. The screening interval adopted by each health authority falls into one of three categories, the nationwide breakdown of which is as follows:[54]

- 3-year screening interval - 60% of cytology services;
- 5-year screening interval - 20% of services;
- Age-related screening interval - 20% of services.

The third category of health authorities have adopted the new recommended policy under which women aged 25-50 are screened every three years, and every five years thereafter,

up to the age of 64, after which screening stops on the condition that the three preceding smears have been negative.

Such differences in policy clearly have an impact upon the number of women being screened in any 6-month period, and this has been accommodated in the "typical" service model, so that 60% of women are screened every three years, 20% screened every five years, and the remainder are screened according to the age distribution of screen-eligible women. For the purposes of the waiting time analysis, in which the timing of referrals is important, the arrival rate of women into the clinics was assumed to be constant over the 6-month period.

6.3 Smear data

Data from the KC61 returns on smears examined by pathology laboratories was used to form the basis of smear test result distribution on routine recall smears [8] . This data relates only to the results of routine smears, and so is not confounded by the different distribution of results which might be found in, for example, the smears of women under surveillance for a borderline abnormality. Table (26) shows the percentage of smears falling into each category in 2003-04: -

Table (26): Smear Results (call / routine re-call smears)

Smear Result	**Percentage of all smears examined**
Negative	86.88%
Inadequate	8.55%
Borderline changes	2.49%
Mild dyskaryosis	1.23%
Moderate dyskaryosis	0.43%
Severe dyskaryosis	0.37%
Suspected invasive carcinoma / glandular	0.05%

neoplasia	

(Source: Statistical Bulletin 2003-04 [7])

Given the expected differences between patients cytology pre- and post-treatment, different data were used to represent smear results for surveillance screens (including post-treatment smears, annual smears and follow-up in the community) .[8] This data is shown in Table (27).

Table (27): Smear results (surveillance smears)

Smear Result	**Percentage of all smears examined**
Negative	85.89%
Inadequate	7.13%
Borderline changes	4.21%
Mild dyskaryosis	1.86%
Moderate dyskaryosis	0.52%
Severe dyskaryosis	0.34%
Suspected invasive carcinoma / glandular neoplasia	0.05%

(Source:Statistical Bulletin 2003-04 [8])

The similarities in the data given in Tables 26 and 27 seem to reflect the uncertainty inherent in the use of the Pap smear as a diagnostic tool, and the fact that it may not always be a good predictor of underlying disease.

6.4 Transition probabilities & colposcopy findings

The movement of patients between different health states is one of the key issues in this project, specifically the probabilities of transitions between cytology results and disease states at six month intervals, and the findings at colposcopy of patients referred with each

category of abnormal cytology result. Where possible, published data were used to define these transition probabilities and correlations, for use in the model. Where published data were not available expert judgement was elicited.

Seven smear states and the reporting of 'inadequate for assessment' were used in the model to reflect cytology states: -

- Negative (i.e. no abnormality);
- Inadequate;
- Borderline changes;
- Mild dyskaryosis;
- Moderate dyskaryosis;
- Severe dyskaryosis;
- Suspected invasive cancer / glandular neoplasia

Transition probabilities were estimated at 6-monthly intervals for cytology findings, as shown in Table (28). These data relate to the likelihood that the smear report of a screening eligible woman changes between recommended surveillance intervals. This includes the likelihood that either smear is false positive or false negative, or that the either smear is over- or under-called, which reflects the recognised nature of cytological assessment. Of note, however, is the reporting of cytology as inadequate, where the transition interval is taken from national KC61 data and is likely to represent a three month interval, as is recommended by national strategy.

Table (28): Transition probabilities at 6-months for cervical cytology

		To this state					
		Negative	Inadequate	Borderline	Mild dyskaryosis	Moderate dyskaryosis	Severe dyskaryosis
From this state	Negative [9]	0.858	0.071	0.044	0.019	0.005	0.004
	Inadequate [9]	0.759	0.184	0.032	0.016	0.005	0.003
	Borderline abnormality (Rawal)	0.546	0.088	0.246	0.084	0.026	0.01
	Mild dyskaryosis (Woodward et al)	0.42	0.004	0.134	0.316	0.082	0.044
	Moderate dyskaryosis *	N/A	N/A	N/A	N/A	N/A	N/A
	Severe dyskaryosis *	N/A	N/A	N/A	N/A	N/A	N/A
	Susp. Inv. carcinoma *	N/A	N/A	N/A	N/A	N/A	N/A

* N/A – Not Applicable - no transition from moderate and severe smear states are recorded, as these patients will be referred for colposcopy at the 'index' smear.

(Source:Statistical Bulletin 2003-04 [8], Rawal et al [33] , Woodward et al [34])

The data used for the transitions from a negative smear state to any other state is derived from the recent Statistical Bulletin,[8] since this reflects outcomes at subsequent smears for women with a previously negative smear. Data on transitions from the inadequate group are also taken from the Bulletin, using data which relates to subsequent smear results for women undergoing repeat cytology for a previously inadequate smear. Whilst this data is not entirely amenable to state transitions over a 6-month period, the absence of more suitable data, combined the validation checks performed on the predicted number of referrals using the above data, suggest that the data are reliable proxy measures for thte transition probablilities.

Six disease states were also considered to represent progression of the true underlying disease as diagnosed at colposcopy (note that these transitions are considered separately from the cytology transitions discussed above): -

- Negative (i.e. no abnormality);
- HPV not achieving diagnostic criteria for CIN (HPV NCIN);
- CIN 1;
- CIN 2;
- CIN 3;
- Invasive cancer.

Transition probabilities for colposcopy findings were estimated at 6-monthly intervals from a meta-analysis of the data from a number of published studies as shown in Table (29). In this case these represent histologically diagnosed disease states, rather than subjective colposcopy assessments.

Table (29): Transition probabilities for disease states at 6-months

		To this state					
		Normal	HPV	CIN 1	CIN 2	CIN 3	Cancer
From this state	Normal	99.76	0.12	0.12	0	0	0
	HPV (NCIN)	6.0	92.5	1.5	0	0	0
	CIN 1	1.0	1.0	89.5	6.0	2.5	0
	CIN 2	0	0	0	85.0	15.0	0
	CIN 3	0	0	0	0	99.0	1.0
	Inv. Carcinoma	0	0	0	0	0	100

(Source:Sherlaw-Johnson et al [18], Richart et al [14], Campion et al [33], Vayrynen et al [35])

One of the key drivers of the model concerns the outcome of colposcopy, which varies according to the severity of the referral smear. Such data has been collected from a number of studies, (ONS KC data [39], Jones et al. [44]), the results of which are shown in Table (30). Again, these constitute histologically confirmed disease states.

Table (30): Colposcopy result by referral smear result

Referral smear	**Colposcopy findings (%)**					
	Negative	*HPV-NCIN*	*CIN 1*	*CIN 2*	*CIN 3*	*Cancer*
Inadequate	53.74	16.46	20.45	6.48	2.62	0.25
Borderline nuclear abnormality	29.55	20.73	30.86	10.18	8.00	0.67
1st mild dyskaryosis	34.0	6.0	24.0	22.0	13.0	1.0
2nd mild dyskaryosis	26.0	11.0	26.0	20.0	15.0	2.0
Moderate dyskaryosis	7.20	5.05	17.95	36.23	32.71	0.87
Severe dyskaryosis	3.55	1.92	5.06	15.00	70.73	3.75
?Inv/ ? Glandular	15.18	2.47	4.93	5.50	33.78	38.14

(Source: ONS-KC61 national data returns [8], Jones et al [44])

6.5 National colposcopy practice data

Given below are some of the key results from the questionnaire responses which have been used to form inputs to the model.

6.5.1 Access policies

Practice was expected to vary in the number of low-grade smears required to trigger colposcopy in the different services. The questionnaire included a tick-box for one, two or three smears of each type triggering referral, with a free-description area to discuss discretionary policies. Table 31 summarises the breakdown of local health authority

referral policies for borderline and mildly dyskaryotic smears (for the purposes of the model, all services are assumed to see women after three consecutive inadequate smears).

Table (31): Smear referral policies

Smear result	Number of abnormal smears required before referral	Number of services	As a percentage of responding services
Borderline abnormality	1	4	3.2%
	2	92	60.3%
	3	56	36.5%
Mild dyskaryosis*	1	27	20.4%
	2	119	79.0%

(Source: BSCCP/NHSCSP National colposcopy questionnaire 2004)

All patients returning cytology with moderate or severe dyskaryosis, or those with suspected invasive cancer or glandular neoplasia should be referred for colposcopy immediately.

6.5.2 Surveillance policies following normal colposcopy

Where the result of colpscopy is a negative assessment after referral, patients may be managed in a number of ways. The majority of services were expected to discharge the patient back to the care of the referring practitioner for repeat cytology at 6 months, whereas a smaller number were expected to follow-up in the colposcopy service at a specific time interval. The questionnaire included a tick-box for the expected policies, with a free-description area to describe protocols relating to referral smear, patient age, or where two different policies were used in a single unit. The results are shown in Table (32).

6.5.3 Management of low-grade disease

The significance of the pre-invasive potential of CIN 1 is debated, and some services routinely offer treatment for this condition. Services were questioned regarding treatment of CIN 1, and management of patients not treated. Services were also questioned as to

their policies of care for patients whose colposcopy assessment demonstrated evidence of HPV infection which does not achieve histological criteria for CIN, which was expected to constitute a low risk diagnosis. The results for surveillance policies are summarised in Table (32).

Table (32): Follow-up / surveillance policies by first colposcopy result

Colposcopy findings	Follow up policy (colposcopy only)	Number of services	As a percentage of responding services
Normal	Not seen in clinic	103	67.8%
	See in 6 months	44	28.9%
	See in 12 months	5	3.3%
HPV NCIN*	Not seen in colp	84	56.6%
	See in 6 months	52	35.5%
	See in 12 months	12	7.9%
CIN 1	Not seen in clinic	29	19.3%
	See in 6 months	104	70.3%
	See in 12 months	13	9.7%

*HPV NCIN = HPV changes not reaching CIN

(Source: BSCCP/NHSCSP National colposcopy questionnaire 2004)

In all situations where returned data contained free description of policies affected by age of patients these were weighted with respect to the national data regarding screened patient demographics.

6.5.4 Type and timing of treatment

Tables (33) & (34) show the results of the questions relating to the type of treatment women with various grades of cervical abnormality at the referral smear would receive. Treatment is either carried out at the same visit as the colposcopy , so called 'see & treat', or at a later visit, 'deferred treatment'. Treatment is either administered excisionally or

destructively within the colposcopy service. Destructive treatment may not be used on a 'see & treat' basis as national guidelines require patients to have a histological diagnosis prior to non-excisional treatment.Almost all high-grade lesions will be treated. The questionnaire indicated that 30.1% of patients with CIN 1 are treated, the presented data relate to this treatment group.

