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R Wade,[1]* E Spackman,[2] M Corbett,[1] S Walker,[2] K Light,[1] R Naik,[3] M Sculpher[2] and A Eastwood[1]

[1]CRD/CHE Technology Assessment Group, Centre for Reviews and Dissemination, University of York, York, UK
[2]CRD/CHE Technology Assessment Group, Centre for Health Economics, University of York, York, UK
[3]Northern Gynaecological Oncology Centre, Gateshead, UK

*Corresponding author

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This report

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Abstract

Adjunctive colposcopy technologies for examination of the uterine cervix – DySIS, LuViva Advanced Cervical Scan and Niris Imaging System: a systematic review and economic evaluation

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[1]CRD/CHE Technology Assessment Group, Centre for Reviews and Dissemination, University of York, York, UK
[2]CRD/CHE Technology Assessment Group, Centre for Health Economics, University of York, York, UK
[3]Northern Gynaecological Oncology Centre, Gateshead, UK

*Corresponding author

Background: Women in England (aged 25–64 years) are invited for cervical screening every 3–5 years to assess for cervical intraepithelial neoplasia (CIN) or cancer. CIN is a term describing abnormal changes in the cells of the cervix, ranging from CIN1 to CIN3, which is precancerous. Colposcopy is used to visualise the cervix. Three adjunctive colposcopy technologies for examination of the cervix have been included in this assessment: Dynamic Spectral Imaging System (DySIS), the LuViva Advanced Cervical Scan and the Niris Imaging System.

Objective: To determine the clinical effectiveness and cost-effectiveness of adjunctive colposcopy technologies for examination of the uterine cervix for patients referred for colposcopy through the NHS Cervical Screening Programme.

Data sources: Sixteen electronic databases [Allied and Complementary Medicine Database (AMED), BIOSIS Previews, Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Database of Abstracts of Reviews of Effects (DARE), EMBASE, Health Management Information Consortium (HMIC), Health Technology Assessment (HTA) database; Inspec, Inside Conferences, MEDLINE, NHS Economic Evaluation Database (NHS EED), PASCAL, Science Citation Index Expanded (SCIE) and Science Citation Index (SCI) – Conference Proceedings], and two clinical trial registries [ClinicalTrials.gov and Current Controlled Trials (CCT)] were searched to September–October 2011.

Review methods: Studies comparing DySIS, LuViva or Niris with conventional colposcopy were sought; a narrative synthesis was undertaken. A decision-analytic model was developed, which measured outcomes in terms of quality-adjusted life-years (QALYs) and costs were evaluated from the perspective of the NHS and Personal Social Services with a time horizon of 50 years.

Results: Six studies were included: two studies of DySIS, one study of LuViva and three studies of Niris. The DySIS studies were well reported and had a low risk of bias; they found higher sensitivity with DySIS (both the DySISmap alone and in combination with colposcopy) than colposcopy alone for identifying CIN2+ disease, although specificity was lower with DySIS. The studies of LuViva and Niris were poorly

reported and had limitations, which indicated that their results were subject to a high risk of bias; the results of these studies cannot be considered reliable. The base-case cost-effectiveness analysis suggests that both DySIS treatment options are less costly and more effective than colposcopy alone in the overall weighted population; these results were robust to the ranges tested in the sensitivity analysis. DySISmap alone was more costly and more effective in several of the referral groups but the incremental cost-effectiveness ratio (ICER) was never higher than £1687 per QALY. DySIS plus colposcopy was less costly and more effective in all reasons for referral. Only indicative analyses were carried out on Niris and LuViva and no conclusions could be made on their cost-effectiveness.

Limitations: The assessment is limited by the available evidence on the new technologies, natural history of the disease area and current treatment patterns.

Conclusions: DySIS, particularly in combination with colposcopy, has higher sensitivity than colposcopy alone. There is no reliable evidence on the clinical effectiveness of LuViva and Niris. DySIS plus colposcopy appears to be less costly and more effective than both the DySISmap alone and colposcopy alone; these results were robust to the sensitivity analyses undertaken. Given the lack of reliable evidence on LuViva and Niris, no conclusions on their potential cost-effectiveness can be drawn. There is some uncertainty about how generalisable these findings will be to the population of women referred for colposcopy in the future, owing to the introduction of the human papillomavirus (HPV) triage test and uptake of the HPV vaccine.

Study registration: PROSPERO Record CRD42011001614.

Funding: The National Institute for Health Research Health Technology Assessment programme.

Contents

Glossary

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context but a glossary is provided for the non-specialist reader.

Acetowhitening Whitening effect following application of acetic acid to epithelial tissue, which is a sign of increased nuclear protein.

Adverse effect An abnormal or harmful effect caused by, and attributable to, exposure to a medication or other intervention, which is indicated by some result such as death, a physical symptom or visible illness. An effect may be classed as adverse if it causes functional or anatomical damage, causes irreversible change in the homeostasis of the organism, or increases the susceptibility of the organism to other chemical or biological stress.

APX 100 A digital image analysing system for detecting cancerous and precancerous cervical tissue. It works by measuring the resistivity (via electrical impedance spectroscopy) of cervical epithelial cells.

Cervical intraepithelial neoplasia A term describing abnormal changes in the squamous epithelial cells of the cervix. The disorder is graded according to its pathological progress, from CIN1 to CIN3.

Colposcope A magnifying instrument designed to facilitate visual inspection of the cervix.

Correlation meeting A meeting where the pathologists and colposcopists discuss the results and the management of patients who have clear colposcopic findings, but moderate or severe cytology results.

DySIS A digital video colposcope using dynamic spectral imaging for detecting cancerous and precancerous cervical tissue. It works, following application of acetic acid, by mapping the acetowhitening of the epithelium of the cervix (the DySISmap). [Note: Subsequent to the production of this report, DySIS Medical informed the assessment group that the current terminology for the DySIS technology is 'DySIS colposcopy' when referring to the DySISmap and colposcopy combined, and 'DySISmap' when referring to the DySISmap alone (this was previously known as 'DSI map' or 'DSI colour-coded map').]

Dyskaryosis A term describing abnormality of the cell nucleus (but not the cytoplasm).

Electrical impedance spectroscopy A form of spectroscopy that works by utilising electric current patterns.

Histology An abbreviation of histopathology.

Histopathology The microscopic study of tissue samples to enable diagnosis.

Human papillomavirus A type of virus that can affect the skin and the moist membranes lining parts of the body. Some types of human papillomavirus (known as high-risk human papillomaviruses) can cause dyskaryosis in the cells of the cervix.

Liquid-based cytology A method of preparing cervical samples for laboratory examination.

LuViva Advanced Cervical Scan A digital image analysing system for detecting cancerous and precancerous cervical tissue. It works by detecting biochemical and morphological changes at the cellular level (using optical spectroscopy).

NHS Cervical Screening Programme The programme set up in the UK aimed at detecting and treating early abnormalities which, if left untreated, could lead to cervical cancer.

Niris Imaging System A digital image analysing system for detecting cancerous and precancerous cervical tissue. It works using optical coherence tomography to produce a two-dimensional image of the tissue.

Optical coherence tomography A technique for creating two- or three-dimensional cross-sectional images of tissue using infrared light.

Pathologist The individual responsible for examining and interpreting cell and/or tissue samples.

Quality of life A concept incorporating all the factors that might impact on an individual's life, including factors such as the absence of disease or infirmity, as well as other factors that might affect the individual's physical, mental and social well-being.

Quality-adjusted life-year An index of health gain by which survival duration is weighted or adjusted by the patient's quality of life during the survival period. Quality-adjusted life-years have the advantage of incorporating changes in both quantity (mortality) and quality (morbidity) of life.

See and treat The removal of an abnormal area during colposcopy.

Spectroscopy An analytical method for studying the structural and biochemical features of tissue, most commonly by utilising electromagnetic spectra readings.

Speculum An instrument for opening a body cavity in order to allow visual inspection.

Statistical significance An estimate of the probability of an association (effect) as large or larger than what is observed in a study occurring by chance, usually expressed as a *p*-value.

Threshold analysis Amount of variation needed in the parameter values of a model to achieve a specified outcome. In the context of cost-effectiveness analysis in the UK NHS, this specified outcome is usually the cost-effectiveness threshold of £20,000–30,000 per additional QALY gained.

Transformation zone An area of the cervix where nearly all precancerous and cancerous changes occur.

List of abbreviations

AGUS	atypical glandular cells of undetermined significance
AiC	academic in confidence
ASC-H	atypical squamous cells with possible high-grade squamous intraepithelial lesion
ATP	according to protocol
CE	Conformité Européenne
CI	confidence interval
CIN	cervical intraepithelial neoplasia
CRD	Centre for Reviews and Dissemination
DSI	dynamic spectral imaging
DySIS	dynamic spectral imaging system
EAG	External Assessment Group
GP	general practitioner
HPV	human papillomavirus
hrHPV	high-risk human papillomavirus
HRQoL	health-related quality of life
HSIL	high-grade squamous intraepithelial lesion
ICER	incremental cost-effectiveness ratio
ITT	intention to treat
LBC	liquid-based cytology
LLETZ	large-loop excision of the transformation zone
LR	likelihood ratio
lrHPV	low-risk human papillomavirus
LSIL	low-grade squamous intraepithelial lesion
NICE	National Institute for Health and Clinical Excellence
NIHR	National Institute for Health Research
NPV	negative predictive value
NR	not reported
OCT	optical coherence tomography
ONS	Office for National Statistics
PCM	pseudocolour map
PPV	positive predictive value
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QALY	quality-adjusted life-year
SIGN	Scottish Intercollegiate Guidelines Network
STARD	STAndards for the Reporting of Diagnostic accuracy studies
TOMBOLA	Trial of Management of Borderline and Other Low-Grade Abnormal Smears

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.

Note

This monograph is based on the Technology Assessment Report produced for NICE. The full report contained a considerable number of data that were deemed commercial-in-confidence and/or academic-in-confidence. The full report was used by the Appraisal Committee at NICE in their deliberations. The full report with each piece of commercial-in-confidence and academic-in-confidence data removed and replaced by the statement 'commercial-in-confidence and/or academic in-confidence information (or data) removed' is available on the NICE website: www.nice.org.uk. The present monograph presents as full a version of the report as is possible while retaining readability, but some sections, sentences, tables and figures have been removed. Readers should bear in mind that the discussion, conclusions and implications for practice and research are based on all of the data considered in the original full NICE report.

Executive summary

Background

Cervical cancer is the most common cancer in women aged <35 years in the UK. Women in England between the ages of 25 and 64 years are invited for regular cervical screening every 3–5 years under the NHS Cervical Screening Programme. Most screening is conducted using liquid-based cytology (LBC).

Women with an abnormal cytology result, or repeated inadequate or borderline results, are referred for colposcopy. Colposcopy is used to visualise the cervix; if any abnormal area is identified, a biopsy is taken and sent for histopathological analysis to assess for the presence of cervical intraepithelial neoplasia (CIN) or cancer. CIN is a term describing abnormal changes in the cells of the cervix, ranging from CIN1 to CIN3 (which is precancerous).

Three adjunctive colposcopy technologies for examination of the uterine cervix have been included in this assessment: Dynamic Spectral Imaging System (DySIS) (developed by DySIS Medical, Edinburgh, UK), the LuViva Advanced Cervical Scan (developed by Guided Therapeutics, Norcross, GA) and the Niris Imaging System (developed by Imalux Corporation, Cleveland, OH). DySIS is a colposcope that incorporates a digital image analysis system [dynamic spectral imaging (DSI)], whereas LuViva and Niris are probes with image analysis systems, which are designed to be used in conjunction with a standard colposcope.

Objective

To determine the clinical effectiveness and cost-effectiveness of adjunctive colposcopy technologies for examination of the uterine cervix for patients referred for colposcopy through the NHS Cervical Screening Programme; the technologies under consideration are DySIS, LuViva and Niris.

Methods

This report contains reference to confidential information provided as part of the NICE appraisal process. This information has been removed from the report and the results, discussions and conclusions of the report do not include the confidential information. These sections are clearly marked in the report.

Clinical effectiveness

A systematic review of the evidence on the clinical effectiveness of DySIS, LuViva and Niris, compared with conventional colposcopy, for examination of the uterine cervix in patients referred for colposcopy through the NHS Cervical Screening Programme was performed. Sixteen electronic databases (including MEDLINE and EMBASE) and two clinical trials registries were searched from January 2000 to September–October 2011.