Table (33): Treatment policy: patients with low-grade disease - of those treated

Policy	*Proportion of services*
Treat on a "see and treat" basis*	15.7%
Treat at a later visit (deferred treatment)	84.3%
- treat excisionally (deferred)	88.9%
- treat destructively (deferred)	11.1%

(Source: BSCCP/NHSCSP National colposcopy questionnaire 2004)

Table (34): Treatment policy: patients with high-grade referral smear

Policy	*Proportion of services*
Treat on a "see and treat" basis*	61.0%
Treat at a later visit (deferred treatment)	39.0
- treat excisionally (deferred)	88.9%
- treat destructively (deferred)	11.1%

(Source: BSCCP/NHSCSP National colposcopy questionnaire 2004)

Services not immediately treating CIN 1 were questionned regarding the length of conservative follow-up prior to recommending treatment if the disease persisted. These results are summarised in Table (35).

Table (35): CIN1 time-to-treatment for services offering follow-up

Time to treatment	*Proportion of services adopting this policy*
Treat at 6 months	17.2%
Treat at 12 months	24.1%
Treat at 18 months	20.7%
Treat at 24 months	37.9%

(Source: BSCCP/NHSCSP National colposcopy questionnaire 2004)

6.5.5 Post-treatment follow-up

Post-treatment follow-up is a key clinic management variable which affects the number of appointments generated per patient. Interpretation of published research regarding risk of further disease following treatment was expected to create the greatest variation in policies. The histology report following excisional treatment is most often used as the indicator of recurrent/residual disease risk, with involved margins and those treated for high-grade disease triggering further colposcopy assessment. Table (36) summarises nationwide policies on follow-up: -

Table (36): Post-treatment clinic policies

Histology result	Number of services (%)
Not seen	33 (21.0)
Involved margins	28 (17.8)
Involved internal Margins	33 (21.0)
Involved external Margins	1 (0.6)
Involved margins or high-grade disease	4 (2.4)
Invoved internal margins or high-grade disease	5 (3.0)

High-grade disease	2 (1.2)
See all	50 (31.8)

(Source: BSCCP/NHSCSP National colposcopy questionnaire 2004)

Using the published research from Murdoch et al, [45] the responses were weighted to represent the expected distribution of histology reports following treatment. Patients are divided into two groups: those seen in colposcopy and those followed by cytology alone. Some services follow patients thought to be at increased risk following treatment for pre-invasive disease on more than one occasion.These policies were included in the weighting process, which are shown in Table (37).

Table (37): Post-treatment clinic policies (following weighting)

Post-treatment policy	*Proportion of services*
Discharge patient to GP or smear only within the service	44.9%
Offer repeat colposcopy 6 months post-treatment	55.1%

(Source: BSCCP/NHSCSP Questionnaire 2004)

6.5.6 Clinic time data

Services were asked as to the number of number of clinic sessions per week and the number of patients seen per clinic in doing so specifying whether the clinics were diagnostic only, treatment only, "see & treat", or a combination of these.

6.6 Attendance parameters

The compliance of patients at diagnosis, treatment, surveillance and follow-up has a direct impact upon service workload. Given the new guidelines on women who do not attend (DNA) at their initial visit (such patients are now offered a further appointment

rather than being discharged to their GP as was previously the case), this is particularly important when attempting to model patient volume. Data from the 2003-04 KC65 returns were used to give the compliance figures shown in Table (38). [8]

Table (38): Attendance rates by visit type

Appointment type	*Proportion who attend*	*Proportion who cancel*	*Proportion who DNA*
Initial visit	78%	12%	10%
Treatment	82%	11%	7%
Follow-up	69%	16%	15%

(Source: ONS-KC61 national data returns [8])

It was assumed in the model that appointments cancelled by the service, or where prior notice was given by the patient, would be re-scheduled. Patients who did not attend their appointments with no prior cancellation would be discharged back to the referring clinician. However, the model retains the capacity to model policies of routinely arranging further appointments after all non-attendance. In terms of appointment scheduling, it is assumed that the appointment slot taken by a patient who DNAs cannot be filled by another patient. This does not apply to patients who cancel their appointment, or whose appointments are cancelled by the service.

6.7 Economic model parameters

The additional costs associated with the new policy are modelled using three separate cost components, relating to screening, colposcopy and treatment. These costs were taken from the updated HTA review [7] and from NHS Reference Costs, where applicable. Table (39) summarises these costs: -

Table (39): Unit costs used in economic model

Cost item	*Unit cost*	*Reference*
Pap Smear (in community)	£22.51	Karnon et al – uplifted to 2004 price [7]
Colposcopy (including any treatment)	£192.35	Cost of gynaecology outpatient visit – uplifted from Karnon et al to 2004 price[7]
Surgery for invasive cancer	£2,194.93	NHS Reference Costs: TNELIP HRG (M07) [55]

The Pap smear cost includes the cost of a GP's time plus the slide processing and repoting cost. The model assumes that the same cost of colposcopy is applied to all women, regardless of whether or not they require treatment. The colposcopy cost of £192.35 is the cost of a colposcopy plus treatment (i.e. a see and treat appointment), which is applied to all women who attend for a colposcopy, regardlesse of whether or not they require treatment, and is therefore likely to overestimate the costs associated with the initial colposcopy. This may be offset somewhat by the fact that some clinics would treat at a separate appointment, which would incur the cost of a further appointment. Data from the Statistical Bulletin was used to update the rate of inadequate smears to a figure of 8.55% of all smears, while discount rates of 3.5% were applied to both costs and QALYs, in line with guidance issued by the National Institute for Clinical Excellence. [56] Estimates of the coverage of the screening programme were also estimated from the Statistical Bulletin, with figures of 80.6% and 70.3% used for the 5-year and 3-year screening intervals respectively. Data from the questionnaire returns was used to reflect the national average policy on the timing of treatment, either at the initial colposcopy visit or at a later appointment. For patients undergoing treatment for low-grade disease, 15.7% are assumed to be treated at their initial visit, compared with 61% of patients requiring treatment for high-grade disease.

In order to determine the health gains associated with the introduction of the new policy in terms of additional QALYs, utility estimates for three health states were taken from the HTA review [7]. Women diagnosed with invasive cancer of the cervix are assumed within the model to have a utility of 0.6, reflecting the deterioration in quality of life for these

patients. There are also assumed to be minor utility decrements associated with undergoing a colposcopy (a decrement of 0.03 is applied to these patients) and for women whose initial smear shows a borderline abnormality but are not referred to colposcopy until they return a second borderline result (for whom a utility decrement of 0.02 is applied).

7.0 Results

This chapter summarises the results of the three service types under consideration (the "typical" service as a measure of nationwide impact, the "high-intensity" service, and the "low-intensity" service). It should be emphasised that the presented data relate to colposcopy workload generated by abnormal cervical cytology only, and does not represent any practice relating to colposcopy performed for other indications, for example patients referred with symptoms of cervical disease. In each case, estimates of the total colposcopy workload per six month period in terms of total number of clinic sessions are presented, over the first 36 months of the implementation of a new mild smear referral policy. For each service this is then followed by a calculation of the changes in the different areas of colposcopy clinic activity: new referral, surveillance and treatment. In this context, treatment denotes any appointment where treatment is performed, either exclusively, or in combination with diagnosis (so-called "see & treat"). Data is then presented to show the expected change in detection of high-grade disease as an indicator of screening/colposcopy success.

The impact on waiting times are given, followed by the results from the adaptation of the ScHARR LBC model are given to allow comparison of the effect of the new policy in terms of the additional costs and associated health benefits associated with the screening programme.

Finally, clinic protocol modifications that might be introduced to ameliorate the predicted workload implications are presented, along with the effects these have on the detection of

high-grade disease, where relevant. Included in this section are the results of the impact of new "call-recall" recommendations on projected workload increases under a single mild referral policy.

7.1 Results of "typical" service analysis

As explained in section 5.1, this service service constitutes an "average" of colposcopy practice across England. This includes the 20% of services who currently already receive women after a single mild smear.

7.1.1 Total clinic workload

Data for the total clinic workload are presented below in two formats in Figure (2) and Table (40). The first format is the projected current and increased number of "typical" clinics required for the service per modelling interval (six-months) under current and single mild referral strategies. This may be difficult to interpret on a clinical practice basis, and is therefore followed by the second format, the percentage increase in workload expected under the single mild referral policy. This percentage increase also represents the expected change in number of colposocpy appointments for abnormal cervical cytology required nationally to accommodate the increased workload generated by referral after a single mild dyskaryosis smear.

Figure (2): 'typical' service - implications of single mild policy change with respect to total clinic workload

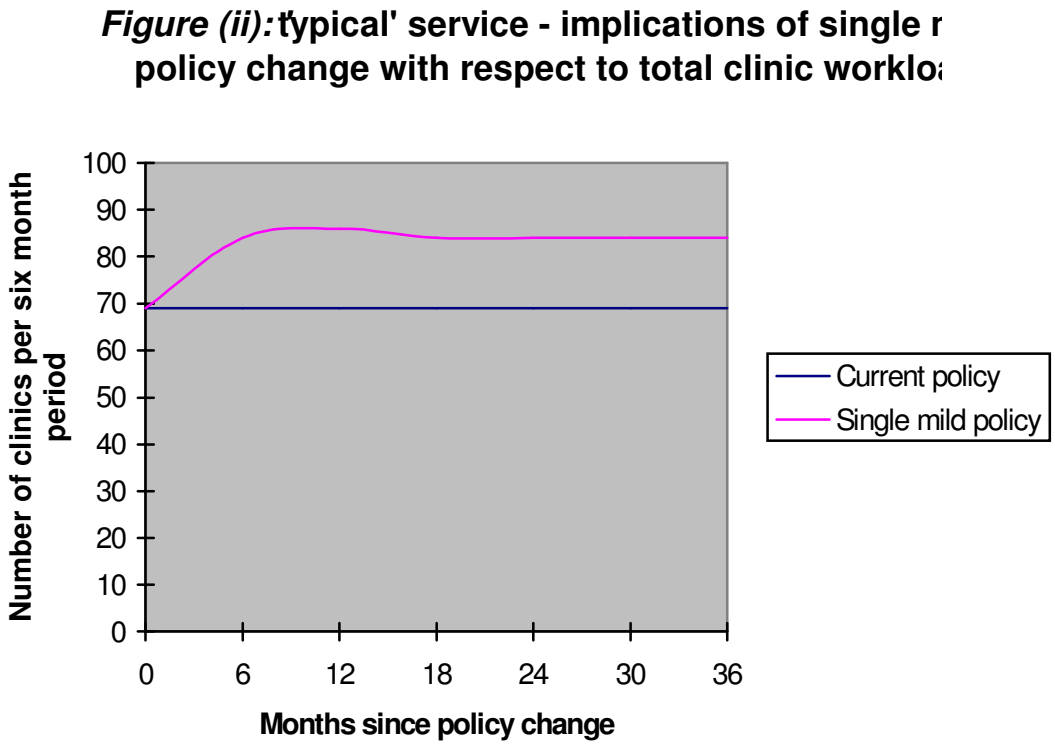


Table (40): Percentage increase in clinic workload for the "typical" service under the one mild policy

	Time since new policy implementation					
	6 months	12 months	18 months	24 months	30 months	36 months
% change in workload with single mild policy	22.0	24.3	21.0	20.9	20.9	20.6

The majority of the impact is therefore expected to be seen within 6 months of the policy change, with a predicted increase in clinic workload of 22%, and hence a proportional increase in the number of clinics required to meet the demand. This increases slightly at 12 months following the implementation of the policy, and then decreases to around 21% before appearing to level off. The sharp increase seen within the first year is attributable not only to the additional referrals of women with mild dyskaryosis on the recall smear, but also to those women who return a mild result when under surveillance for a

borderline or inadequate smear on routine “recall”, and to those who are under surveillance from a mild smear prior to the change in referral policy. The lower figure at 18 months and thereafter, can be attributed to the latter group of women no longer being under surveillance. It should be noted that these figures are likely to overestimate the total number of referrals, since this analysis assumes that women are screened every three years up to the age of 50, and every five years thereafter up to the age of 64. Although these are now the recommended screening intervals they were, until recently, relatively rare in practice, and the cut-off age at which women are screened every five years may be somewhat lower than age 50.