Data were extracted on study and participant characteristics and outcomes. Where sufficient data were available, the following diagnostic accuracy statistics [with 95% confidence intervals (CIs)] were calculated: sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR) and negative LR. Where data were missing from publications or other study reports, the authors were contacted.

The quality of the included studies was assessed using the QUADAS-2 quality assessment tool for diagnostic studies, along with additional review-specific questions. The included studies were

heterogeneous in terms of participant characteristics and the different comparator technologies used, therefore, meta-analysis was not appropriate; the studies were grouped according to the adjunctive technology used and a narrative synthesis was presented.

Cost-effectiveness

A systematic review was conducted to identify potentially relevant studies for inclusion in the assessment of cost-effectiveness of colposcopy and the colposcopy adjuncts (DySIS, LuViva and Niris). No economic evaluation studies were found which met the inclusion criteria. However, a number of studies were identified examining different points in the management pathway, which contained useful inputs for the modelling process, several of which were UK based. Following contact with the authors of these reports, we were able to gain access to a recent electronic model (Kim E-J. *Modelling the cost-effectiveness of human papillomavirus (HPV) testing for triage of women with low-grade abnormal cervical smears: a study within the TOMBOLA trial*. MSc thesis. Sheffield: The University of Sheffield; 2010) (referred to here as the Sheffield model), examining the cost-effectiveness of screening in the UK.

The model was developed to assess the cost-effectiveness of the three devices compared with colposcopy for examination of the uterine cervix for the detection of cancerous and precancerous cervical tissue in patients referred for colposcopy through the NHS Cervical Screening Programme. The model measured outcomes in terms of quality-adjusted life-years (QALYs) and costs are evaluated from the perspective of the NHS and Personal Social Services with a time horizon of 50 years. The model involved two stages: first, a decision tree to model the diagnostic and treatment pathways for patients referred to colposcopy from the NHS Cervical Screening Programme; and, second, a Markov model based on the Sheffield model, which simulates the natural history of patients and captures future cytological screening and referrals to colposcopy to estimate the outcomes of the initial diagnosis and treatment choices.

Cost-effectiveness was assessed using incremental cost-effectiveness ratios (ICERs). Results were presented for each reason for referral to colposcopy from the NHS Cervical Screening Programme, as well as for the whole population referred. Sensitivity analyses were undertaken to examine the impact of different assumptions and sources of uncertainty on results. Secondary analyses were also undertaken assuming a higher QALY decrement and cost associated with excision treatment biopsy, as these were shown to be of importance in the model. As a result of the weaknesses in the studies of Niris and LuViva, these devices were excluded from the main analysis, with only indicative analyses undertaken.

Results

Clinical effectiveness

The systematic review identified a limited evidence base for the three adjunctive colposcopy technologies: two studies of DySIS, one study of LuViva and three studies of Niris.

The two studies of DySIS were well reported; the most recent and most clinically relevant study found that the sensitivity of DySIS for identifying CIN2+ disease was statistically significantly higher than the sensitivity of conventional colposcopy, although specificity was significantly lower with DySIS. Taking both sensitivity and specificity into account, the overall diagnostic accuracy was similar to that of conventional colposcopy. The combination of DySIS (the DSI colour-coded map) and conventional colposcopy resulted in the highest result for sensitivity, although specificity was lowered further. Based on study quality assessment, these results are likely to be reliable.

Poor reporting of the remaining studies, along with a high risk of bias in certain areas and concerns about applicability, meant that the results for LuViva and Niris are likely to be unreliable and of limited clinical relevance.

Cost-effectiveness

In the base case, for most reasons for referral, colposcopy alone was dominated by DySIS or DySIS plus colposcopy (i.e. colposcopy alone had worse expected outcomes in terms of QALYs and was more costly than either of the DySIS arms). However, even in cases where colposcopy alone was not dominated by DySIS alone, DySIS alone was still cost-effective at accepted thresholds for cost-effectiveness, with ICERs of £593, £1545 or £1687 per QALY for the referral groups possible invasion, possible neoplasia or inadequate cytology, respectively. For all reasons for referral, DySIS alone was more costly and less effective than DySIS plus colposcopy (i.e. DySIS alone was dominated). Therefore, the base case indicates that DySIS plus colposcopy was cost-effective at accepted cost-effectiveness thresholds. These results were found to be robust by sensitivity analyses.

One feature of the model using base-case parameter values was that a higher specificity for a given management option resulted in worse outcomes and a higher ICER. This reflects the fact that the model suggests that treatment of CIN1 cases is more effective and cost-effective than watchful waiting with the base-case values for the cost and QALY decrement associated with an excision biopsy. This may suggest that these parameter values are too low. Separate secondary analyses were, therefore, undertaken in which the QALY decrement of treatment biopsy was increased (to 0.13 from 0.005 in the base case) or the cost of treatment biopsy was increased (to £2758 from £97 in the base case). Even with these values, DySIS alone and DySIS plus colposcopy appeared cost-effective for most of the reasons for referral and cost-effective for the overall (weighted) population.

Threshold analyses were also undertaken to find at what QALY decrement or cost of treatment biopsy DySIS alone or DySIS plus colposcopy would be considered not cost-effective for the total patient population at a threshold of £20,000 per QALY. It was established that the QALY decrement of treatment biopsy would have to be 0.38 (or 139 healthy days) for DySIS alone not to be cost-effective, or 0.42 (or 153 healthy days) for DySIS plus colposcopy not to be cost-effective, compared with colposcopy alone. The cost of treatment biopsy would have to increase to £7968 for DySIS alone or £8912 for DySIS plus colposcopy (compared with £97 in the base case) for either to appear not cost-effective compared with colposcopy alone at a cost-effectiveness threshold of £20,000 per QALY.

Two further analyses were undertaken comparing LuViva and Niris with DySIS plus colposcopy. As a result of the unreliability of the clinical evidence on the LuViva and Niris devices, these analyses are indicative only and should be interpreted with caution. Assuming the devices exhibit the same specificity of DySIS plus colposcopy, the sensitivity of LuViva would have to be 83% and the sensitivity of Niris 86% for either to be considered cost-effective compared with DySIS plus colposcopy at a threshold of £20,000 per QALY.

Conclusions

DySIS, particularly when combined with colposcopy, has higher sensitivity than conventional colposcopy alone. There is no reliable evidence on the clinical effectiveness of the other adjunctive colposcopy technologies, LuViva and Niris.

The results of the economic analysis suggest that DySIS plus colposcopy is less costly and more effective than both DySIS alone or colposcopy alone, and that these results are robust to the numerous sensitivity analyses that were undertaken. Given the lack of reliable evidence on LuViva and Niris, only indicative sensitivity analyses based on the costs of these devices were undertaken, which do not allow us to draw any conclusions regarding their potential cost-effectiveness.

There is some uncertainty about how generalisable these findings will be to the population of women referred for colposcopy in the future, owing to the introduction of the human papillomavirus (HPV) triage test and uptake of the HPV vaccine.

Implications for service provision

The introduction of any of these new devices may require additional staff training, which may result in additional upfront costs that were not considered in the analysis. These costs may be actual training costs paid to the manufacturer but might also be costs associated with the additional time or initial accuracy of staff as they learn to use the new device.

Suggested research priorities

In light of the risk of bias affecting the results of the studies of LuViva and Niris, further well-designed studies are needed to reliably evaluate their diagnostic accuracy. The bias risk was a result of the reference standard methodologies used, with further uncertainty about study reliability stemming from the unclear reporting in relation to other possible sources of bias.

Further research is needed to inform the appropriate management of CIN1 and assess the robustness of the current model findings regarding the cost-effectiveness of CIN1 treatment.

Future studies on the diagnostic accuracy of such technologies should provide results for each diagnostic category (clear, CIN1, CIN2, CIN3, possible invasion and possible neoplasia) rather than sensitivity and specificity at a single cut-off.

Study registration

This study is registered as PROSPERO Record CRD42011001614.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Chapter 1 Background and definition of the decision problem

Condition and aetiology

In 2007, 2828 women were diagnosed with cervical cancer in the UK, making it the 11th most common cancer in women, and accounting for around 2% of all cancers among women. Cervical cancer is the most common cancer in females aged <35 years; 702 women aged <35 years were diagnosed with cervical cancer in the UK in 2007.[1] Women will develop changes in the cervix many years before any progression to cancer. These precancerous changes are described as being high-grade cervical intraepithelial neoplasia (CIN); women may also develop low-grade CIN, which is not precancerous but can cause changes that can be detected at cervical screening.

Infection with certain genotypes of human papillomavirus (HPV), in particular HPV16 and HPV18, has been shown to be associated with the development of cervical cancer and CIN; almost all cervical cancers contain high-risk human papillomavirus (hrHPV) DNA. However, most HPV infections will not progress to CIN; the cell changes associated with HPV will regress to normal. Certain risk factors are associated with the progression of HPV infection to CIN, including the HPV genotype, early age at first intercourse, long duration of the most recent sexual relationship and cigarette smoking.[1]

Women in England who are between the ages of 25 and 64 years are invited for regular cervical screening every 3 years (if aged between 25 and 49 years) or every 5 years (if aged between 50 and 64 years) under the NHS Cervical Screening Programme.[2] Most screening is conducted using liquid-based cytology (LBC); a sample of exfoliated cells is brushed from the transformation zone of the cervix for assessment in a pathology laboratory. Cytological assessment is performed to detect nuclear abnormalities, which are described as dyskaryotic. The degree of dyskaryosis can range from mild to severe, or borderline changes may be seen. There are three main terminology systems for reporting cervical cytology results. *Table 1* shows a comparison of cytology classification systems.[3] At the scoping workshop, it was agreed that, where possible, the dyskaryosis terminology should be used in this assessment.[3]

Just under 3.3 million women aged between 25 and 64 years attended for cervical screening in 2009–10; the percentage of eligible women who were recorded as screened at least once in the previous 5 years was 78.9%. Approximately 3.7 million samples were examined in 2009–10, of which 3.4 million (92.9%) were submitted by general practitioners (GPs) and NHS community clinics (suggesting that they were part of the NHS Cervical Screening Programme).[4]

Overall, 2.9% of tests did not have a result, owing to an inadequate sample. This means that the sample did not contain sufficient cervical cells for analysis. This figure has dropped significantly (from approximately 9%) since the introduction of LBC, rather than the Papanicolaou test (known as the Pap test or smear test). Women with an inadequate sample should be recalled for a repeat test; if women have three consecutive inadequate results, they should be referred for colposcopy.

Table 2 presents a summary of cytology test results and management options for patients with an adequate test result, submitted by GPs and NHS community clinics. These recommendations are taken from the NHS Cervical Screening Programme guidelines published in 2010;[2] however, the management of patients will change with the introduction of new guidelines for HPV triage, implemented in 2011–12.[5] These are discussed further below.

TABLE 1 Comparison of cytology classification systems

Bethesda system	Dyskaryosis system	Papanicolaou system
Normal limits	Normal	I
Infection	Inflammatory atypia	II
Reactive and reparative changes		
Atypical squamous cells of undetermined significance	Squamous atypia/HPV atypia	IIR
LSIL	Mild dyskaryosis	
HSIL	Moderate dyskaryosis	III
	Severe dyskaryosis	IV
	Carcinoma in situ	
Squamous cell carcinoma	Squamous cell carcinoma	V

HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion.

TABLE 2 Cytology test results and management options

Result	Definition	Action[a]	Proportion (2009–10),[b] (%)
Negative	No nuclear abnormalities	Place on routine recall	93.2
Borderline changes	Nuclear changes that are not normal are present. Unsure whether the changes are dyskaryosis	Repeat the test in 6 months. Most will have reverted to normal. After 3 consecutive normal results, return to routine recall. If abnormality persists (three times) or worsens, refer for colposcopy. If in a 10-year period there are three borderline or more severe results, refer for colposcopy	3.8
Mild dyskaryosis	Nuclear abnormalities that are indicative of low-grade CIN	Refer for colposcopy (although it remains acceptable to repeat the test in 6 months instead – most will have reverted to normal after 6 months). Refer to colposcopy if changes persist on two occasions	1.9
Moderate dyskaryosis	Nuclear abnormalities reflecting probable CIN2	Refer for colposcopy	0.5
Severe dyskaryosis	Nuclear abnormalities reflecting probable CIN3	Refer for colposcopy	0.6

a Recommendations taken from Colposcopy and Programme Management.[2]

b Figures taken from Cervical Screening Programme England 2009–10.[4]

There were 155,414 referrals for colposcopy in 2009–10; 78.6% of these were as a result of screening and 17.5% were clinically indicated, while 3.9% were for reasons not otherwise specified. Of women referred for colposcopy via the NHS Cervical Screening Programme, 48.8% were referred for borderline changes or mild dyskaryosis, 12.3% were referred for moderate dyskaryosis and 15.8% were referred for severe dyskaryosis or worse. There were a total of 453,947 appointments at colposcopy clinics in 2009–10, 41.9% of which were new appointments, 7.9% were return appointments for treatment and 50.2% were follow-up appointments.[4]

In total, 27% of appointments were not attended: 2.6% were cancelled by the patient on the day, 10.2% were cancelled in advance, 10.5% were not attended with no advance warning and 3.7% were cancelled by the clinic.[4]

Overall, 63.5% of women attending for colposcopy had some treatment or procedure at their first attendance, the most common being diagnostic biopsy, carried out at 45.5% of first attendances. For women referred for low-grade abnormalities, the most common procedure at first attendance was diagnostic biopsy and for women referred for high-grade abnormalities it was excision. The majority of those women presenting with high-grade abnormalities who had either no treatment or only diagnostic biopsy at first attendance, are likely to have received therapeutic treatment at a subsequent attendance.[4]

New guidelines implemented in 2011/12 state that cytology samples from women with low-grade abnormalities (borderline changes or mild dyskaryosis) should be tested for hrHPV for triage for referral for colposcopy.[5] The test is performed on the LBC sample already obtained as part of the NHS Cervical Screening Programme. Women who test positive for hrHPV should be referred for colposcopy, whereas women who test negative for hrHPV should be returned to routine recall.

These new guidelines present the protocol for managing women in the NHS Cervical Screening Programme with the introduction of HPV triage.[5] The Guidelines for the NHS Cervical Screening Programme present additional treatment guidelines.[2]

Treatment and screening options available include:

1. return to NHS Cervical Screening Programme (3- or 5-year recall, depending on age)
2. refer for rescreen at 6 months, with or without colposcopy
3. a diagnostic (punch) biopsy
4. a treatment biopsy
5. a treatment biopsy followed by cancer treatment.

If colposcopic findings are clear but cytology results are moderate or severe, then patients are reviewed at a 'correlation meeting' where the pathologists and colposcopists discuss the results and the management of patients. There is some variation in patient management among clinicians. Treatment and screening options are discussed further in *Chapter 2* (see *Model inputs*).

The patient group of interest for this assessment is women referred for colposcopy through the NHS Cervical Screening Programme. Women referred because of symptoms indicative of cervical cancer (e.g. postcoital bleeding or appearance suggestive of cancer) are not of relevance to this assessment. Where possible, separate analyses will be performed according to cytology findings; these technologies may be more appropriate for patients with borderline changes, or mild or moderate dyskaryosis, as more severe abnormalities are easier to detect with standard colposcopy.

Description of the technologies under assessment

Three technologies have been included in this assessment: Dynamic Spectral Imaging System (DySIS), LuViva Advanced Cervical Scan and Niris Imaging System. All three are used as an adjunct to standard colposcopy, although LuViva also aims to reduce the number of patients requiring a colposcopy by screening out some patients referred for colposcopy. DySIS is a colposcope that incorporates a digital image analysis system [dynamic spectral imaging (DSI)], whereas LuViva and Niris are probes with image analysis systems designed to be used in conjunction with a standard colposcope.

DySIS (developed by DySIS Medical, Edinburgh, UK)

The Dynamic Spectral Imaging System (DySIS) is a digital video colposcope that incorporates a digital image analysing system (DSI) designed to detect cancerous and precancerous cervical tissue. DySIS can be used for full colposcopic evaluations of the vulva, vagina and cervix. DySIS maps the whitening effect following application of acetic acid (acetowhitening) on the epithelium of the cervix, to assist the clinician in selecting areas for biopsy and treatment. It does this by producing a quantitative measurement of the

rate, extent and duration of acetowhitening, which is highly correlated with the altered structure and functionality of abnormal epithelial cells of the cervix. The dynamic map produced (known as DySISmap) can be overlaid on a colour image to assist in determining the presence and grade of any neoplastic lesion. DySIS is designed to work in conjunction with a bespoke DySIS speculum.

DySIS consists of an optical head with a white light-emitting diode for uniform illumination, magnification optics coupled to a digital colour charged, coupled device camera for image capture, and a computer and control electronics unit with a thin-film transistor monitor for image and data display. Linear polarisers are used in both the imaging and illumination pathways to reduce surface reflection (which might obscure the acetowhitening effect). The optical head does not come into contact with the tissue and magnifies images between 10 and 27 times.[6] It is mounted on a mechanical arm to position and stabilise it, and locked on to an extension shaft attached to the speculum, to ensure a stable field of view during image acquisition. For this reason, the speculum used with DySIS is different from the standard speculum used in colposcopy and gynaecology practice. The average length of use per examination is <15 minutes.

New users can be trained in the use of DySIS, and in interpreting the DySISmap, in 2–4 hours. DySIS has a CE (Conformité Européenne) mark and the cost in the UK ranges from £18,000 to £22,000. Costs for specula are £3.50 per examination.[3]

LuViva Advanced Cervical Scan (developed by Guided Therapeutics, Norcross, GA)

LuViva distinguishes between normal and diseased tissue by detecting biochemical and morphological changes at the cellular level. This is done using optical spectroscopy; light is directed at the cervix and the resulting fluorescence and reflectance spectra are collected and analysed. Areas with suspected disease are then identified and displayed. LuViva consists of a base unit with a results display, and a single-use guide, which is placed on the surface of the cervix.[7] LuViva is intended to be used before colposcopy to eliminate unnecessary colposcopies; a subset of patients would then go on to have colposcopy for additional assessment or to allow 'see and treat'. The average length of use per examination (additional to colposcopy) is around 2 minutes.

New users can be trained in around 30 minutes. LuViva costs £11,500 and the single-use guide costs £17.25 per patient.[3] It was expected to receive a CE mark in 2012.

Niris Imaging System (developed by Imalux Corporation, Cleveland, OH)

The Niris Imaging System utilises optical coherence tomography (OCT) and is designed to work in conjunction with a standard speculum. Its imaging console produces near infrared light which is directed at the cervix. Optical light is backscattered from the tissue, collected by a detachable fibre optic probe, and combined with an internal reference signal to produce a high spatial resolution two-dimensional image of the superficial tissue microstructure. The intensity of light reflected back is a function of tissue structure and content, allowing differentiation of normal and abnormal tissue.

The system includes built-in protocols for image comparison with automated calculations for intensity and distance, with raw data also reported. Images can be monitored over time, allowing side-by-side comparisons of a patient's results from two time periods (images are exportable to an ancillary monitor). Niris is used following colposcopy in order to evaluate all abnormalities found during colposcopy.

Niris probes have a limited useful life of around 200 patient procedures but can be processed for re-use. The average length of use per examination (additional to colposcopy) is around 4 minutes. A probe sheath is used to provide physical stability and help prevent cross-contamination.

New users can be trained in around 2 hours. The Niris Imaging System costs US$49,500 (around £31,000) plus taxes and shipping. The probe costs US$2700 (around £1700) and a disposable sheath costs US$30

(around £19).[3] The device has received a CE mark and is now available in the UK. [Note: this is based on subsequent information from Imalux Corporation.]

Comparators

Standard colposcopy, with directed biopsy/treatment when necessary, is the current usual management for women referred with abnormal cytology results. A colposcope is a binocular field microscope used to examine the cervix following sequential application of saline, 3–5% acetic acid, and sometimes Lugol's iodine to identify any epithelial changes or capillary vessel patterns suggestive of disease. Histological examination of any biopsied tissue, which is the gold standard for diagnosis of CIN or invasive cervical cancer, is then undertaken. The initial outcome of colposcopy is classified as being adequate, where the whole of the transformation zone (and any lesions) can be viewed, or inadequate, where full visualisation is not possible, and where further investigation may be required. The skills of the colposcopist relate to training, experience, and the volume of patients seen. Colposcopy involves a significant amount of subjective assessment – results from the same patient may vary when assessed by different colposcopists.[8] Details of referral cytology results, other clinical information, the type of management available and the number of biopsies taken are also relevant when interpreting the results of colposcopy.

Typical durations of colposcopic procedures are 20 minutes for a new patient in whom large-loop excision of the transformation zone (LLETZ) is unnecessary, 30 minutes for a new patient who needs a LLETZ, and 15 minutes for a follow-up appointment (information supplied by clinical advisor). Colposcopes are also used for identifying other clinical conditions, such as vulval or vaginal intraepithelial neoplasia.

A meta-analysis of nine studies published in 1998 estimated the sensitivity and specificity of colposcopy as being 96% and 48%, respectively, for detecting normal tissue from any abnormal tissue, and 85% and 69%, respectively, for differentiating between normal/low-grade CIN and high-grade CIN/cancer,[9] although most of the included studies appeared to be subject to bias.[10] More recently, better-quality studies have reported a sensitivity of around 57% for detecting CIN2+[11] and around 56% for detecting CIN3+.[12]

A standard colposcope costs around £17,500 (information provided by clinical advisors) and a disposable speculum costs £2.

Care pathways

Women with an abnormal cytology result, or repeated inadequate or borderline cytology results, are referred for colposcopy. According to the new HPV triage guidelines implemented in 2011–12, women with a borderline or mild dyskaryosis result should be referred for colposcopy only if they also test positive for hrHPV.[5] Colposcopy is used to visualise the cervix; if any abnormal area is identified then a biopsy is taken and sent for histopathological analysis. Colposcopy clinics are usually located within gynaecology or genitourinary medicine departments of general hospitals, although some colposcopy clinics may take place in primary care in the future.

Outcomes

The clinical outcomes of interest are diagnostic test accuracy outcomes (e.g. sensitivity and specificity), adverse effects and patient experience. Where other patient health outcomes are reported (e.g. morbidity and mortality from cancer or treatment) these will be included in the assessment.

Decision problem

The aim of this project is to determine the clinical effectiveness and cost-effectiveness of adjunctive colposcopy technologies for examination of the uterine cervix for patients referred for colposcopy through the NHS Cervical Screening Programme; the technologies under consideration are DySIS, LuViva Advanced Cervical Scan and Niris Imaging System.

Chapter 2 Assessment design and results by condition or aetiology

Systematic review of clinical effectiveness

Background

A systematic review was undertaken to assess the clinical effectiveness of adjunctive colposcopy technologies DySIS, LuViva Advanced Cervical Scan and Niris Imaging System for patients referred for colposcopy through the NHS Cervical Screening Programme.

The original scope for the assessment also included the APX 100 device (developed by Zilico Ltd, Manchester, UK).[3] However, this technology was removed from the assessment in December 2011, after the inclusion screening stage of the assessment.

Methods for reviewing clinical effectiveness

The systematic review was conducted following the general principles recommended in the Centre for Reviews and Dissemination (CRD) guidance[13] and the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement.[14]

Search strategy

The literature search aimed to systematically identify research related to the clinical effectiveness and cost-effectiveness of adjunctive colposcopy technologies.

The base search strategy was constructed using MEDLINE and then adapted to the other resources searched. The search included the following components:

1. terms for cervix, *and*
2. terms for colposcopy (including both general colposcopy terms as well as specific technologies).

Searches of major bibliographic databases were limited by date (2000 onwards) reflecting the date of development of the new technologies. No language, study design or other limits were applied. Reference lists of all included studies were hand-searched to identify further relevant studies. Where necessary, authors of eligible studies were contacted for further information.

Search strategies were developed by an information specialist with input from the project team. The search strategy was checked by a second information specialist. Sources of information were identified by an information specialist with input from the project team.

As the technologies involved are relatively new, particular attention was given to identifying sources for ongoing trials and conference reports (by searching specialist sources such as Inside Conferences and ClinicalTrials.gov). Details of the search strategies are presented in *Appendix 1*.