7.1.2 Workload change by type of clinical activity

The distribution of workload by type is presented in Figure (3) and Table (41), in terms of percentage change in three areas of clinical activity: new referral workload, surveillance appointments and treatment appointments. This is presented for service planning, to identify where colposopy services will expect to find changes in workload. In this situation “treatment” activity describes any appointment where treatment is performed, either “see & treat” or deferred appointment.

Figure (3): "typical" service- percentage changes in clinical workload by clinical activity

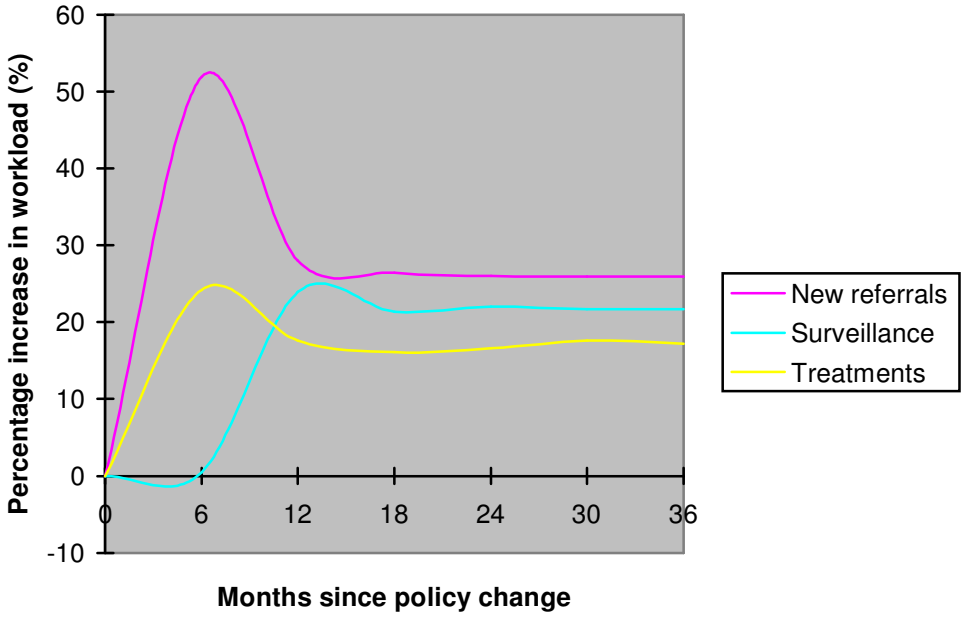


Table (41): Percentage increase in clinic worklad for the "typical" service under the one mild policy, by clinical activity

Clinical activity	Time since new policy implementation					
	6 months	12 months	18 months	24 months	30 months	36 months
New referrals	51.9	28	26.4	26	25.9	25.9
Surveillance	0.5	23.9	21.4	22	21.7	21.7
Treatment	24.2	17.6	16.1	16.6	17.6	17.2

This breakdown of the clinic workload demonstrates the impact seen not only in terms of the additional initial colposcopies required, but in terms of further appointments for these patients, such as surveillance colposcopies and treatment appointments. Clearly within the first 6 months, the impact is seen most prominently in the number of new referrals and treatment visits. The surveillance appointment workload increases sharply after 6

months, since it is during this period that the new referrals from the first 6 months would be followed up.

7.1.3 Total workload change and detection of high-grade disease

Detection of high-grade disease is presented to represent the outcome of cerivical screening and colposocpy. The ultimate goal of screening is the treatment of pre-invasive disease, and where changes of policy are to be introduced, it will be important that this is seen to have no effect on, or improve the detection of, high-grade CIN. This is presented with increased total workload to highlight the benefits resulting from the extra resources required, in Figure (4) and Table (42).

Figure (4):"typical" service- total workload increase vs detection of high-grade disease

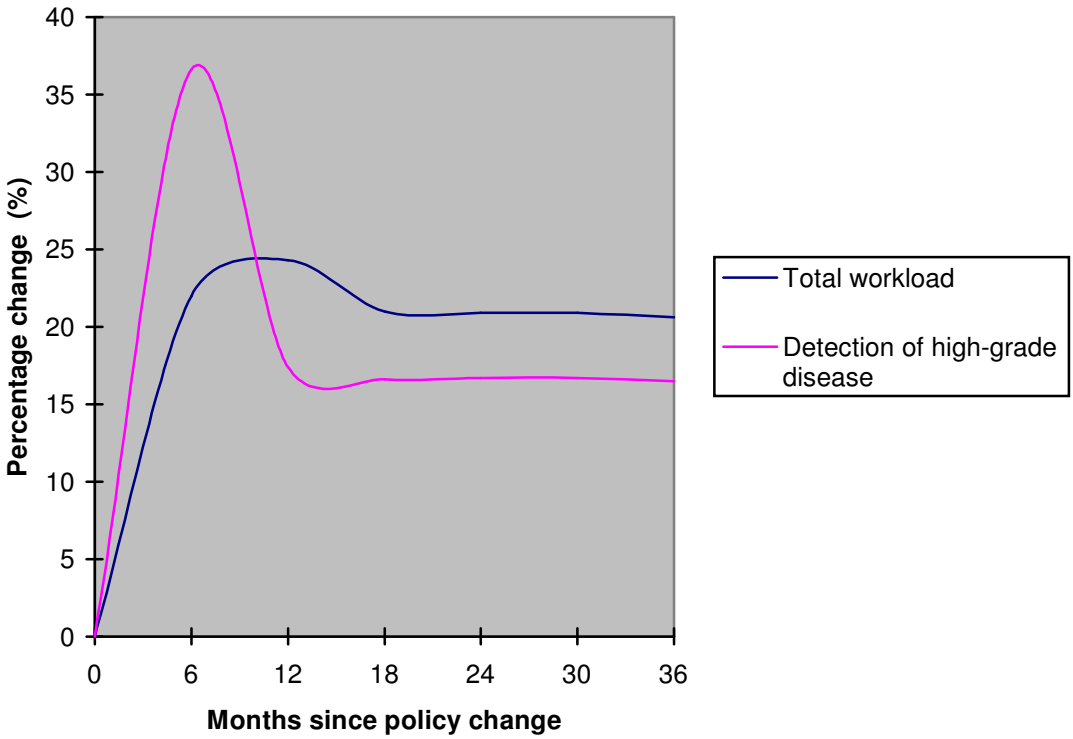


Table (42): Percentage increase in detection of high-grade disease for the "typical" service under the one mild policy

	Time since new policy implementation					
	6 months	12 months	18 months	24 months	30 months	36 months
Change in detection of high-grade disease	36.6	17.4	16.6	16.7	16.7	16.5

These results indicate that although clinic workload is expected to increase significantly, the policy change will increase the detection og high-grade disease by around 17% after two years. This could be expected to decrease after 3 years, since the women screened immediately following the policy change would be more likely to be free of disease than under the previous mild referrals policy.

7.1.4 Waiting times

The impact of the new policy on patient waiting times is driven by the number of appointment slots available for new referrals within each service's capacity planning. The waiting time analysis used a number of scenarios by varying the assumptions regarding how many clinics each colposcopy service would run per week.

Under the assumptions used in the "typical" service analysis, the impact of the new policy on units running 4 or more clinics per week would be negligible in terms of capacity issues, since there would be enough space on the clinic registers for the additional referrals to be seen within the recommended period of time. This may, however, have staffing implications from time to time given that units are likely to run the number of clinics required in a given week to meet the demand, rather than running the same number of clinics each and every week.

Problems with failure to meet waiting time criteria would be expected in units of this nature which run 3 or fewer clinics per week. Since high-grade referrals have priority over those with low-grade smear abnormalities, the impact on waiting times is greatest amongst the latter group of patients. By the end of the first year following the change in the policy, it is anticipated that women referred with low-grade abnormalities may have to wait up to 9 weeks for their initial appointment in the colposcopy clinic. This is due primarily to the increase in referrals, but is also due to the additional follow-up and surveillance workload associated with these patients. Because the waiting list of these patients would continue to rise in the absence of additional clinic capacity, this waiting time would be expected to continue to rise. This impact could be offset by improving the efficieny of the policies influencing patient flow.

7.2 Results of "most efficient" service analysis

As discussed in section 5.1, this service is presented as the service likely to produce the minimum number of colposcopy appointments for patients referred with abnormal cytology. It is assumed for the purpose of this study that this service currently operates a two mild dyskaryosis access policy. The characteristics of these service are: -

- Access to colpscopy after 3 borderline smears;
- Screening of women every 5 years;
- Discharge patients with negative result, HPV or CIN1 at colposcopy;
- See and treat all patients;
- Don't follow up post-treatment (discharge back to community cytology).

It is important to note that screening of women every five years would not be considered an acceptable practice for any health authority; this is modelled simply to indicate the differences in colposcopy workload for a spectrum of scenarios.

7.2.1 Total clinic workload

Data for the total clinic workload are again presented in two formats in Figure (5) and Table (43): the projected current and increased number of clinics required for the service per modelling interval (six-months), and the percentage change in workload.