The following resources were searched for relevant clinical effectiveness and cost-effectiveness research:

- Allied and Complementary Medicine Database (AMED): via OvidSP, using the segment 1985 to September 2011, searched on 22 September 2011
- BIOSIS Previews: via Dialog, using the segment 1993 to 2011 week 2 October, searched on 19 October 2011

- Cochrane Database of Systematic Reviews (CDSR): via Wiley Cochrane Library website, Issue 9 of 12, September 2011, searched on 22 September 2011
- Cochrane Central Register of Controlled Trials (CENTRAL): via Wiley Cochrane Library website, Issue 3 of 4, July 2011, searched on 22 September 2011
- Cumulative Index to Nursing and Allied Health Literature (CINAHL): via EBSCO, using the segment 1981 to 16 September 2011, searched on 22 September 2011
- ClinicalTrials.gov: via website www.clinicaltrials.gov/, using the segment to September 2011, searched on 28 September 2011
- Current Controlled Trials (CCT): via website www.controlled-trials.com/, using the segment to September 2011, searched on 28 September 2011
- Database of Abstracts of Reviews of Effects (DARE): via Wiley Cochrane Library website Issue 3 of 4, July 2011, searched on 22 September 2011
- EMBASE: via OvidSP, using the segment 1996 to week 37 2011, searched on 22 September 2011
- Health Management Information Consortium (HMIC): via OvidSP, using the segment 1985 to September 2011, searched on 22 September 2011
- Health Technology Assessment (HTA) database (via Wiley Cochrane Library website Issue 3 of 4, July 2011, searched on 22 September 2011
- Inspec: via OvidSP, using the segment 1969 to week 36 2011, searched on 22 September 2011
- Inside Conferences: via Dialog, using the segment 1993 to 18 October 2011, searched on 19 October 2011
- MEDLINE: via OvidSP, using the segment 1948 to September week 2 2011, searched on 22 September 2011
- NHS Economic Evaluation Database (NHS EED): via Wiley Cochrane Library website Issue 3 of 4, July 2011, searched on 22 September 2011
- PASCAL: via Dialog, using the segment 1973 to 2011 week 2 October, searched on 19 October 2011
- Science Citation Index Expanded (SCIE): via Web of Knowledge, using the segment 2000 to 22 September 2011, searched on 23 September 2011
- Science Citation Index (SCI) – Conference Proceedings: via Web of Knowledge, using the segment 1990 to 22 September 2011, searched on 23 September 2011.

Additional searches were conducted to identify systematic reviews of colposcopy in an attempt to ascertain the diagnostic accuracy of colposcopy:

- CDSR: via Wiley Cochrane Library website Issue 10 of 12, October 2011, searched on 25 October 2011
- DARE: via CRD administration database, using the segment to 25 October 2011, searched on 25 October 2011
- DARE: via Wiley Cochrane Library website Issue 4 of 4, October 2011, searched on 25 October 2011.

The following websites were searched for guidelines and care pathways:

- Scottish Intercollegiate Guidelines Network (SIGN) (www.sign.ac.uk/, searched on 16 June 2011)
- National Institute for Health and Clinical Excellence (NICE) (www.nice.org.uk/, searched on 16 June 2011)
- National Guideline Clearinghouse (www.guidelines.gov/, searched on 16 June 2011)
- National Institute for Health Research (NIHR) Health Technology Assessment programme (www.hta.ac.uk/, searched on 16 June 2011)
- NHS Evidence (www.evidence.nhs.uk/, searched on 16 June 2011)
- TRIP database (www.tripdatabase.com/, searched on 16 June 2011).

Inclusion and exclusion criteria

Two reviewers independently screened all titles and abstracts. Full paper manuscripts of any titles/abstracts that appeared to be relevant were obtained, where possible, and the relevance of each study independently assessed by two reviewers according to the inclusion and exclusion criteria below. Studies

that did not meet all of the criteria were excluded and their bibliographic details listed with reasons for exclusion. Any discrepancies were resolved through consensus, with involvement of a third reviewer when necessary.

As stated earlier, the original scope for the assessment also included the APX 100 device, developed by Zilico Ltd.[3] Since this technology was removed from the assessment in December 2011, after the inclusion screening stage of the assessment, inclusion criteria refer to the APX 100 device.

- *Study design* Comparative studies, including diagnostic test accuracy studies and controlled trials, were included in the evaluation of clinical effectiveness, as this study design allows a comparison to be made between the new technology and current practice, which is essential for the economic model.
- *Intervention* Studies assessing DySIS, LuViva Advanced Cervical Scan, Niris Imaging System or APX 100, alone or alongside colposcopy, were included in the evaluation of clinical effectiveness.
- *Comparators* Studies that compared one of the adjunctive colposcopy technologies with standard colposcopy were included in the evaluation of clinical effectiveness.
- *Participants* The population of interest is women referred for colposcopy through the NHS Cervical Screening Programme. Therefore, studies of women referred for colposcopy because of an abnormal cytology result were included in the evaluation of clinical effectiveness. Studies that also included women referred for colposcopy because of symptoms indicative of cervical cancer (e.g. postcoital bleeding) or women referred for colposcopy for follow-up of CIN were also eligible for inclusion; however, studies that included only women referred for symptoms or for follow-up were not eligible for inclusion.
- *Outcomes* The clinical outcomes of interest were diagnostic test accuracy outcomes (e.g. sensitivity and specificity), adverse effects and patient experience. Where other patient health outcomes were reported (e.g. morbidity and mortality from cancer or treatment), these were also included in the assessment.

Data extraction strategy

Data on study and participant characteristics and outcomes were extracted by one reviewer using a standardised data extraction form and independently checked for accuracy by a second reviewer. Disagreements were resolved through consensus, with involvement of a third reviewer when necessary.

Where sufficient data were available, the following diagnostic accuracy statistics [with 95% confidence intervals (CIs)] were calculated, for each study, using the Canadian Institute of Health Research's Knowledge Translation statistics calculator:[15] sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR), and negative LR. Subsequently, accuracy was also calculated (the proportion of true-positive and true-negative results).

To allow consistency when comparing studies, in our results section we have reported our calculated results, rather than those reported in the study reports (as our results sometimes differed slightly from those in the study reports). Where data were missing from publications or other study reports, the authors were contacted (via NICE in the case of the manufacturers of the technologies). Data from multiple publications of the same study were extracted as a single study. The data extraction tables are presented in *Appendix 2*.

Quality assessment strategy

The quality of the included studies was assessed using the QUADAS-2 quality assessment tool for diagnostic studies.[16] As well as adding review-specific questions to domains 2 and 3, three further quality-related questions were assessed (see *Appendix 3* for details). The assessment was performed by one reviewer and independently checked by a second. Disagreements were resolved through consensus, with involvement of a third reviewer when necessary. Further details about QUADAS-2 and results of the quality assessment are presented in *Chapter 2* (see *Quality of research available*) and *Appendix 3*.

Data analysis

In view of the heterogeneity between the included studies, in terms of participant characteristics and the different comparator technologies used, formal meta-analysis was not appropriate. Therefore, the studies were grouped according to the adjunctive technology used and a narrative synthesis was presented.

Results of the review of clinical effectiveness

Quantity of research available

A total of 7835 records were identified from the clinical effectiveness searches and an additional 69 records were identified via hand-searching or contact with the manufacturers (via NICE) (*Figure 1*).

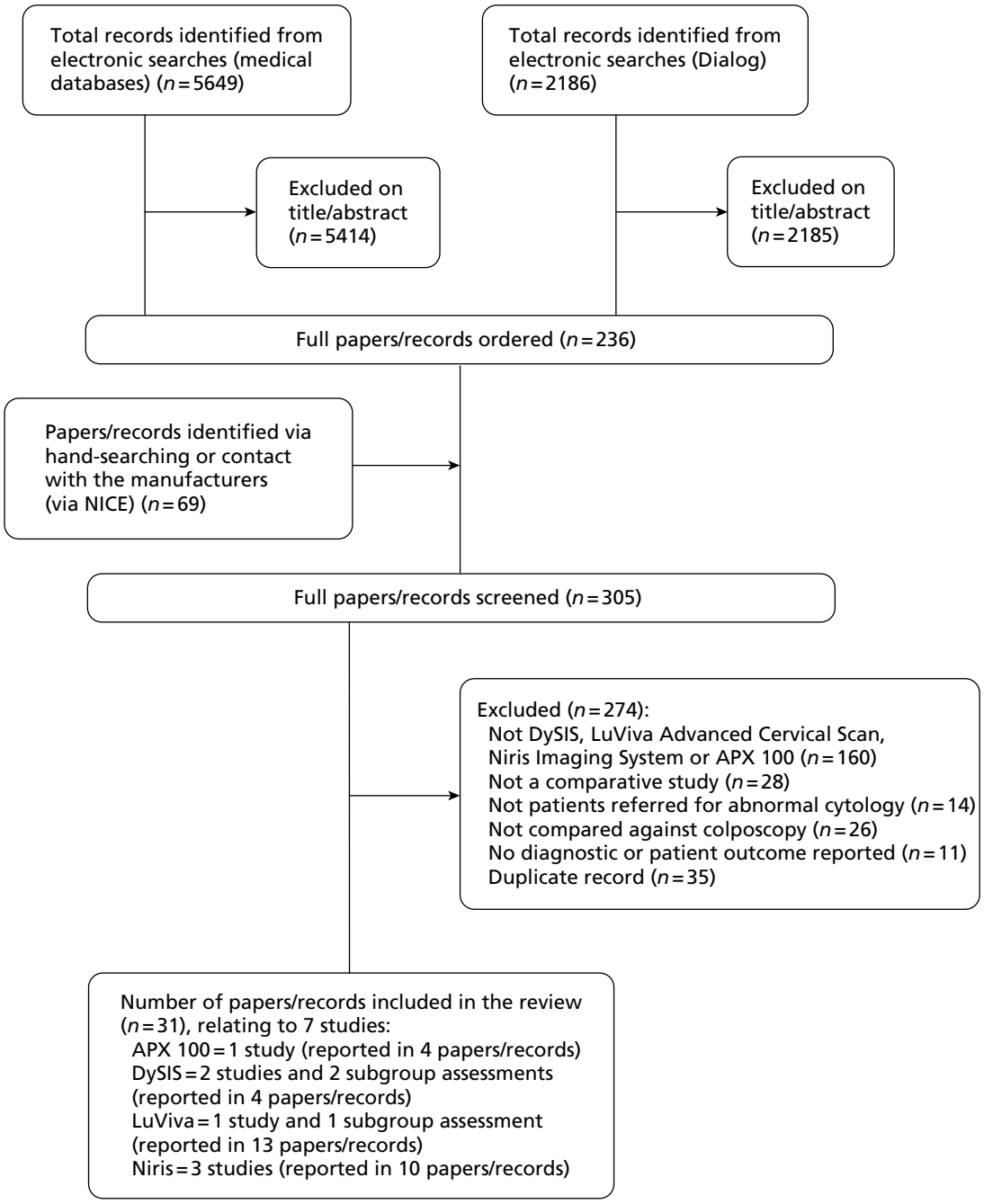


FIGURE 1 Flow diagram of the study selection process.

Seven studies (reported in 31 references) met the inclusion criteria. Details of studies excluded at the full publication stage are provided in *Appendix 4*.

On 21 December 2011, after we had finished screening studies for inclusion, we were informed by NICE that the APX 100 device, developed by Zilico Ltd, should be omitted from the assessment (one study, reported in four references). Therefore, six studies (reported in 27 references) were included in the review.

There were two main studies of the DySIS technology[6,17] and two additional subgroup assessments; the two main studies[6,17] were published in full, whereas one of the subgroup assessments was an unpublished draft manuscript (Zaal *et al*., The VU University Medical Center, Amsterdam, the Netherlands, 2011) and the other subgroup assessment[18] was reported in a conference abstract.

There was one study (Flowers *et al*., University of Emory School of Medicine, Atlanta, GA, 2011) and one subgroup assessment[19] of the LuViva Advanced Cervical Scan. The main study was an unpublished draft manuscript, whereas the subgroup assessment was reported in a conference poster.[19] The remaining 11 records were conference abstracts,[20–23] presentations,[24–26] a flyer,[27] a ClinicalTrials.gov record,[28] the manufacturer's presentation for NICE[29] and the manufacturer's response to a question from the US Food and Drug Administration (FDA).[30] In addition, we received further clarification of methods and additional results via personal correspondence with the manufacturer on a number of occasions. However, there were some inconsistencies in the information we received; therefore, we are not entirely confident in the accuracy of these additional data. Results data received via personal correspondence have been highlighted as such in the summary of study characteristics and results (see *Table 6*) and the data extraction tables in *Appendix 2*.

There were three studies of the Niris Imaging System, all published in full.[31–33] The remaining seven records were conference abstracts,[34–35] presentations[36] and posters,[37–38] the draft manuscript for one of the published papers (Liu *et al*., Peking University Shenzhen Hospital, Shenzhen, China, 2009) and a draft book chapter that described one of the published studies.[39]

Quality of research available

The QUADAS-2 tool, developed to improve, and to allow greater rating transparency than the original QUADAS tool, separates the evaluation of study quality into two main areas: risk of bias, and concerns regarding applicability. The tool consists of four domains: patient selection, index test, reference standard, and flow and timing. For individual studies each domain is assessed as being at a high, low, or unclear risk of bias, with the first three domains also assessed in terms of applicability concerns (also using high, low, or unclear ratings). The domains are supported by signalling questions, to help judge risk of bias.[16]

Table 3 summarises the results of the QUADAS-2 assessments. Across almost all of the studies there were few applicability concerns in relation to appropriate patient recruitment and reference standard use. However, for the majority of studies, there were often difficulties in appraising risk of bias due to poor reporting, and there were also various applicability concerns about the conduct or interpretation of the adjunctive technologies. In general, study quality differed according to the type of adjunctive technology.

DySIS

The two DySIS studies were judged to be at low risk of bias in terms of both patient selection and conduct and interpretation of the DySIS and colposcopy examinations.[6,17] However, there were applicability concerns in both studies relating to the conduct of colposcopy; video colposcopy using the DySIS colposcope was used, rather than the conventional colposcopy methods and equipment used in the NHS. The accuracy of colposcopy in these studies may therefore not be an accurate reflection of current NHS practice. Furthermore, in the earlier study a precommercial model was used, raising both applicability and bias concerns; around one-third of patients were excluded, largely due to equipment or software developmental problems.[17] These problems lessened during the later study, although 13% of patients were still excluded.[6] The earlier study clearly reported that histopathologists were unaware of DySIS results prior

to assessing biopsies;[17] details were unclear for the later study.[6] [Note: DySIS Medical have subsequently confirmed that histopathologists were unaware of DySIS results prior to assessing biopsies for this study also.]

LuViva Advanced Cervical Scan

The only study of LuViva (Flowers *et al*., University of Emory School of Medicine, Atlanta, GA, 2011, unpublished) utilised two prototype systems that were referred to as LightTouch, rather than LuViva. The risk of bias assessment was hindered by poor reporting; it was unclear whether patients were enrolled consecutively, and there were uncertainties regarding possible bias arising from the conduct of the tests (most importantly, there was a lack of reporting on the level of training LightTouch assessors had been given). It was unclear whether the standard of care results could possibly have been influenced by knowledge of the biopsy results. The reference standard biopsy procedure was also poorly reported. After seeking further clarification from the manufacturers, it became apparent that only areas seen as being abnormal according to colposcopy were biopsied, with endocervical curettage and/or diagnostic excision biopsy being used for other patients. Applicability concerns regarding the conduct and interpretation of the tests were low for standard of care (where results were interpreted in the knowledge of both cytology and HPV test results) and high for LightTouch (where the cytology and HPV results were not used).

Niris Imaging System

For all three studies of the Niris Imaging System there was an unclear risk of bias in terms of patient selection (none of the studies indicated whether or not patients were recruited consecutively).[31–33] [Note: Imalux Corporation have subsequently confirmed that patients were enrolled consecutively in the study by Liu *et al*.[32]] Similarly, all three studies were at an unclear risk of bias arising from the conduct of the tests (arising particularly from the absence of reporting on the level of training Niris assessors had been given). [Note: Imalux Corporation have subsequently confirmed that in the study by Liu *et al*.[32] expert colposcopists undertook the colposcopy examination and an OCT expert provided the OCT impression.] The risk of bias relating to the conduct and interpretation of biopsies was low in the two studies reporting that Niris images were anonymised,[31,33] but was unclear in the remaining study.[32] [Note: Imalux Corporation have subsequently confirmed that histopathologists were unaware of Niris results prior to assessing biopsies for this study also.] The most recent study was at a high risk of bias for the flow and timing domain, since biopsies were taken only from suspicious areas (meaning false-negative results would not be identified).[33] For the earliest study the risk was low (random biopsies were performed).[31] For the remaining study the risk was unclear (it was unclear whether all recruited patients were included in the analyses).[32] Applicability concerns were high for all three studies regarding the conduct and interpretation of the Niris test. In both the earlier studies the Niris system could not provide cut-offs more specific than being 'normal', 'abnormal' or 'indeterminate' (see the data extraction table for the Escobar *et al.* study,[31] in *Appendix 2*, for definitions),[31–32] whereas for the latest study although results using CIN1+, CIN2+, and CIN3+ as cut-offs were provided, the images were not interpreted during the colposcopic examination.[33] Applicability concerns relating to colposcopy were low for the two earlier studies where the procedure was clearly described,[31–32] and unclear for the later study where few details were provided.[33]

Synthesis of the included studies

Table 4 displays the participant characteristics and comparator technologies used in the included studies. There was considerable heterogeneity between the included studies, in terms of participant characteristics and comparator technologies used, therefore no quantitative synthesis has been undertaken. The studies have been synthesised, narratively, for each adjunctive technology separately.

DySIS

The main characteristics and results of the included DySIS studies are presented in *Table 5*; further details are presented in *Appendix 2*. There were two main studies of the DySIS technology[6,17] and two additional subgroup assessments; one subgroup assessment of women according to their hrHPV type [HPV16 vs non-16 hrHPV (Zaal *et al*., The VU University Medical Center, Amsterdam, the Netherlands, 2011, unpublished)] and one subgroup assessment[18] of women according to the cytology test result (high grade vs low grade).

TABLE 3 Summary of QUADAS 2 assessment results

	Concerns								
	Risk of bias					Applicability			
		Index test					Index test		
Study	Patient selection	Adjunct	Comparator	Reference standard[a]	Flow and timing	Patient selection	Adjunct	Comparator	Reference standard
Soutter,[17] DySIS	Low	Low	Low	Low	High	Low	High	High	Low
Louwers,[6] DySIS	Low	Low	Low	Unclear[b]	Low	Low	Unclear[b]	High	Low
Flowers, unpublished, LuViva	Unclear	Unclear	Unclear	Low	High	Low	High	Low	Low
Escobar,[31] Niris	Unclear	Unclear	Unclear	Low	Low	Low	High	Low	Low
Liu,[32] Niris	Unclear[b]	Unclear[b]	Unclear[b]	Unclear[b]	Unclear	Low	High	Low	Low
Gallwas,[33] Niris	Unclear	Unclear	Unclear	Low	High	Low	High	Unclear	Unclear

a In the NHS, histopathologists do not normally use colposcopy results to inform their diagnoses, therefore knowledge of colposcopy results before interpreting biopsy results was not assessed, although knowledge of adjunctive technology results was assessed.

b Note: based on subsequent information from DySIS Medical/Imalux Corporation, this should read 'Low'.

TABLE 4 Summary of participant characteristics and comparator technologies used in the studies

DySIS

	Study			
	Louwers *et al.*, 2011[6]	Zaal *et al.*, unpublished	Soutter *et al.*, 2009[17]	Soutter *et al.*, conference abstract[18]
Participant characteristics	239 women with abnormal cervical cytology or follow-up of a CIN1 or 2 lesion	Subgroup assessment of women in Louwers study[6] who had an adequate HPV test result ($n = 177$)	308 women with abnormal cervical cytology or symptoms suggesting the possibility of cervical neoplasia	Subgroup assessment of women in Soutter study[17] in which the grade of the abnormal smear was known ($n = 299$)
	Prevalence of CIN2+ = 45.2%	Prevalence of CIN2+ = 48%	Prevalence of CIN2+ = 23.4%	• Prevalence of CIN2+ in women referred with a low-grade smear = 13.8% • Prevalence of CIN2+ in women referred with a high-grade smear = 53.3%
	Analysis: per patient	Analysis: per patient	Analysis: per patient	Analysis: per patient
Comparator technology	Colposcopy using DSI colposcope	Colposcopy using DSI colposcope	Colposcopy using DSI colposcope	Colposcopy using DSI colposcope
	Diagnostic accuracy (CIN2+): Sensitivity = 51.9% Specificity = 81.7%	Diagnostic accuracy (CIN2+): Sensitivity = 55% Specificity = 85%	Diagnostic accuracy (CIN2+): Sensitivity = 48.6% Specificity = 89.4%	Diagnostic accuracy (CIN2+): *Women referred with a low-grade smear*: Sensitivity = 19.4% Specificity = 93.3% *Women referred with a high-grade smear*: Sensitivity = 72.5% Specificity = 68.6%

LuViva Advanced Cervical Scan

	Study	
	Flowers *et al.*, unpublished	Flowers and Tadros, conference poster[19]
Participant characteristics	AiC information removed	Subgroup assessment of women in Flowers *et al.*, unpublished study; women aged 16–20 years ($n = 245$) Prevalence of CIN2+ = 18.8% Analysis: per patient
Comparator technology	AiC information removed	Current standard of care (consisting of Pap result, HPV and colposcopically directed biopsy) Diagnostic accuracy (CIN2+): Sensitivity = 80%

TABLE 4 Summary of participant characteristics and comparator technologies used in the studies (*continued*)

Niris Imaging System

	Study		
	Gallwas *et al.*, 2011[33]	**Liu *et al.*, 2010[32]**	**Escobar *et al.*, 2006[31]**
Participant characteristics	Women with abnormal cervical cytology (number unknown)	299 women with abnormal cervical cytology or HPV positive for one of the hrHPV types (1237 paired images)	212 women with abnormal cervical cytology or suspicious lesions (1215 images)
	Prevalence of CIN2+ = 52.9%	Prevalence of CIN2+ = 18%	Prevalence of CIN2+ = 15.3%
	Analysis: per image	Analysis: per patient, per lesion and per 'most severe biopsy per woman'	Analysis: per patient and per lesion
Comparator technology	Conventional colposcopy	Conventional colposcopy	Conventional colposcopy
	Diagnostic accuracy (CIN2+): Sensitivity = 99% Specificity = 61%	Diagnostic accuracy (CIN2+): *Low grade*: Sensitivity = 74% Specificity = 67% *High grade*: Sensitivity = 22.6% Specificity = 96.3%	Diagnostic accuracy (CIN2+): Sensitivity = 37.5% Specificity = 70.6%

AiC, academic in confidence.

The participants in the main studies were similar: women referred for colposcopy with an abnormal cervical cytology result or follow-up of a CIN1 or CIN2 lesion,[6] or women referred with an abnormal cervical cytology result or symptoms suggesting the possibility of cervical neoplasia.[17] However, the prevalence of CIN2+ was considerably higher in the study by Louwers *et al.*,[6] at 45%, than in the study by Soutter *et al.*[17] (23%). The average age of participants was 37 years in both of the main studies. The Louwers *et al.*[6] results presented below are those for the 'intention-to-treat' (ITT) cohort of patients, rather than the 'according-to-protocol' (ATP) cohort, from which 56 women were excluded as their management did not strictly adhere to the protocol.[6] Results for the ATP cohort are reported in *Appendix 2*.

The DySIS technology used in the earlier study by Soutter *et al.*[17] was a precommercial model (FPC-03), which had some technical problems relating to the software, speculum and a batch of faulty disposable nozzles, leading to the exclusion of a large proportion of participants from the analyses.[17] DySIS v2.1 was used in the later study by Louwers *et al.*;[6] therefore, this study is the most relevant for clinical practice. Both studies used the DySIS colposcope as a regular video colposcope as the comparator technology, and histology result was the reference standard. All patients underwent both DySIS colposcopy and the comparator colposcopic examination during the same appointment.