Figure (5): "most efficient" service- implications of single mild policy change with respect to total clinic workload

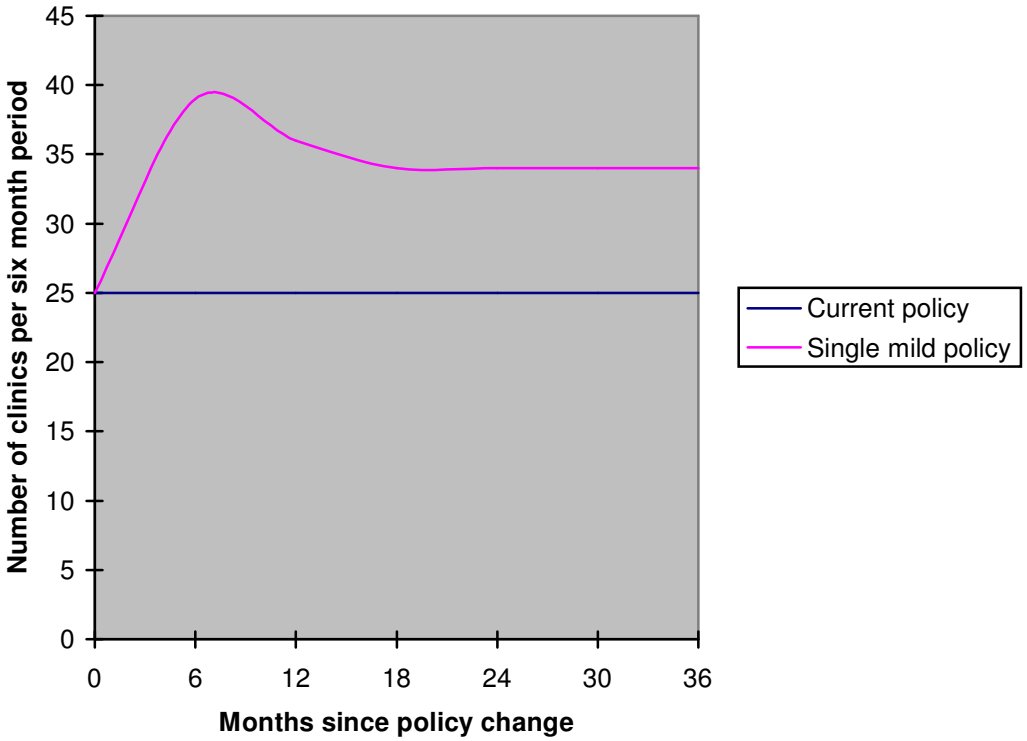


Table (43): Percentage increase in clinic workload for the theoretically "efficient" service under the one mi ld policy

	Time since new policy implementation					
	6 months	12 months	18 months	24 months	30 months	36 months
Change in workload with single mild policy	55.8	42.4	36.3	35.5	34.8	34.9

Owing to the efficiency of this theoretical clinic type, the percentage increase in clinic workload is seen to be greater than for the "typical" clinic. However, theis is due to the high efficiency of the clinic prior to the policy change – the direct increase in the number of clinics required is in fact smaller than for the "efficient" clinic type, with approximately 10 additional clinics required per 6 months after two years. The pattern in the numbers (when compared to the "typical" clinic) is similar, with the highest increase

seen in the first six months, owing to the additional referrals from the inadequate and borderline surveillance groups.

7.2.2 Workload change by type of clinical activity

The distribution of workload by type for this service is again presented in terms of percentage change in each area of clinical activity, in Figure (6) and Table (44). This service offers very little colposocpy surveillance, as patients with all grades of CIN are treated, and normal and patients post-treatment are discharged.

Figure (6):"most efficient" service- percentage changes in clinical workload by clinical activity

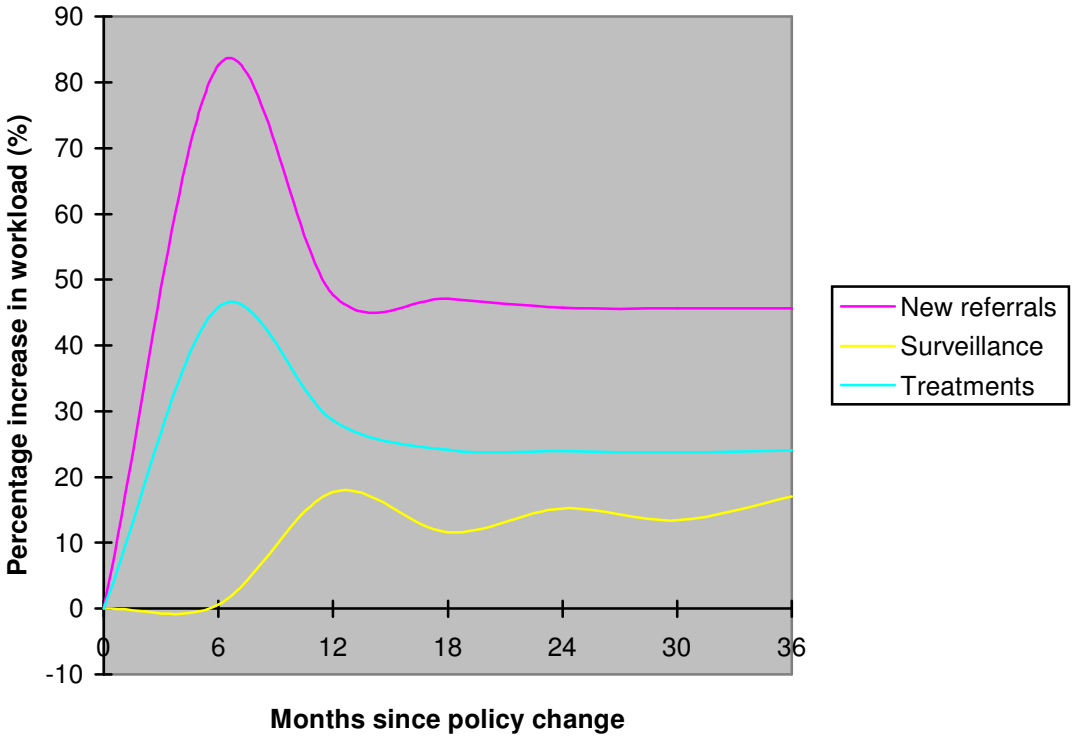


Table (44): Percentage increase in clinic activities for the theoretically "efficient" service under the one mild policy, by clinical activitiy

Clinical activity	Time since new policy implementation					
	6 months	12 months	18 months	24 months	30 months	36 months
New referrals	82.6	47.7	47.1	45.7	45.6	45.6
Surveillance	0.6	17.7	11.6	15.2	13.4	17.0
Treatment	45.8	28.6	24.1	23.9	23.7	24.0

These figures again indicate that the additional low-grade referrals impact on clinic workload beyond the initial visit, with subsequent increases in treatment and surveillance appointments generated and sustained over time. The shape of the three curves differs slightly from those derived from the "typical" clinic analyses (see Figure 3), due to the different policies adopted. For example, the "treatment" curve peaks earlier under the "efficient" clinic scenario since this type of clinic treats all of its patients on a see and treat basis, rather than entering some of them into a surveillance programme. Furthermore, the "surveillance" curve is lower for the "efficient" programme than for the "typical" programme, since women are discharged post-treatment and not followed up.

7.2.3 Total workload change and detection of high-grade disease

Detection of high-grade disease is again presented to represent the outcome of cervical screening and colposocpy along with total workload increases, presented in Figure (7) and Table (45).

Figure (7): "most efficient" service- total workload increase vs detection of high-grade disease

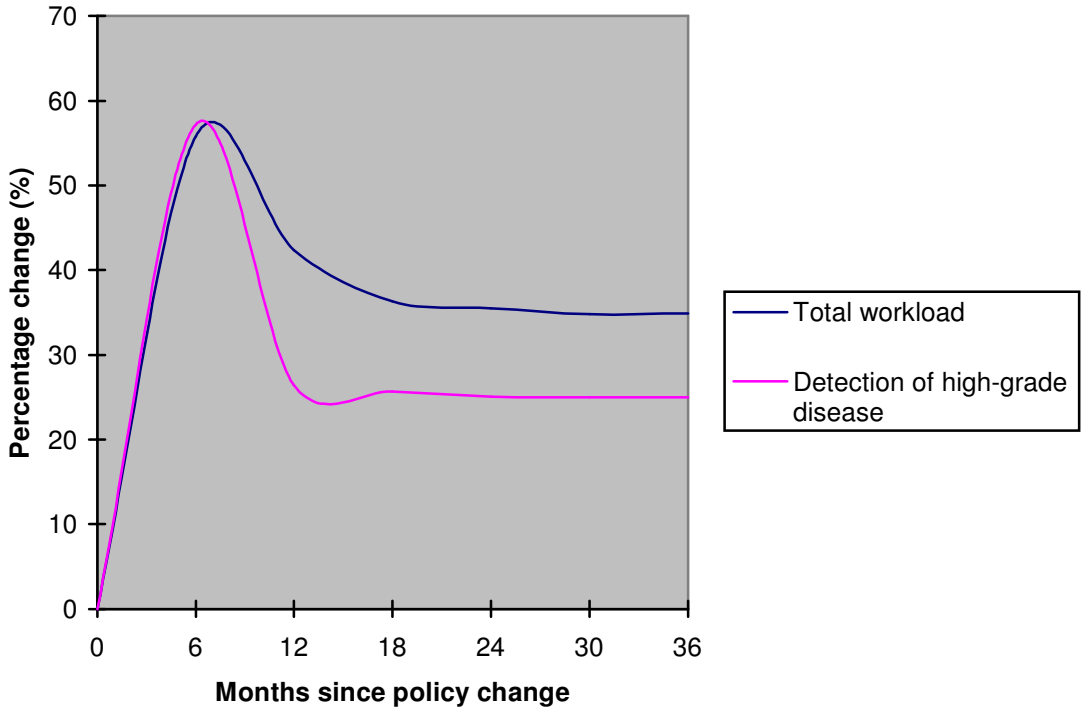


Table (45):Percentage increase in detection of high-grade disease for the "efficient" service under the one mild policy

	Time since new policy implementation					
	6 months	12 months	18 months	24 months	30 months	36 months
Change in detection of high-grade disease	57.2	26.4	25.7	25.1	25.0	25.0

The greatest impact on detection of high-grade disease is seen within the first 6 months, for reasons discussed previously. Thereafter, the detection is expected to be 25% higher than under the previous mild dyskaryosis policy, broadly mirroring the increase in clinic workload associated with the policy change.

7.2.4 Waiting times

A similar analysis was conducted for this clinic type to that presented in Section 7.1.4. Since this efficient type of clinic is intended to give a lower bound on the expected additional workload associated with the new policy, the impact on patient waiting times is expected to be low. Patients referred to efficient units running at least 2 clinics per week would not be affected greatly, with both new low- and high-grade referrals being offered an initial appointment within the required time horizon. The impact in such units would be seen in terms of the additional referrals, though the non-intensive clinic policies adopted mean that these patients only generate a small number of appointments for follow-up or surveillance, and so the impact upon patient waiting times (for the initial appointment) is likely to be minimal.

The waiting time model suggests that waiting times would only be affected significantly if such units were running only one clinic per week. In this instance, it is anticipated that a backlog of low-grade referrals would build up very quickly because of a lack of clinic capacity, a situtation which would deteriorate over time in the absence of additional clinics, as the waiting list increases in length. It is not anticipated that high-grade referrals would be affected in this way, given the existing capacity.

7.3 Results of "least efficient" service analysis

As discussed in section 5.1, this service constitutes a service identified as likely to produce the maximum number of colposcopy appointments for patients referred with abnormal cytology. This service currently operates a two mild dyskaryosis access policy. The characteristics of these service are: -

- Refer after 2 borderline smears
- Screen all women every 3 years;
- Surveillance for negative colposcopy;
- Surveillance for CIN1 (treat at 24 months);

- Colposcopy and treatment take place at separate visits;
- Follow-up in the service (i.e. with further colposcopy).