The sensitivity of DySIS was higher than that of conventional colposcopy (using the DySIS colposcope as a regular video colposcope) for distinguishing between normal or low-grade (CIN 0–1) and high-grade (CIN2+) disease: 64.8% compared with 51.9% in the study by Louwers *et al.*[6] and 79.2% compared with 48.6% in the study by Soutter *et al.*[17] However, the specificity was lower with DySIS; 70.2% compared with 81.7% in the study by Louwers *et al.*[6] and 75.8% compared with 89.4% in the study by Soutter *et al.*[17] The sensitivity and specificity of DySIS (the DSI colour-coded map) combined with conventional colposcopy were 79.6% and 62.6% respectively, compared with 51.9% and 81.7% for conventional colposcopy alone.[6] The differences in sensitivity and specificity between DySIS and conventional colposcopy and between DySIS combined with conventional colposcopy and conventional colposcopy alone were statistically significant (asymptotic McNemar test in the study by Louwers *et al.*,[6] Fisher's exact two-sided test in the study by Soutter *et al.*[17]).

TABLE 5 Summary of study characteristics and results: DySIS studies

	Study			
	Louwers *et al.*, 2011[6]	Zaal *et al.*, unpublished	Soutter *et al.*, 2009[17]	Soutter *et al.*, conference abstract[18]
Recruitment dates	1 July 2008 to 1 September 2009		August 2004 to July 2005	
Number recruited	275		447	
Number analysed	239	177	308	299
Patient inclusion criteria	Women with abnormal cervical cytology or follow-up of a CIN1 or 2 lesion	Subgroup assessment of women in Louwers *et al.*[6] study assessed as per protocol, who had an adequate HPV test result	Women with abnormal cervical cytology or symptoms suggesting the possibility of cervical neoplasia	Subgroup assessment of women in Soutter *et al.*[17] for whom the grade of the abnormal smear was known
Patient age	Mean: 36.7 (range 18.7–62.6) years	Median: 33.6 (range 18.7–62.6) years	Median 37 years (upper and lower quartiles 29–46)	NR
Other relevant patient information	Result of last smear: *normal* = 5 (2.1%), borderline or mild dyskaryosis = 153 (64.0%), worse than borderline/mild dyskaryosis = 81 (33.9%) *hrHPV test*: negative = 73 (30.5%), positive = 158 (66.1%), not performed = 8 (3.3%)	Result of last smear: *normal* = 4 (2.3%), borderline or mild dyskaryosis = 113 (63.8%), worse than borderline/mild dyskaryosis = 60 (33.9%) *hrHPV test*: positive = 133 women; 10 lrHPV+, 80 non-16 hrHPV+, 42 hrHPV16+, in one case the typing was inconclusive	No women with clinically apparent cancer were included Four women were referred with AGUS cervical cytology result	224 women were referred with a low-grade smear, 75 women were referred with a high-grade smear
Adjunctive technology characteristics	DSI colposcope – DySIS v2.1, with colour-coded map	DSI colposcope – DySIS v2.1, with colour-coded map	Precommercial DySIS model (FPC-03), with PCM	Precommercial DySIS model (FPC-03), with PCM
Colposcopy characteristics	Colposcopic examination using DySIS as a regular video colposcope	Colposcopic examination using DySIS as a regular video colposcope	Colposcopic examination using DySIS as a regular video colposcope	Colposcopic examination using DySIS as a regular video colposcope

	Study			
	Louwers *et al.*, 2011[6]	Zaal *et al.*, unpublished	Soutter *et al.*, 2009[17]	Soutter *et al.*, conference abstract[18]
Reference standard	Histology result. Biopsies were taken from all suspicious areas identified by the DySIS colour-coded map or colposcopic impression. If both tests evaluated the cervix as normal, one biopsy was taken from the transformation zone at the 12 o'clock position	Histology result. Biopsies were taken from all suspicious areas identified by the DySIS colour-coded map or colposcopic impression. If both tests evaluated the cervix as normal, one biopsy was taken from the transformation zone at the 12 o'clock position	Histology result. Biopsies were taken from all suspicious areas identified by the DySIS colour-coded map or colposcopic impression, and also from sites that did not seem to contain CIN in order to reduce verification bias	Histology result. Biopsies were taken from all suspicious areas identified by the DySIS colour-coded map or colposcopic impression, and also from sites that did not seem to contain CIN, in order to reduce verification bias
Analysis presented	Per patient, ITT	Analysis: per patient, per protocol	Per patient	Per patient
Primary outcome	Histologically confirmed high-grade cervical disease (CIN2+)	Difference in colposcopic impression and histological outcome in women positive for HPV16 (HPV16+) vs women negative for HPV16 but positive for at least one hrHPV type (non-16 hrHPV+)	Incremental DySIS test characteristics over conventional colposcopy, using histology as a reference	The sensitivities and specificities of DySIS and conventional colposcopy were calculated separately for patients referred with low-grade smears and patients referred with high-grade smears
Diagnostic accuracy results for DySIS adjunctive technology	*CIN2+* Sensitivity = 64.8% (95% CI 55.4 to 73.2) Specificity = 70.2% (95% CI 61.9 to 77.4) PPV = 64.2% (95% CI 54.9 to 72.6) NPV = 70.8% (95% CI 62.4 to 77.9) Accuracy = 67.8% LR+ = 2.18 (95% CI 1.62 to 2.93) LR– = 0.50 (95% CI 0.38 to 0.66) Prevalence = 45.2%	*CIN2+* Total population: Sensitivity = 80% (95% CI 70 to 88) Specificity = 77% (95% CI 67 to 85) Non-16 hrHPV+ population: Sensitivity = 74% (95% CI 57 to 87) Specificity = 67% (95% CI 50 to 80) HPV16+ population: Sensitivity = 97% (95% CI 84 to 100) Specificity = 100% (95% CI 69 to 100)	*High-grade disease* Sensitivity = 79.2% (95% CI 68.4 to 86.9) Specificity = 75.8% (95% CI 70.0 to 80.9) PPV = 50.0% (95% CI 41.0 to 59.0) NPV = 92.3% (95% CI 87.6 to 95.3) Accuracy = 76.6% LR+ = 3.28 (95% CI 2.54 to 4.23) LR– = 0.28 (95% CI 0.17 to 0.43) Prevalence = 23.4%	*Patients referred for a low-grade smear* Sensitivity = 77.4% Specificity = 77.2% Patients referred for a high-grade smear: Sensitivity = 80.0% Specificity = 74.3%

continued

TABLE 5 Summary of study characteristics and results: DySIS studies (*continued*)

	Study			
	Louwers *et al.*, 2011[6]	**Zaal *et al.*, unpublished**	**Soutter *et al.*, 2009[17]**	**Soutter *et al.*, conference abstract[18]**
Diagnostic accuracy results for colposcopy	*CIN2+* Sensitivity = 51.9% (95% CI 42.5 to 61.0) Specificity = 81.7% (95% CI 74.2 to 87.4) PPV = 70.0% (95% CI 59.2 to 78.9) NPV = 67.3% (95% CI 59.7 to 74.1) Accuracy = 68.2% LR+ = 2.83 (95% CI 1.89 to 4.24) LR– = 0.59 (95% CI 0.48 to 0.73) Prevalence = 45.2%	*CIN2+* Total population: Sensitivity = 55% (95% CI 44 to 66) Specificity = 85% (95% CI 76 to 91) Non-16 hrHPV+ population: Sensitivity = 61% (95% CI 43 to 76) Specificity = 83% (95% CI 69 to 93) HPV16+ population: Sensitivity = 53% (95% CI 35 to 71) Specificity = 90% (95% CI 55 to 100)	*High-grade disease* Sensitivity = 48.6% (95% CI 37.4 to 59.9) Specificity = 89.4% (95% CI 84.8 to 92.7) PPV = 58.3% (95% CI 45.7 to 69.9) NPV = 85.1% (95% CI 80.1 to 89.0) Accuracy = 79.9% LR+ = 4.59 (95% CI 2.96 to 7.13) LR– = 0.58 (95% CI 0.46 to 0.72) Prevalence = 23.4%	*Patients referred with a low-grade smear* Sensitivity = 19.4% Specificity = 93.3% *Patients referred with a high-grade smear*: Sensitivity = 72.5% Specificity = 68.6%
Diagnostic accuracy results for DySIS adjunctive technology and colposcopy combined	Sensitivity = 79.6% (95% CI 71.1 to 86.1) Specificity = 62.6% (95% CI 54.1 to 70.4) PPV = 63.7% (95% CI 55.3 to 71.3) NPV = 78.8% (95% CI 70.0 to 85.6) Accuracy = 70.3% LR+ = 2.13 (95% CI 1.67 to 2.71) LR– = 0.33 (95% CI 0.22 to 0.48) Prevalence = 45.2%			
Adverse effects	No adverse events were reported during the study period	NR	No adverse events were reported	NR
Patient satisfaction	DSI colposcopy, compared with conventional colposcopy, was no extra burden for the majority of women	NR	NR	NR

AGUS, atypical glandular cells of undetermined significance; lrHPV, low-risk human papillomavirus; NR, not reported; PCM, pseudocolour map.

In the study by Louwers *et al*.[6] the overall diagnostic accuracy of DySIS was similar to that of conventional colposcopy: 67.8% compared with 68.2%. In the study by Soutter *et al*.[17] the overall diagnostic accuracy of DySIS was slightly lower than that of conventional colposcopy: 76.6% compared with 79.9%. The accuracy of DySIS combined with conventional colposcopy was also assessed using data from the study by Louwers *et al*.,[6] and was similar to that of conventional colposcopy alone, 70.3%.

In a subgroup assessment of women referred with a high-grade cytology test result, both sensitivity and specificity were higher with DySIS than conventional colposcopy; 80% compared with 72.5% for sensitivity and 74.3% compared with 68.6% for specificity, although this was based on a subgroup assessment of just 75 women.[18] In a subgroup of women referred with a low-grade cytology test result, sensitivity was higher with DySIS (77.4% compared with 19.4%), but specificity was lower (77.2% compared with 93.3%), based on a subgroup assessment of 224 women.[18]

In a subgroup assessment of women with hrHPV16, both sensitivity and specificity were higher with DySIS than conventional colposcopy: 97% compared with 53% for sensitivity and 100% compared with 90% for specificity, although this was based on a subgroup assessment of just 42 women. In the subgroup of women with non-16 hrHPV, sensitivity was higher with DySIS (74% vs 61%), but specificity was lower (67% vs 83%), based on a subgroup assessment of 80 women (Zaal *et al.*, unpublished).

The two main studies stated that no adverse events were reported.[6,17]

The study by Louwers *et al*.[6] assessed patient satisfaction using a questionnaire; the majority of women reported that DySIS was no extra burden compared with conventional colposcopy.

LuViva Advanced Cervical Scan

The main characteristics and results of the included LuViva study are presented in *Table 6*; further details are presented in *Appendix 2*. There was one main study of LuViva (Flowers *et al*., unpublished) and one additional subgroup assessment of women aged 16–20 years.[19] However, women in England are not invited for cervical screening under the NHS Cervical Screening Programme until the age of 25 years;[2] therefore, the subgroup population is not of direct relevance to this assessment.

The main study of LuViva was reported in an academic-in-confidence (AiC) unpublished report; therefore, the data cannot be presented in this report.

The name of the technology has been changed since the study was conducted; at the time of the study the LuViva Advanced Cervical Scan was called LightTouch. The comparator used in the study was the 'current standard of care', consisting of the cytology test result, HPV test result and colposcopically directed biopsy. Histology result was the reference standard; however, this was based on biopsy for abnormal-looking areas, and endocervical curettage when no lesion was seen on colposcopy [although if patients had been referred with low-grade squamous intraepithelial lesion (LSIL), atypical squamous cells with possible high-grade squamous intraepithelial lesion (ASC-H) or high-grade squamous intraepithelial lesion (HSIL), diagnostic excision biopsy was performed]. In addition, around half of the patients had 2-year clinical follow-up. All patients underwent the LightTouch scan during the standard colposcopy appointment.