7.3.1 Clinic workload

Again, the total clinic workloads are presented in two formats: the projected current and increased number of “least efficient” clinics equired for the service per modelling interval (six-months); and the percentage change in workload, in Figure (8) and Table (46).

Figure (8): "least efficient" service- implications of single mild policy change with respect to total clinic workload

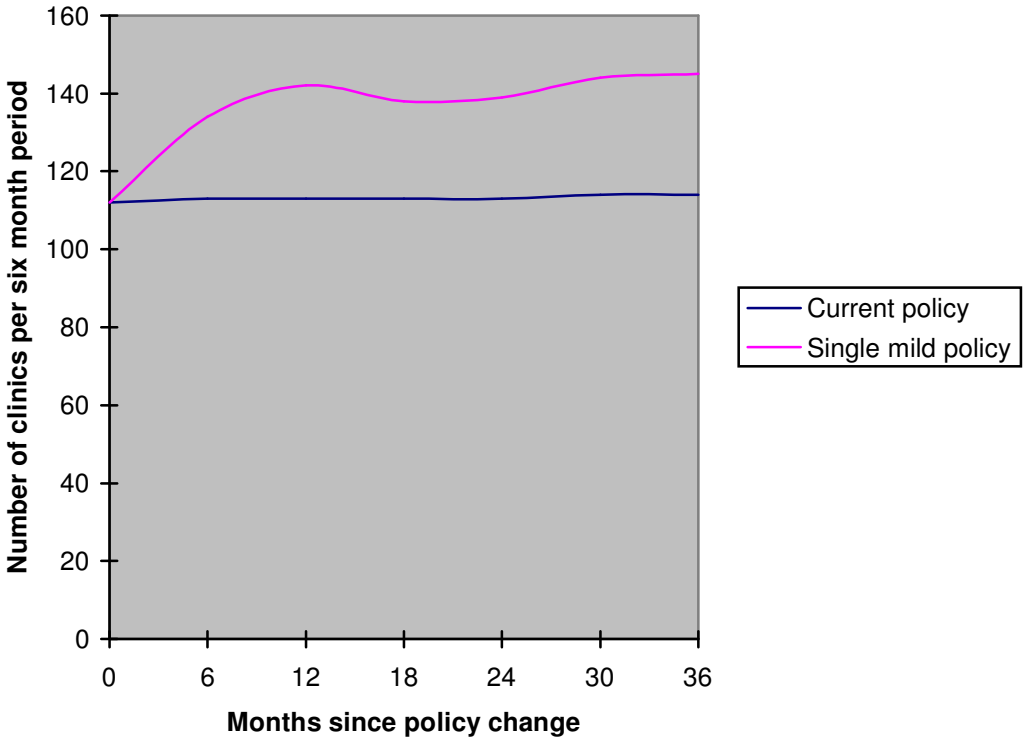


Table (46): Percentage increase in clinic workload for the theoretically "inefficient" service under the one mild policy

	Time since new policy implementation					
	6 months	12 months	18 months	24 months	30 months	36 months
% change in workload with single mild policy	19.1	26.2	22.3	22.8	26.5	27.0

It is noticeable that the percentage increase in clinic workload within the first 6 months is considerably lower than for the two other clinic scenarios discussed previously. This is due to the inefficiency of such clinics prior to the policy change i.e. the clinics were already overworked because of the extensive follow-up and surveillance policies adopted that the additional referrals make less of a difference in terms of percentages. However, when the absolute increase figures are considered, it can be seen that a 26% increase in clinic workload for this inefficient clinic equates to approximately 30 additional clinics being required per 6 months to meet the additional demand. It should be noted that the predicted workload decreases after 12 months and then begins to rise again. This is due to the high number of follow-up and surveillance appointments generated by the initial cohort of new patients.

7.3.2 Workload change by type of clinical activity

The distribution of workload by type for this service is again presented in Figure (9) and Table (47), in terms of percentage change in each area of clinical activity. This service operates significant numbers of colposocpy surveillance appointments, as patients will have further colposcopy both if assessment is normal, CIN 1 and following treatment.

Figure (9) "least efficient" service- percentage changes in clincal workload by clinical activity

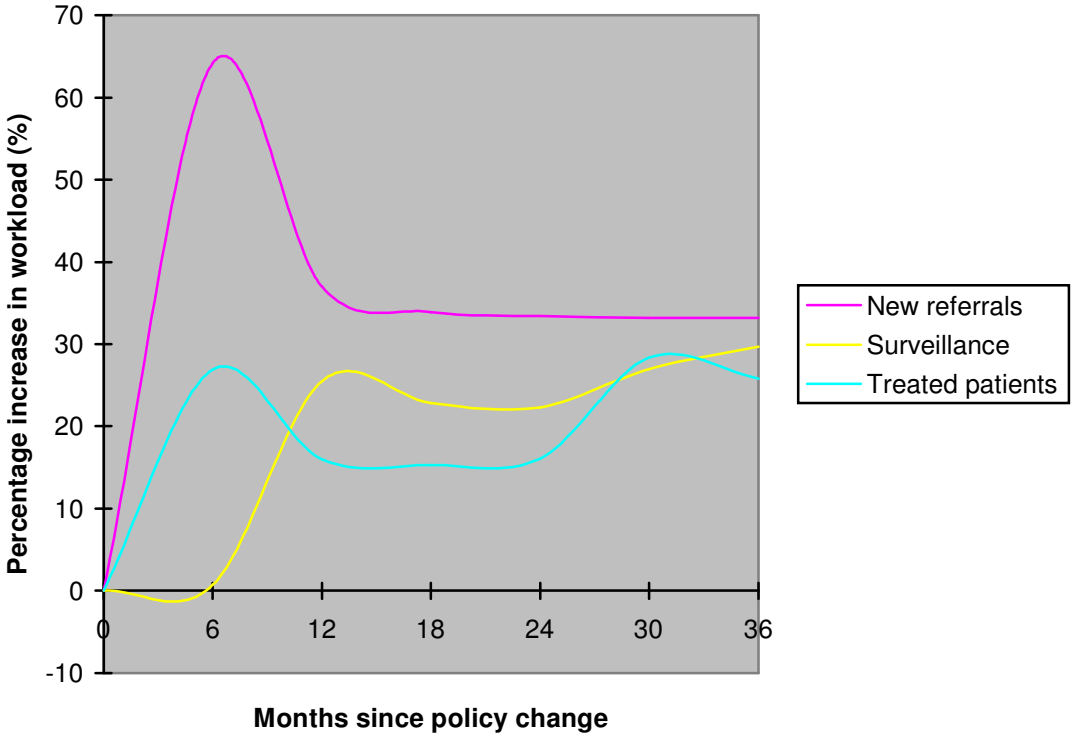


Table (47): Percentage increase in clinic activities for the theoretically "inefficient" service under the one mild policy, by clinical activity

Clinical activity	Time since new policy implementation					
	6 month	12 months	18 months	24 months	30 months	36 months
New referrals	64.2	37.0	33.9	33.4	33.2	33.2
Surveillance	0.7	25.5	22.8	22.3	27.0	29.7
Treatment	26.9	16.0	15.3	16.1	28.4	25.8

The results are similar to those from the "typical" clinic type (see Figure 3), in that the immediate impact is seen in terms of the additional mildly dyskaryotic referrals, which then has a knock-on effect upon the treatment and surveillance workload. It is likely that the number of surveillance appointments required would continue to increase given the additional referrals combined with the intensity of the follow-up period. The increase in

the number of women treated seen between 24 and 30 months reflects the policy of this clinic type with regard to CIN 1 management; women whose initial colposcopy showed CIN 1 would be offered repeat colposcopies at 6 month intervals up to 24 months after the initial colposcopy. Assuming that they had not progressed during this time, they would be treated at 24 months, hence the increase seen (a small proportion of these patients would be expected to progress to CIN 2 and so would be treated prior to 24 months).

7.3.3 Total workload change and detection of high-grade disease

Detection of high-grade disease is presented in Figure (10) and Table (48) to represent the outcome of cervical screening and colposocpy along with total workload increases.

Figure (10): "least efficient" service- total workload increase vs detection of high-grade disease

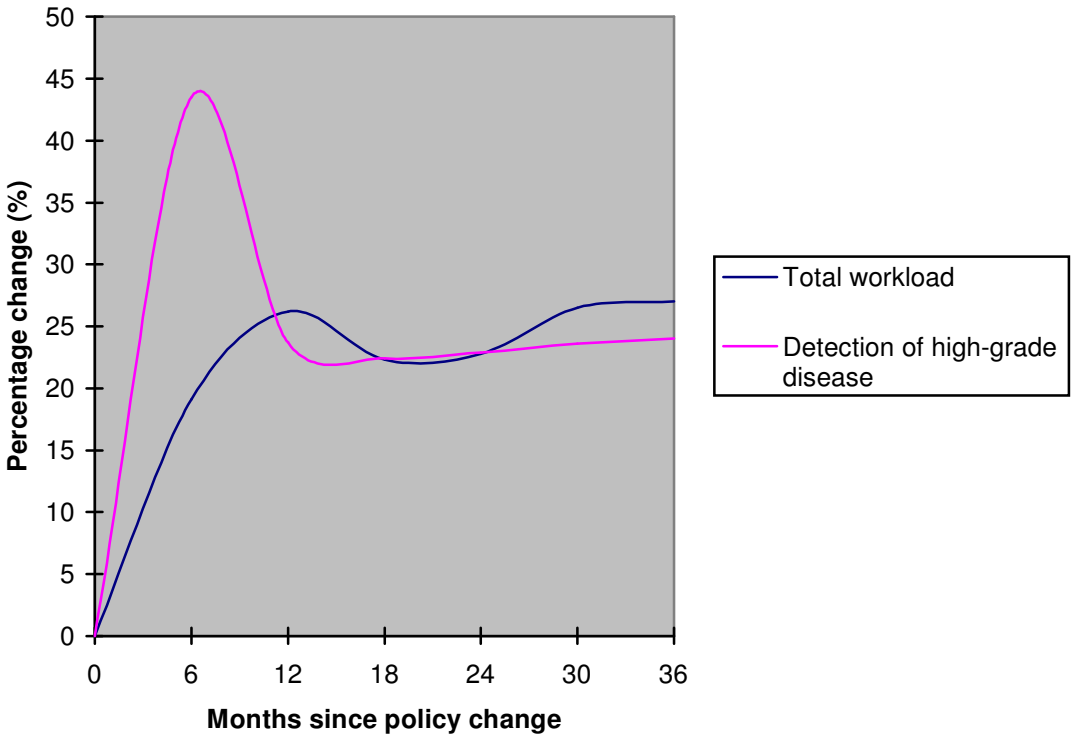


Table (48):Percentage increase in detection of high-grade disease for the "inefficient" service under the one mild policy

	Time since new policy implementation					
	6 months	12 months	18 months	24 months	30 months	36 months
Change in detection of high-grade disease	43.5	23.7	22.4	22.9	23.6	24.0

The improved detection of high-grade disease associated with the "inefficient" clinic type is in fact similar to that under the "efficient" clinic scenario, with an improvement of 24% expected when compared to the previous mild dyskaryosis referrals policy. However, the detection rate is highest after a longer period of time, since the follow-up policies adopted are likely to mean that disease will be detected at a later appointment (for example, the "inefficient" clinic type follows women for up to 24 months after a CIN 1 result at the initial colposcopy, and so high-grade disease would be detected in those women whose disease progressed during that time period).

7.3.4 Waiting times

The inefficiency of this third type of clinic is likely to have the greatest impact upon patient waiting times. Although the additional number of referrals is similar to that of the other two clinic types, the intensity of the follow-up and surveillance policies for this clinic type means that patients stay on the clinic register for longer, leaving less clinic time for new referrals.

Patients attending units which run six or more clinics of this type per week are not expected to encounter delays in being offered an appointment beyond the recommended waiting time. However, if such a unit were to run five clinics per week, this would have a detrminetal effect upon the waiting time of new referrals with low-grade abnormalities. Within 6 months of the policy change, the waiting time model predicts that new low-grade referrals will have to wait more than 4 weeks for their initial appointment, rising to 20 weeks at the end of the first year. The situation is expected to continue to deteriorate thereafter, in the absence of additional clinics or improve clinic efficiency thereafter, as

the waiting list builds up. As before, new patients being referred with high-grade disease would be unaffected by these delays given their priority over patients with low-grade disease.

7.4 Health Economics

The ScHARR LBC model was adapted as described in Section 6.7 to give estimates of the cost-effectiveness of the new policy by relating the expected health gains to the increased cost of referring a significant number of additional women. Two separate scenarios were modelled, using both 3- and 5-year screening intervals.

Table 49 summarises the results of the incremental cost-effectiveness analyses (comparing the new mild dyskaryosis policy against the previous policy): -

Table (49): Incremental cost-effectiveness results

Screening interval	Cost per QALY gained
3 years	£5,521.07
5 years	£1,405.22
Mixed-interval	£3,258.30

As mentioned earlier, these figures should not be assumed to be exact estimates of cost-effectiveness, for the reasons described in Section 5.3. The costs are likely to be underestimates, since the LBC model takes no account of post-treatment follow-up, nor of follow-up for patients under surveillance for CIN 1 or HPV. Despite this, the change in policy would seem, based upon these figures, to be considered cost-effective to organisations such as NICE.

Since the costs are likely to have been underestimated, sensitivity analyses have been performed to assess the impact of increasing the number of appointments per patient, and therefore the costs associated with diagnosing and treating women in the clinics. The base

case analysis assumes that each woman has one clinic appointment, which constitutes a colposcopy and any necessary treatment (with the exception of those diagnosed with invasive cancer). It would seem more realistic to assume two appointments per patient, as this would take into account the fact that treatment often takes place at a separate appointment, that women who are treated would often have a follow-up apointment to check for residual disease, and because many clinics employ surveillance strategies for women with low-grade disease, generating further appointments. Making this assumption the incremental cost per QALY associated with the new policy is estimated to be £2,897 for a 5-year screening interval, £11,197 for a 3-year screening interval, or £6,753 for a mixed-interval strategy. Further sensitivity analyses have not been performed on the utility estimates due to a lack of suitable evidence concerning utility loss associated with colposcopy and treatment.

It is anticipated that the true cost-effectiveness of the new policy would not be seen in the first few years following the policy change, because the improvement in detection of high-grade disease within the first year would only become apparent at subsequent screens for this group of patients. Given the more rigourous approach to detecting cervical disease which the new policy incorporates, the long-term benefits in terms of both costs and health benefits are expected to be greater than in the short-term.

7.5 Sensitivity Analyses

Given the expected impact of the new policy, particularly on clinic capacity, a series of sensitivity analyses were carried out through modifying other clinic protocols to ameliorate the implications of the new referral strategies. The impact of the following 6 such additional policy changes was modelled: -

- Refer women to colposcopy only after 3 borderline smears;
- Adopt an age-related screening interval, such that women aged 25-49 are screened every 3 years, and those aged 50-64 are screened every 5 years;

- Discharge women from the clinic after their treatment visit (i.e. offer no folow-up appointments);
- Treat CIN 1 immediately;
- See and treat all patients with high-grade disease;
- Discharge women with negative colposcopy to cytological surveillance.

As discussed in section 2.4, recommendations for strategies regarding the referral of patients to colposcopy services are produced by the NHSCSP directorate. A significant proportion of services were recognised to not follow national directives. The first change in clinical protocol examined were the adoption of the policy of patients requiring three borderline smears prior to referral. The model was constructed to assume current national policies regarding inadequate referral smear policies are followed to avoid complicating the process further. However, significant workload savings may also be achieved where this policy is not followed.

The new national guidelines also include other changes in recommnended practice. As discussed in section 2.4, previously patients were invited for their first smear at 20 to 24 years old, and patient recall patterns are organised locally, generally either 3 or 5 year periods. The new recommendation is for the first smear to be performed at the age of 25 and the patient then has 3 yearly smear until 49, with patients from 50 to 64 have 5 yearly smears.[4] This additional policy was modelled for both the "typical" and theoretically "least efficient" clinic. The "typical" service is modelled under current national practice data regarding "call-recall", while the "least efficient" service was originally modelled as accepting patients referred from a three year recall strategy.

As discussed previously, a significant number of services operate clinics with diagnosis and treatment at a single visit. This is known as "see and treat", and is generally thought to be a more efficient method of managing patients. This analysis presents the impact of adopting a see and treat policy for all patients with high-grade disease, for the typical and "least efficient" clinic types, but not for the "most efficient" clinic, which already incorporates this policy.

The questionnaire returns indicated a range of policies regarding management of patients with CIN 1. Altering the national policy to recommend that all such women are treated immediately, rather than being followed up, would obviate the need for extensive follow-up appointments, which is particularly relevant given the relatively slow progression rate between CIN 1 and CIN 2.

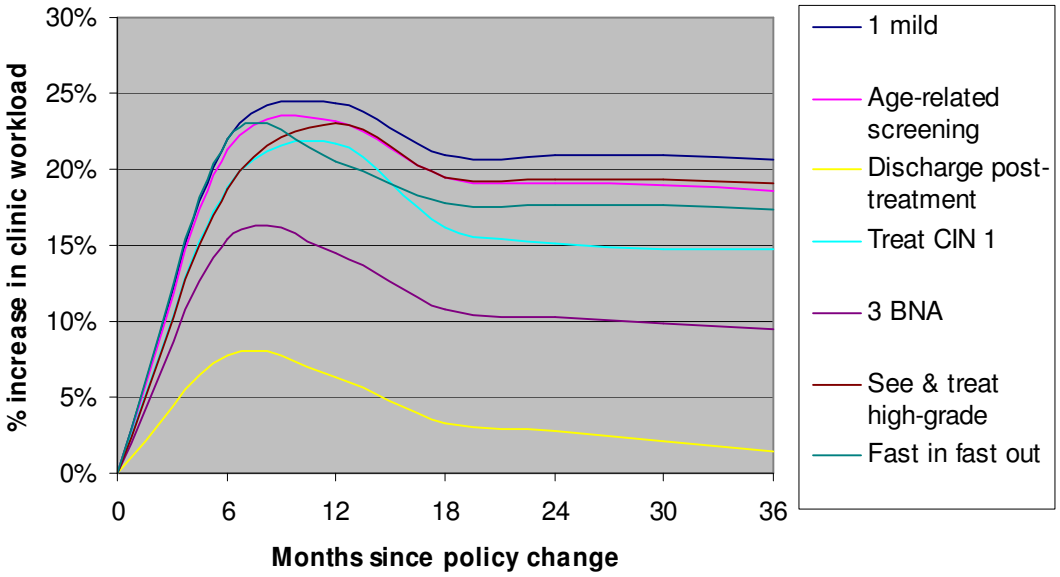
The predicted impact on clinic workload and disease detection of discharging all women from the clinic after their treatment visit was modelled for the "typical" and "inefficient" clinics (the "efficient" clinic type already incorporated this policy). This was demonstrated to be the area with greatest variability in current clinical practice nationwide.

New national policy recommendations include advice regarding the follow-up of patients if the referral smear is low-grade and the initial assessment is adequate and normal. In this circumstance the patient may be discharged to cytology surveillance. This approach is sometimes referred to as 'fast in – fast out', and its impact is explored further in these analyses.

7.5.1 Impact of policy changes on "typical" clinic

Figure (11) shows the predicted percentage increase in clinic workload for the "typical" clinic type, when compared to current practice, associated with the 5 additional policy changes mentioned above.

Figure (11): Impact of further policy changes on clinic workload (typical clinic)



The results demonstrate the relative impact of each individual policy change on the expected workload for a typical clinic. The greatest reduction in workload is likely to be seen through discharging women following treatment, with no further follow-up in the clinic setting. This is primarily because residual disease which would have been picked up at follow-up visits now goes undetected until the next screening round, and so the longer-term impact of changing this policy may not be as great as the data for the first 3 years suggest. The second largest reduction in workload is seen through referring women to the clinic only after three borderline smears; although this is already national policy, the questionnaire results suggest that many health authorities prefer to refer women after 2 borderline smears. If all women with CIN 1 were treated immediately rather than being entered into a surveillance programme, this would reduce the impact of the new mild dyskaryosis policy in terms of additional workload from 21% to around 15% after 3 years.

The impact of employing an age-related screening interval is seen to be minimal, as does that of treating all women with high-grade disease on a see and treat basis, since the majority of clinics already do this. Discharging patients with a negative colposcopy has

little effect for the same reason, plus the fact that only a small number of these women will have disease progression over a 6-month period.

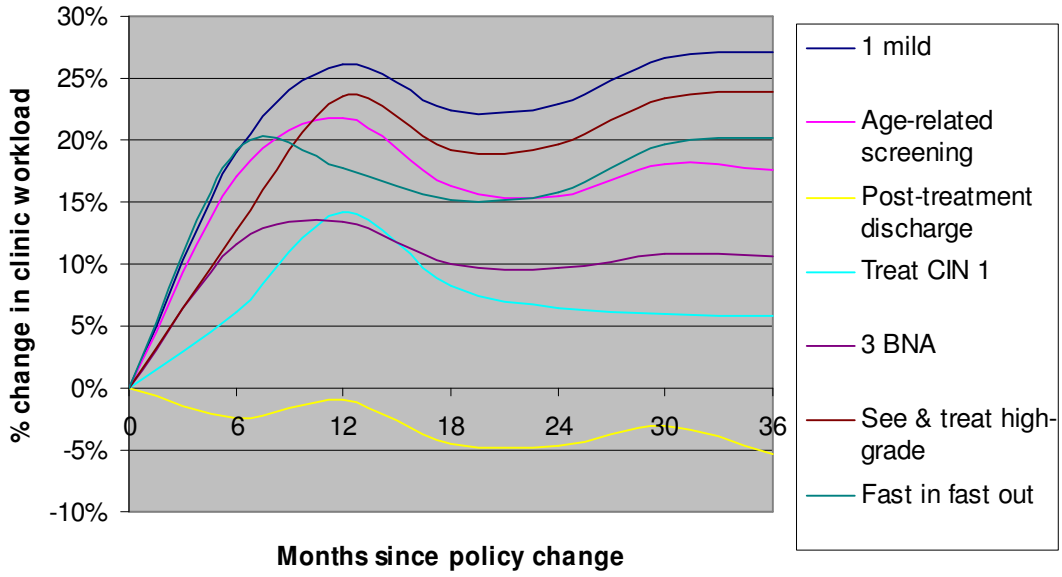
7.5.2 Impact of policy changes on "efficient" clinic

Given the nature of the policies incorporated within the theoreticaly "most efficient" clinic, it would be impossible to reduce clinic workload any further, and therefore no sensitivity analyses have been conducted within this scneario.