Niris Imaging System

The main characteristics and results of the included Niris studies are presented in *Table 7*; further details are presented in *Appendix 2*. There were three studies of the Niris Imaging System.[31–33]

The participants were similar in all three studies: women referred for colposcopy with an abnormal cervical cytology result,[33] women referred with an abnormal cervical cytology result or hrHPV,[32] or women referred with an abnormal cervical cytology result or suspicious lesions.[31] However, the prevalence of CIN2+ was considerably higher in the study by Gallwas *et al*.,[33] at 53%, than in the study by Liu *et al*.[32] (18%) and

TABLE 6 Summary of study characteristics and results: LuViva studies

	Study	
	Flowers *et al.*, unpublished	Flowers and Tadros, conference poster[19]
Recruitment dates	AiC information has been removed	
Number recruited		
Number analysed		245
Patient inclusion criteria		Subgroup assessment of women in Flowers *et al.*, unpublished study; women aged 16–20 years
Patient age		16–20 years
Other relevant patient information		
Adjunctive technology characteristics		MHS LightTouch
Comparator technology characteristics		Current standard of care (consisting of Pap result, HPV and colposcopically directed biopsy)
Reference standard		Histology result and clinical follow-up
Analysis presented		Per patient
Primary outcome		Prevalence of CIN2+ or worse disease in women of <21 years and performance of MHS in this population
Diagnostic accuracy results for LuViva adjunctive technology		*CIN2+* Sensitivity = 91.3% (95% CI 79.7 to 96.6) Specificity = 28.6% (95% CI 22.8 to 35.3) PPV = 22.8% (95% CI 17.4 to 29.4) NPV = 93.4% (95% CI 84.3 to 97.4) Accuracy = 40.4% LR+ = 1.28 (95% CI 1.13 to 1.45) LR– = 0.30 (95% CI 0.12 to 0.79) Prevalence = 18.8%
Diagnostic accuracy results for the current standard of care		*CIN2+* Sensitivity = 80%
Adverse effects		NR
Patient satisfaction		NR

MHS, multimodal hyperspectroscopy; NR, not reported.

the study by Escobar *et al*. (15%).[31] The average age of participants in the studies was between 31 and 37 years.

In the study by Gallwas *et al*.,[33] Niris images were evaluated as normal, inflammation, CIN1, CIN2, CIN3 or squamous carcinoma.[33] In the earlier study by Liu *et al*.,[32] Niris images were evaluated as normal, indeterminate or abnormal.[32] In the earliest study by Escobar *et al*.,[31] the system was referred to as the Imalux OCT device, it had different technical specifications to the other two studies,[32,33] and this study[31] also evaluated images as normal, indeterminate or abnormal. Images were evaluated as being normal if a well-organised, simple two-layer structure with a sharp interface between the surface epithelium and underlying stromal layer was seen. Images were evaluated as being abnormal if the tissue was unstructured with no apparent interface present. Images were evaluated as being indeterminate if

irregularities on the images suggested artefacts or physiological alterations and did not meet criteria for normal or abnormal. The study by Gallwas *et al*.[33] is the most relevant for clinical practice because of the cut-offs used for categorising images.

All three studies[31–33] used conventional colposcopy as the comparator technology, and histology result was the reference standard. However, biopsies were taken from only the suspicious areas in the study by Gallwas *et al*.,[33] therefore the results from this study are unreliable. All patients underwent OCT imaging using the Niris technology during the standard colposcopy appointment.

TABLE 7 Summary of study characteristics and results: Niris studies

	Study		
	Gallwas *et al*., 2011[33]	Liu *et al*., 2010[32]	Escobar *et al*., 2006[31]
Recruitment dates	July 2008 to May 2010	NR	NR
Number recruited	Unclear, although 1375 images were taken from 120 women (1165 images were from unsuspicious areas, and 210 were compared with histology)	Unclear	220
Number analysed	210 images (number of women unknown)	299 women (1237 paired diagnoses)	212 (1215 images)
Patient inclusion criteria	Women with abnormal cervical cytology	Women with abnormal cervical cytology or a positive test for one of the high-risk types of HPV	Women with abnormal cervical cytology or suspicious lesions
Patient age	Mean: 31.1 (range 18–46) years	Median: 36.7 (range 19.2–67.9) years	Mean: 35.5 (range 18–80) years
Other relevant patient information	*Result of last smear* PAP II, 19; PAP IIW, 14; PAP III, 5; PAP IIID, 44; PAP IVA, 32; PAP IVB, 5; PAP V, 1 *hrHPV test* 93 women tested positive	10% of women were menopausal	*Result of last smear* 48 (23%) had ASCUS, 142 (67%) had LSIL, 22 (10%) had HSIL 189 were premenopausal and 23 were postmenopausal
Adjunctive technology characteristics	Colposcopy-guided OCT using the Niris Imaging system	Niris Imaging System	Imalux OCT device
Colposcopy characteristics	Conventional colposcopy	Conventional colposcopy	Conventional colposcopy
Reference standard	Histology result. Biopsies were taken from suspicious areas identified using OCT. (Biopsy procedure details were unclear for the colposcopy assessment.)	Histology result. Biopsies were taken at all positive areas and at the 2, 4, 8 and 10 o'clock positions at the squamocolumnar junction. Endocervical curettage was also performed on every patient	Histology result. Biopsies were taken at all positive areas and at the 2, 4, 8 and 10 o'clock positions at the squamocolumnar junction. Endocervical curettage was also performed on every patient
Analysis presented	Per image	Per patient, per lesion and per 'most severe biopsy per woman'	Per patient and per lesion
Primary outcome	CIN using cut-offs at CIN1+, CIN2+ and CIN3+	CIN using cut-offs at indeterminate or abnormal	CIN using cut-offs at indeterminate or abnormal

continued

TABLE 7 Summary of study characteristics and results: Niris studies (*continued*)

	Study		
	Gallwas *et al.*, 2011[33]	Liu *et al.*, 2010[32]	Escobar *et al.*, 2006[31]
Diagnostic accuracy results for Niris adjunctive technology	*CIN1+* Sensitivity = 97.9% (95% CI 94.1 to 99.3) Specificity = 39.1% (95% CI 28.1 to 51.3) PPV = 78.6% (95% CI 72.1 to 83.9) NPV = 89.3% (95% CI 72.8 to 96.3) Accuracy = 80.0% LR+ = 1.61 (95% CI 1.32 to 1.96) LR– = 0.05 (95% CI 0.02 to 0.17) Prevalence = 69.5% *CIN2+* Sensitivity = 86.5% (95% CI 78.9 to 91.6) Specificity = 63.6% (95% CI 53.8 to 72.4) PPV = 72.7% (95% CI 64.6 to 79.6) NPV = 80.8% (95% CI 70.7 to 88.0) Accuracy = 75.7% LR+ = 2.38 (95% CI 1.81 to 3.12) LR– = 0.21 (95% CI 0.13 to 0.35) Prevalence = 52.9% *CIN3+* Sensitivity = 87.2% (95% CI 78.0 to 92.9) Specificity = 81.1% (95% CI 73.5 to 86.8) PPV = 73.1% (95% CI 63.3 to 81.1) NPV = 91.5% (95% CI 85.0 to 95.3) Accuracy = 83.3% LR+ = 4.60 (95% CI 3.20 to 6.62) LR– = 0.16 (95% CI 0.09 to 0.28) Prevalence = 37.1%	*Per-patient analysis* *CIN2+* Indeterminate/abnormal Sensitivity = 45.3% (95% CI 32.7 to 58.5) Specificity = 86.1% (95% CI 81.2 to 89.9) PPV = 41.4% (95% CI 29.6 to 54.2) NPV = 87.9% (95% CI 83.2 to 91.5) Accuracy = 78.9% LR+ = 3.26 (95% CI 2.12 to 5.02) LR– = 0.64 (95% CI 0.50 to 0.82) Prevalence = 17.8% Abnormal Sensitivity = 32.1% (95% CI 21.1 to 45.5) Specificity = 93.1% (95% CI 89.2 to 95.6) PPV = 50% (95% CI 34.1 to 65.9) NPV = 86.4% (95% CI 81.7 to 90.0) Accuracy = 82.2% LR+ = 4.62 (95% CI 2.53 to 8.45) LR– = 0.73 (95% CI 0.61 to 0.88) Prevalence = 17.8%	*Per-patient analysis* *CIN2+* Indeterminate/abnormal Sensitivity = 93.8% (95% CI 79.9 to 98.3) Specificity = 10.7% (95% CI 7.0 to 16.2) PPV = 16.0% (95% CI 11.4 to 21.9) NPV = 90.5% (95% CI 71.1 to 97.3) Accuracy = 23.4% LR+ = 1.05 (95% CI 0.95 to 1.16) LR– = 0.58 (95% CI 0.14 to 2.38) Prevalence = 15.3% Abnormal Sensitivity = 56.3% (95% CI 39.3 to 71.8) Specificity = 59.3% (95% CI 52.0 to 66.3) PPV = 20.0% (95% CI 13.0 to 29.4) NPV = 88.2% (95% CI 81.2 to 92.9) Accuracy = 58.9% LR+ = 1.38 (95% CI 0.97 to 1.97) LR– = 0.74 (95% CI 0.49 to 1.11) Prevalence = 15.3%

TABLE 7 Summary of study characteristics and results: Niris studies (*continued*)

	Study		
	Gallwas *et al.*, 2011[33]	Liu *et al.*, 2010[32]	Escobar *et al.*, 2006[31]
Diagnostic accuracy results for colposcopy	*CIN1+* Sensitivity = 99% Specificity = 19% *CIN2+* Sensitivity = 99% Specificity = 61% *CIN3+* Sensitivity = 78% Specificity = 74%	*Per-patient analysis* *CIN2+* Low grade Sensitivity = 74% (95% CI 60 to 84) Specificity = 67% (95% CI 61 to 73) High grade Sensitivity = 22.6% (95% CI 13.5 to 35.5) Specificity = 96.3% (95% CI 93.2 to 98.1) PPV = 57.1% (95% CI 36.5 to 75.5) NPV = 85.3% (95% CI 80.6 to 88.9) Accuracy = 83.3% LR+ = 6.19 (95% CI 2.75 to 13.94) LR– = 0.80 (95% CI 0.69 to 0.93) Prevalence = 17.7%	*CIN2+* Sensitivity = 37.5% (95% CI 22.9 to 54.7) Specificity = 70.6% (95% CI 63.5 to 76.8) PPV = 18.8% (95% CI 11.1 to 30.0) NPV = 86.2% (95% CI 79.7 to 90.9) Accuracy = 65.6% LR+ = 1.28 (95% CI 0.77 to 2.11) LR– = 0.89 (95% CI 0.67 to 1.18) Prevalence = 15.3%
Adverse effects	NR	NR	NR
Patient satisfaction	NR	NR	NR

ASCUS, atypical squamous cells with uncertain significance; NR, not reported.

In the study by Gallwas *et al.*[33] the sensitivity of Niris was lower than that of conventional colposcopy for detecting CIN2+ disease: 86.5% and 99%, respectively. However, the sensitivity of 99% for conventional colposcopy is not representative of colposcopy in practice. In this study, biopsies for reference standard assessment were taken only from suspicious areas; thus, false-negative results would not have been detected, resulting in a falsely increased sensitivity result.[33] Therefore, the results from this study are unreliable. The specificity of Niris was similar to that of colposcopy: 63.6% and 61% respectively. The overall accuracy of Niris was 75.7%; it was not possible to calculate overall accuracy for conventional colposcopy. However, the lack of reference standard assessment of patients for whom no suspicious areas were identified also affects the specificity and overall accuracy results.

For detecting CIN1+ disease, the sensitivity of Niris was 97.9% compared with 99% for colposcopy, specificity was 39.1% for Niris and 19% for colposcopy, and accuracy was 80% for Niris. For detecting CIN3+, disease the sensitivity of Niris was 87.2% compared with 78% for colposcopy, specificity was 81.1% for Niris and 74% for colposcopy, and accuracy was 83.3% for Niris.[33] Again, these results are unreliable, owing to biopsies for reference standard assessment being taken only from suspicious areas.

In the study by Liu *et al.*,[6] the sensitivity of Niris was higher than that of conventional colposcopy for distinguishing between normal/indeterminate and abnormal lesions: 32.1% compared with 22.6%.[32] The specificity of Niris was slightly lower than that of conventional colposcopy: 93.1% compared with 96.3%.

The overall diagnostic accuracy of Niris was similar to that of conventional colposcopy: 82.2% compared with 83.3% for conventional colposcopy (for determining 'high-grade' lesions with colposcopy).

For distinguishing between normal and indeterminate/abnormal lesions, the sensitivity of Niris was lower than that of colposcopy; 45.3% compared with 74% for conventional colposcopy (for determining 'low-grade' lesions with colposcopy). The specificity of Niris was higher than that of colposcopy: 86.1% compared with 67% for conventional colposcopy. The overall diagnostic accuracy of Niris was 78.9%; overall accuracy was not reported for conventional colposcopy.