7.5.3 Impact of policy changes on "inefficient" clinic

Equivalent analyses were performed on the theoretically most inefficient clinic, to identify potential areas for improvement in terms of clinic efficiency. Figure (12) shows the predicted impact of such policy changes: -

Figure (12): Impact of further policy changes on clinic workload (inefficient clinic)



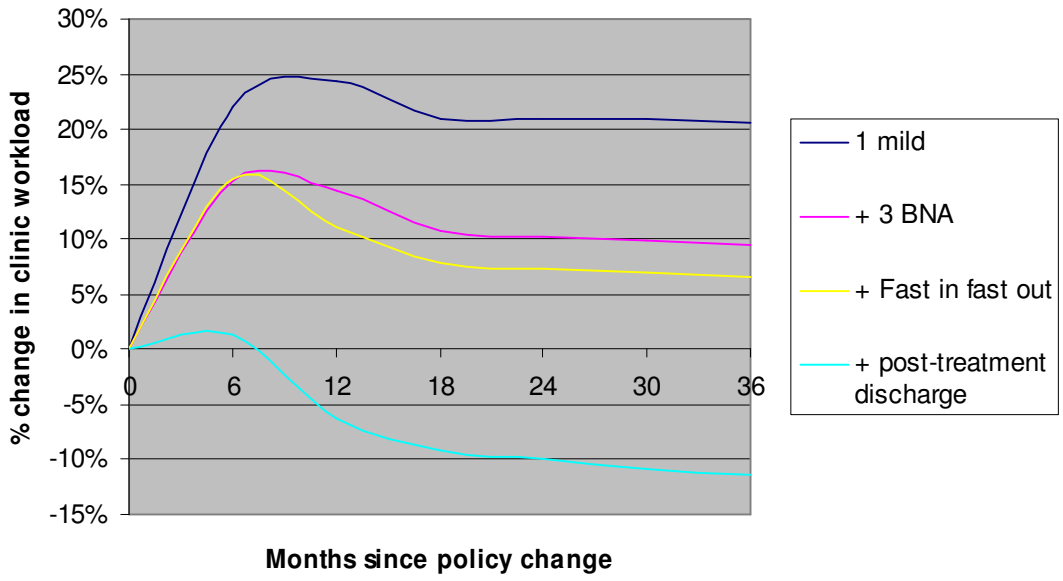
As with the "typical" clinic, the greatest improvement in efficiency could be achieved by discharging women back to the routine screening programme following treatment. Under

this scenario, the workload of such a clinic would be expected to be lower than before the new mild dyskaryosis policy was introduced. Again, this would not be the case in the longer term, as women with residual disease would be picked up at future screening rounds. Immediately treating all women with CIN 1 would also offset the impact of the mild policy considerably, with the percentage increase in workload being reduced from 27% at 3 years to around 6%. Referring women after 3 borderline smears would have a similar effect on overall workload, and would represent considerable savings in terms of the number of clinic sessions required and would also mitigate the impact on patient waiting times. The introduction of either an age-related nationwide screening programme, a policy of treating women with high-grade disease at the initial visit, or of discharging women with a negative colposcopy would have less of an effect.

7.5.4 National policy modelling

The final modelling for policy changes performed is the combined effects of changing clinical protocols. The results on workload and detection of high-grade disease of three changes in clinic policies implemented sequentially in the "typical" service are given as an example of the effects on services if these NHSCSP recommendations were introduced into clinical practice. These changes are shown incrementally for the typical clinic in Figure 13: -

Figure (13): Impact of NHSCSP recommendations on clinic workload ("typical" clinic)



These results emphasise the impact of adherence to national guidelines, particularly those relating to referral of women with borderline smears and of post-treatment follow-up. Adherence to all three policies in the future would reduce the level of clinic workload to a level below the corresponding figure prior to the mild dyskaryosis policy change.

7.6 Model validation

The first model validation performed is to compare the modelled services with the available national data. The total number of patients referred for colposcopy in the model was similar to those nationally (approx. 100,000 for abnormal cytology). The distribution of referred patients by smear category was also similar in the modelled services compared to national data returns. The estimates of the number of cancers detected in each period under the different policies was matched against incidence data from the latest Statistical Bulletin, which reported the number of cancers detected by screening in the 20-64 age group as 1,746. The pathway model predicted an incidence of 1,488 cancers per year, which when coupled with cancers detected via appointments for clinical indications (estimated to be 18% of all colposcopy clinic workload) gives a figure of

1,755. The model was validated further through analysis of the breakdown of referrals to colposcopy by smear result. These figures were compared with data from the 2001-02 KC65 returns, and found to be extremely similar.

8.0 Conclusions and discussion

Cervical screening directed towards the identification and treatment of 'pre-invasive' high-grade CIN has significantly reduced the incidence of, and mortality from, squamous carcinoma of the cervix in the UK. Appropriate selection of patients for referral to colposcopy services is fundamental to screening practice. Available evidence suggests that detection of high-grade disease is imporoved by changing current practice from two mild dyskaryosis smears being required prior to referral, to a single smear triggering colposcopy attendance. This is appreciated to increase number of patients referred to each service, but the full implications of a shift in policy are presented for here for the first time. The discussion of the implications of changing policies is divided into the sub-sections presented in the results above.

8.1 Clinical workload and detection of high-grade disease

8.1.1 Total clinic workload.

All services not currently seeing patients after a single mild dyskaryosis will experience significant increases in clinical workload if policy is changed. The numbers of extra clinics to cover demand associated with such a shift is related to current operational strategies. If the service is currently offering colposcopy appointments to patients in a wide variety of clinical situations (in this study "least efficient" service) then the total increase in number of clinics will be significant, with a 27% increase in workload over the first three years. The percentage change in workload over the same time period, is magnified (34.9%) for the "most efficient" service due to the limited number of clinic appointments currently generated per patient referred.

The "typical" service gives an indication of the national effect of implementing new guidelines. Although this "service" incorporates the 20% of services currently seeing patients after a single mild dyskaryosis, the average workload increase experienced in services nationwide would be 20.6% over three years.

8.1.2 Workload by clinical activity

The distribution of workload increases caused by new mild dyskaryosis referral is divided fairly evenly across areas of clinical activity: new referrals, surveillance colposopies and treatments. Increases in new referrals are characterised in the model by a large initial wave of workload. This is caused by the combined effect of those who are referred from the previous time period and who under the original strategy would have waited for repeat cytology, added to the patients within the time period following strategy change, who are referred with a single dyskaryosis. Once this period has passesd, the new referral group remains significantly elevated in all service types. Similar increases are seen in the surveillance groups for all service types, although very little surveillance is performed in the "most efficient" service under either referral strategy. As discussed in the results section, in this instance treatment is defined as any appointment intended to achieve treatment of CIN of any grade. Increases are also significant in all service types in this activity.

8.1.3 Detection of high-grade disease

To prevent cervical carcinoma by cervical screening, detection and treatment of high-grade disease is of paramount importance. In the results detection of high-grade disease, and by implication its treatment, is used as a surrogate for coloscopy success. The increase in detection of CIN 2/3 is significant in all service types, 16.5% for the "typical" service, 25.0% and 24.0% for "most" and "least" efficient, respectively. Detection is again characterised by an initial "peak" in detection, with the large volume of new patient referrals in the first six month period. However, increased detection of high-grade disease

is sustained in the model data at three years from change in referral policies, and is likely to persist at these levels until disease prevalence is reduced in the community by ongoing screening practice..

8.2 Waiting times

From a clinical perspective, the waiting time analyses are the hardest to interpret in terms of implications on service activity. The construction of the model required the services to be populated from "no patients" in the service. This is performed by recruiting patients to the theoretical services on the basis of current cytology result reporting and predicting disease transition from published research. In terms of clinic activity this includes CIN only and patient care resulting from this. True clinic activity is of course more complex. Some services are involved in the long term care of women previously treated for micro- and macro-invasive disease and in the care of women with vaginal, vulval or peri-/anal intraepithelial neoplasia.

As discussed below, the assessment of women with cervical abnormalities or gynaecologic symptoms is often performed in colposcopy clinics. Some patients may also require increased colposcopy surveillance as a result of being immunocompromised or as a consequence of HIV disease. This results in true clinic activity being far greater than the management of patients with pre-invasive cervical disease, and the ability of services to accommodate with a significant increase in workload without effects on target and recommended waiting times presented is inaccurate. What the results do demonstrate is the significant effect that new referral strategies will have on services, particularly those currently running few clinics per week and operating in an "inefficient" service manner.

8.3 Health Economics

Although a comprehensive economic analysis has not been performed due to inconsistencies between the clinic pathway model and the ScHARR model for assessing the cost-effectiveness of screening with LBC, the preliminary analysis suggests that the change in the mild dyskaryosis referral policy is cost-effective, with the benefits achieved through the improved detection of high-grade disease outweighing the additional costs of referring more women to the colposcopy clinics. Some of the costs of follow-up and surveillance were not included in the cost-effectiveness analysis, but these are not expected to increase the costs to a level at which the new policy would be deemed unacceptably expensive. The estimates derived suggest that the policy change is more cost-effectiven than many recent treatment interventions which have been recommended for use by NICE.

8.4 Modification of workload increases

It is expected that the increased detection of high-grade disease and QALY assessment is likely to be viewed as desirable to commissioning authorities for cervical screening. However, it is expected that some colposcopy services are likely to experience difficulty in implementing new referral guidelines without significant increases in the number of clinical sessions being operated. For some services increased activity will be inevitable, but others may find changes to clinical protocols advantageous to allow increased referral rates to be accommodated. It should be emphasised that every change in protocol may not be appropriate for each service, but they may provide a guide to where workload savings could be made.

8.4.1 Access policies

National referral policy recommendations have existed for 12 years. Referral strategies for borderline and inadequate smear categories have been the subject of extensive research and debate, and reflect the prevalence of true pre-invasive disease in these groups. However, there are psychological implications for patients following any non-

negative smear result, and reassurance may well be a driving force behind early referral of patients with these smear states.[57] In the questionnaire phase of this exercise, we identified that over 60% of NHS services currently accept access to colposcopy services after two smears demonstrating borderline nuclear change, contrary to national guidance.

In these services, considerable workload and waiting time savings are available by the adoption of the national recommendations; in the 'high intensity' service presented projected workload increases are reduced by over half (12.8% vs 27.0%), by the implementation of national criteria for borderline smear abnormalities alone; and just under half (10.9% vs 20.6%) for the "typical" service over three years. Detection of high-grade disease over three years is however predicted to be significantly affected by changing referral patterns as a consequence of the reduced number of patients undergoing colposopy. These reductions are 12.9% with single mild referral plus 3 borderline referral compared to 24.0% for the "least efficient" service over the first three years. This change is 9.8% vs 16.5% for the "typical" service. This significantly blunts the advantages of policy changes now these referral policies are in place, and will become an issue for debate where these two borderline referral policies are in place.

To avoid over complicating this model, services were assumed to see patients after three inadequate smears. In services seeing patients after a smaller numbers of consecutive inadequate smears, workload savings may be in the region of those for borderline smears, with less compromise in detection of high-grade disease, as these patients have much lower disease rates. This is discussed further in section 9.0.

Changing age-related call-recall policy is a fundamental change in practice recommended by the new national guidelines for practice.[4] This will have a fairly marginal effect on the "typical" service in terms of colposcopy workload (18.6% for new call-recall vs 20.6% for current practice), as a variety of policies exist nationally which are averaged to produce these results. More dramatic effects are seen when the individual modelled services are examined. The "least efficient" service currently operates a 3 yearly recall policy, and workload increases over three years reduce from 27.0% to 18.6% with the

change in policy. The “most efficient” service currently operates a 5 yearly recall policy at all ages. This service sees workload increases from 34.9% under current strategy to a dramatic 76.0%. Detection of high-grade disease is affected by any policy to increase screening intervals in any patient groups. However, in this model a single transition exists for CIN in patients of all ages. With increasing age, time of progression from one disease state to another may be reduced, thus detection of high-grade disease may be affected less than suggested above, as the model does not account for this.

Included in the national colposcopy guidelines for practice management was advice regarding patients with symptoms or signs suggestive of cervical disease. Previous advice recommended patients presenting with post-coital bleeding or an abnormal looking cervix with normal cytology were seen in colposcopy. It is recognised that few of these patients benefit from colposcopy services, the prevalence of pre-invasive disease is low in this group, and they often require gynaecology services in a wider setting. The new guidelines recommend these patients are seen in general gynaecology, seeing colposocpy as a tertiary service only if cytological abnormalities are detected. KC 65 returns indicate that 17% of colposcopy referrals are made for these “clinical indications”. In the national colposcopy questionnaire it was determined that 53% of colposcopy services are seeing patients if presenting with symptoms such as post-coital bleeding, and 70% of colposocpy services are seeing patients if the cervix is described as abnormal. These patients lie without the remit of this model which determines colposocpy practice based on cervical cytology referral only. It is not currently known how many patients will ultimately access colposocpy services after triage in general gynaecology. The possibility of incorporating this in future work is discussed further in section 9.0

8.4.2 Follow up after normal colposcopy

The new national colposcopy guidelines included new recommendations for the care of women referred with low-grade cytology found to have no evidence of CIN at colposcopy. 37.1% of colposcopy services currently perform colposcopy on a futher occasion for these patients, presumably to check for the presence of disese. Indeed, it has been demonstrated that women referred with abnormal cytology and normal colposcopy

assessment remain at higher risk of significant cervical disease than the background population. In addition, whilst the Receiver Operating Curves for colposcopy based on cytology approach an ideal 'fit', [58] false negative colposocopy remains inherent to the screening programme. However, repeat colposcopy may well have no basis in the immediate care of this patient group, and patients with a normal colposcopy are recommended to be 'discharged' to cytology follow-up.

This so-called 'fast in – fast out' approach puts added emphasis on making a reliable diagnosis for the patient at the first visit, but for services not currently operating this policy, significant workload savings are available. In the presented "least efficient" service, the total workload increase is reduced from 27.0% to 22.6% without significant effect on detection of high-grade disease. Due to the number of services currently operating this policy, the effect is reduced in the "typical" service (20.6% vs 18.9%), but again there is no effect on the detection of high-grade disease.

8.4.3 Management of low-grade disease

Currently there is no consensus on the best management of women with biopsy proven low-grade disease, with approximately 30% of the services in the UK offering treatment, whilst others recommend conservative expectant management. This is a marked reduction in the use of treatment for low-grade disease from previous questionnaires. Longitudinal studies demonstrate regression of CIN 1 in a significant number of patients. This evidence is used to support management strategies involving surveillance of low-grade cervical findings, particularly in patients of reproductive age, where multiple treatments may compromise the performance of the uterine cervix during pregnancy. However, services which employ a conservative approach will experience significant workload implications. Clinical workload implications may be ameliorated somewhat by shifting to more treatment orientated policies. For the "least efficient" service, even when CIN 1 treatment is performed at a deferred outpatient appointment, there are considerable workload savings available, total workload is predicted to increase only 6.7% with treatment for CIN 1, versus 27.0% with six-monthly surveillance. Again, the effect on the "typical" service is reduced by the number of services offering treatment at some stage in

follow-up of CIN 1. Detection of high-grade disease is not presented as this is unaffected by change in policy.

It will be noted that there are increases in workload with deferred treatment for CIN 1 in the "most efficient" service in treatment activity. This service is characterised by offering treatment on a "see & treat" basis to patients with CIN 1, and so increased appointments are generated by applying a policy of deferred treatment.

The treatment of CIN 1 is a matter for discussion in individual services, dependent on the availability of colposcopists trained in treatment modalities, and the needs of the patient group. However, the national trends observed in clinical practice are away from treatment based management policies for low-grade disease, and increases in use of treatment for patients in this group may be agreed to be undesirable.

8.4.4 Timing of treatment

Policies incorporating diagnosis and treatment of CIN in a single visit ('see & treat'), may be utilised to reduce workload implications of new referral strategies,and are widely used in the practice reported in the national questionnaire. Patients referred with moderate or severe dyskaryosis, in particular, are likely to have high-grade CIN requiring treatment, and in 61% of services this is offered. There are minimal workload savings to be made in all service types adopting this policy. While the number of clinic appointments for each patient referred reduces with the removal of a deferred treatment visit, the increased time required for a 'see & treat' visit, including the counselling involved, reduces any benefits which might instinctively be expected. Coupled with the need for training in what will constitute an extended role for many people practising colposcopists, it may be considered that any further increases in utilisation of 'see & treat' are undesirable and unattainable.

8.4.5 Post treatment follow-up

The most impressive workload savings are expected with the discharge of patients following treatment for CIN. The "typical" service, where workload is predicted to rise

by 27.0% under single mild referral, this is almost cancelled out by a change in policy to discharge post-treatment, with an increase of just 2.8% over three years. For the "least efficient" a predicted increase of 27.0% under single mild referral is reversed to a reduction of workload by 3.3% after three years by not offering follow up after treatment. In the national questionnaire the greatest range of clinical management policies was found in post treatment care. It is well documented that certain groups of patients are at risk of residual/recurrent disease, particularly patients over 50 years old, and those where disease is not fully removed at the internal (or endocervical) margin of treatment, and these "at risk" groups are often targeted for further colposcopy assessment. However, the role of colposcopy in this setting is debated, and the new national guidelines recommend that cytology is adequate assessment for the majority of patients, whereas it may be more appropriate to re-treat the small group of patients over 50 with evidence of disease at the internal resection margin. Services using colposopy extensively in patient follow-up after treatment may find significant savings made by reducing its use.

8.4.6 Combined changes to National policy

The final modelling results show the combined changes of the new national guidelines employed in the "typical" colposcopy service. Introducing the three guidelines: three borderline referral, "fast in – fast out" and discharge post-treatment, allows the referral of single mild referral with an overall reduction in workload of approximately 10%. However, this is associated with a reduction in the detection of high-grade disease from 10.1% to 6.0%.

8.5 Summary and validation

Single mild dyskaryosis referral is expected to, and in this modelling exercise, delivers improved detection of high-grade cervical pre-invasive disease. This, naturally, implies significant increases in colposcopy clinic activity for all services. Some services, in this report known as "inefficient" services, could accommodate this increased workload with changes in clinical practice. However, some changes in practice are seen to compromise detection of high-grade disease at least in the short-term. Some services, in this report

noted to approach the practice of an "efficient" services, cannot change clinical protocols to improve patient throughput, and may require significant increases in resources. This will be further exacerbated if changes in age-related "call-recall" strategy are also implemented to a region currently seeing patients on a five year recall basis.

In terms of model validation, due to the excellent response in colposcopy questionnaire return, the authors' confidence in the model is high because it is based on data from a significant proportion of national services. The modelled increases are not unprecedented. Pilot studies introducing the reflex testing of low-grade of low-grade smears for Human Papilloma Virus (HPV) and referral of patients who test positive, found high rates of virus positivity (>85%) in the mild dyskaryosis groups. As a consequence the majority of patients were referred after a single mild smear, and colposcoy services were quickly overwhelmed. In subsequent discussion, this increased workload was thought to represent a 'one-off' wave of referrals; the model presented predicts the increased workload will be sustained.

One service local to the authors' unit has shifted from two mild to single mild referral strategies, and reports a significant increase in colposcopy workload.
Conversely, another local unit has recently shifted from the 2 borderline to 3 borderline access policy, and is experiencing significant workload savings. It is hoped both these services will be amenable to examination of changes in workload for compare with the predicted modelled outcomes.

9.0 Further Work

The recommended "roll-out" of the use of Liquid-Based Cytology (LBC) as the primary screening method will have an impact upon the number of women being referred to colposcopy services, due to the reduction in inadequate smears from 9% to around 3%. This reduction would also reduce the number of women being referred to colposcopy

with persistently inadequate smears, many of whom test negative at colposcopy. It would be possible to re-model services with respect to LBC.

For many years it has been known that cervical cancer and CIN are caused by certain strains of Human Papilloma Virus (HPV). It is now possible to test for HPV on cervical swab samples and LBC diluent, which has led to areas of recommended implementation, for example, triage of low-grade smears and triage of patients following treatment. There is also scope for expansion of the model to include the impact on colposcopy services of the introduction of HPV testing in the community and in colposocpy practice.

The results presented here have attempted to give the nationwide impact of the new mild smear policy, in additional to the impact on two example services to demonstrate the likely range of the effect on colposcopy services. Of more practical use to clinicians, would be a version of the model into which each clinic's population data and clinical policies could be input, to predict the impact of the policy, and indeed that of any subsequent changes to policy management variables such as follow-up and surveillance. This could be in the form of a version of the model downloadable from the ScHARR website, which would enable decision making at a local level in order to improve clinic efficiency and throughput of patients.

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Appendix A: An excerpt from a conceptual model of clinical pathways