In the study by Escobar *et al*.,[31] the sensitivity of Niris was higher than that of colposcopy for distinguishing between normal/indeterminate and abnormal lesions: 56.3% compared with 37.5%. However, the specificity of Niris was lower than that of colposcopy: 59.3% compared with 70.6%. The overall diagnostic accuracy of Niris was lower than that of conventional colposcopy: 58.9% compared with 65.6% for conventional colposcopy.

For distinguishing between normal and indeterminate/abnormal lesions, the sensitivity of Niris was 93.8% and the specificity was 10.7%. The overall diagnostic accuracy of Niris was 23.4%.

Summary of results for the most clinically relevant studies

Table 8 summarises the diagnostic accuracy results for the three most clinically relevant studies: the study of the most recent model of the DySIS technology by Louwers *et al*.,[6] the study of the LuViva Advanced Cervical Scan (under its former name of LightTouch) by Flowers *et al*. (unpublished) and the study of the most recent model of the Niris Imaging System by Gallwas *et al*.[33] (the only Niris study to report results using a CIN2 cut-off).

The results of the studies suggest that the sensitivity of the adjunctive technologies is higher for DySIS, DySIS plus conventional colposcopy, and LuViva than conventional colposcopy alone, and for LuViva sensitivity is also higher than the current standard of care (consisting of the cytology test result, HPV test result and colposcopically directed biopsy). For DySIS the specificity is lower for DySIS and DySIS plus conventional colposcopy than conventional colposcopy alone; resulting in an overall diagnostic accuracy similar to that of conventional colposcopy alone. The specificity of LuViva is lower than that of colposcopy alone, although the specificity of LuViva cannot be compared against the standard of care, as the relevant data were not reported. The sensitivity of Niris was found to be lower than that of conventional colposcopy and the specificity of Niris appears to be similar to that of conventional colposcopy. However, the results from this study[33] are unreliable because biopsies for reference standard assessment were taken only from suspicious areas.

Discussion

Interpretation of study results and quality assessment

The systematic review identified a limited amount of evidence on the three adjunctive colposcopy technologies: two studies of the DySIS colposcope,[6,17] one study of the LuViva Advanced Cervical Scan (Flowers *et al*., unpublished) and three studies of the Niris Imaging System.[31–33]

Both studies of the DySIS colposcope[6,17] found that the sensitivity of DySIS was statistically significantly higher than that of conventional colposcopy for identifying CIN2+ disease, although specificity was significantly lower with DySIS.[6,17] Taking both sensitivity and specificity into account, the overall diagnostic accuracy was similar to that of conventional colposcopy. The LRs indicated that DySIS was only a fair predictor of how much a test result will change the (pre-test) odds of having CIN2+. The combination of the DSI colour-coded map and conventional colposcopy resulted in the highest result for sensitivity, although specificity was lowered further.[6] The authors did not define what was meant by 'DSI colour-coded map and conventional colposcopy combined', although it appears that patients were considered positive if either the DSI colour-coded map or conventional colposcopy were positive. [Note: DySIS Medical

TABLE 8 Summary of diagnostic accuracy results for determining CIN2+: results of the most clinically relevant studies

Study							
Louwers *et al.*, 2011[6]			Flowers *et al.*, unpublished			Gallwas *et al.*, 2011[33]	
DySIS alone	**DySIS + conventional colposcopy**	**Conventional colposcopy**	AiC information has been removed	AiC information has been removed	AiC information has been removed	**Niris Imaging System**	**Conventional colposcopy**
Sensitivity = 64.8% (95% CI 55.4 to 73.2)	Sensitivity = 79.6% (95% CI 71.1 to 86.1)	Sensitivity = 51.9% (95% CI 42.5 to 61.0)				Sensitivity = 86.5% (95% CI 78.9 to 91.6)	Sensitivity = 99%
Specificity = 70.2% (95% CI 61.9 to 77.4)	Specificity = 62.6% (95% CI 54.1 to 70.4)	Specificity = 81.7% (95% CI 74.2 to 87.4)				Specificity = 63.6% (95% CI 53.8 to 72.4)	Specificity = 61%
Accuracy = 67.8%	Accuracy = 70.3%	Accuracy = 68.2%				Accuracy = 75.7%	NR
LR+ = 2.18 (95% CI 1.62 to 2.93)	LR+ = 2.13 (95% CI 1.67 to 2.71)	LR+ = 2.83 (95% CI 1.89 to 4.24)				LR+ = 2.38 (95% CI 1.81 to 3.12)	NR
LR– = 0.50 (95% CI 0.38 to 0.66)	LR– = 0.33 (95% CI 0.22 to 0.48)	LR– = 0.59 (95% CI 0.48 to 0.73)				LR– = 0.21 (95% CI 0.13 to 0.35)	NR
Prevalence = 45.2%	Prevalence = 45.2%	Prevalence = 45.2%				Prevalence = 52.9%	NR

NR, not reported (data not available).

has subsequently confirmed that this assumption is correct.] It appears that this would be workable in clinical practice, with the colposcopist performing the examination using DySIS as a conventional colposcope, followed by assessment using the DSI colour-coded map.

The sensitivity of DySIS remained high in the subgroup of women referred for colposcopy with a low-grade cytology test result, whereas the sensitivity of conventional colposcopy was low in this subgroup of women.[18]

In a subgroup analysis, the sensitivity of DySIS was higher in women with hrHPV16 than in women with non-16 hrHPV. Therefore, when the prevalence of hrHPV16 reduces in the screening population, as females who have been vaccinated against this strain of HPV reach the age for cervical cancer screening, DySIS sensitivity will reduce. However, the sensitivity of DySIS was still higher than that of conventional colposcopy in women with non-16 hrHPV, as well as women with hrHPV16 (Zaal *et al*., unpublished).

The study of the LuViva Advanced Cervical Scan (Flowers *et al.,* unpublished) reported higher sensitivity than the standard of care (consisting of the cytology test result, HPV test result and colposcopically directed biopsy) for identifying CIN2+ disease, although the specificity of LuViva was low. The authors of the study (Flowers *et al*., unpublished) stated that the study evaluated the potential of the new technology to effectively triage women at risk for moderate and high-grade dysplasia rather than as an adjunct to colposcopy.

The most recent study[33] of the Niris Imaging System was the most relevant for clinical practice because of the cut-offs used for categorising patients. This study reported a lower sensitivity for Niris for identifying CIN2+ disease than with conventional colposcopy, and a similar specificity.

From the results of our quality assessment, it appears that only the results of the DySIS study by Louwers *et al*.[6] can be interpreted as being both reliable and clinically applicable. The only concern with this study[6] was whether conventional colposcopy was represented appropriately, although the authors pointed out that the results were similar to other studies evaluating conventional colposcopy. The authors also noted a limitation in that a second DySIS examination could not be performed after the first (the acetowhitening effect can last up to 45 minutes, which can interfere with DySIS measurements). This would restrict the use of DySIS when a repeat examination was required e.g. when only part of the transformation zone could be visualised in the first examination. For most of the other studies, the lack of clear reporting meant that the risk of bias was often 'unclear', although the reported issues that cast doubt on their reliability or relevance included a high dropout rate;[17] use of different reference standard procedures across the population (Flowers *et al*., unpublished); lack of a clinically relevant cut-off;[31–32] reference standard not performed for all patients; and results not provided in real time.[33]

Test accuracy may be overestimated in studies at risk of bias.[40] The STARD (STAndards for the Reporting of Diagnostic accuracy studies) statement was produced with the aim of improving the quality of reporting of diagnostic accuracy studies;[41–42] although it appears so far to have had a minimal tangible effect on reporting quality, even in papers published in journals which explicitly endorse the STARD statement.[43–44] This has led to a call for authors, editors and peer reviewers to adhere to, and enforce, STARD statement guidelines.[44]

Strengths and limitations

This systematic review addressed a clear research question using predefined inclusion criteria. Comprehensive literature searches were performed to locate all relevant published and unpublished studies without any language restrictions, thereby minimising the potential for publication bias and language bias. Hand-searching was also performed in order to identify additional relevant studies and the manufacturers were asked whether any other potentially relevant studies were available. Study selection was undertaken independently by two reviewers. Data extraction and quality assessment were checked by a second reviewer to minimise the potential for reviewer bias or error. The authors of studies were contacted, when

necessary, for clarification of study details and for additional diagnostic accuracy data. Study quality assessment was undertaken using a validated checklist for diagnostic studies, with additional review-specific quality assessment items added. We are therefore confident that we have identified all relevant evidence and have appropriately critically appraised and synthesised the included studies.

However, the studies included in the review were clinically and methodologically heterogeneous, which meant that statistical pooling of results was not appropriate. The ways in which the studies varied, and the implications of the variation, are discussed below.

Participants

Women in England are not invited for cervical screening under the NHS Cervical Screening Programme until the age of 25 years. The studies included in the review included women aged 18 years, so the youngest women included in the studies would not be seen in practice. The mean or median age of participants was >35 years for all studies except the study by Gallwas *et al*.[33] (mean age 31 years) and the study by Flowers *et al*. (unpublished), in which the mean age was not reported. From the data presented in the study by Flowers *et al*. (unpublished) it was apparent that around one-third of the participants were aged <25 years. This limits the applicability of this study's results to an NHS setting.

The prevalence of CIN2+ varied considerably between studies, demonstrating heterogeneity between participants in the included studies. The reasons for this variation are not clear, although the inclusion criteria differed slightly between studies, and there was some variation in the setting of the included studies; the studies were conducted in the Netherlands, England and Greece, the USA, Germany, China, and the USA and the Dominican Republic. The two studies with the highest prevalence of CIN2+ were conducted in the Netherlands and Germany.[6,33]

The implications of this variation in prevalence of CIN2+ on the results are that the sensitivity may be reduced in studies with a lower prevalence of CIN2+, as colposcopists who are less familiar with the characteristics of CIN2+ may be less able to recognise them on colposcopic examination.

Intervention

Some studies of both DySIS[17] and the Niris Imaging System[31,32] related to earlier versions of the technology, meaning that their results were of limited clinical value and/or more prone to bias; in addition, the earlier Niris studies[31,32] did not use clinically appropriate cut-offs for categorising patients. In clinical practice, patient management decisions are made based on the colposcopist's impression of CIN grade and the reason for referral for colposcopy from the NHS Cervical Screening Programme.

The authors of the study of the LuViva Advanced Cervical Scan (Flowers *et al*., unpublished) suggest that the intended use of the technology is to triage women for colposcopy, rather than as an adjunct to colposcopy. Therefore, this technology has a different place in the care pathway from the other technologies included in this assessment.

In clinical practice, colposcopists have access to cytology test results and are aware of other patient characteristics, such as age, etc. However, in most of the included studies it was unclear whether these data were available to colposcopists when interpreting the results of the new technology. Only two studies[17,31] reported that cytology test results were available when interpreting the results of the new technology. [Note: Based on subsequent information from DySIS Medical and Imalux Corporation, four studies[6,17,31,32] reported that cytology test results were available when interpreting the results of the new technology.]

Comparator

The comparators used varied across the technologies. In the studies of DySIS,[6,17] the comparator was video colposcopy using the DySIS colposcope, rather than the conventional colposcopy methods and equipment used in the NHS. Therefore, the accuracy of conventional colposcopy in these studies may

not be an accurate reflection of current NHS practice. In the study of the LuViva Advanced Cervical Scan (Flowers *et al*., unpublished) the comparator was 'standard of care', which consisted of the cytology test result, HPV test result and colposcopically directed biopsy. The comparator used in the studies[31–33] of the Niris Imaging System was conventional colposcopy.

The accuracy of colposcopy varied considerably between studies, which may reflect differences in colposcopic examination and biopsy procedures, the expertise of colposcopists and also the differences in prevalence of CIN2+ between studies.

Reference standard

The reference standard was histology for all of the included studies, although in the study of the LuViva Advanced Cervical Scan (Flowers *et al*., unpublished) some patients also had 2-year clinical follow-up. Both of the studies of DySIS[6,17] used random biopsies to assess negative colposcopy results. In the study of the LuViva Advanced Cervical Scan the histology result was based on biopsy for abnormal-looking areas and endocervical curettage when no lesion was seen on colposcopy (although some women may have had diagnostic excision biopsy), which has implications for the reliability of the reference standard. In the most clinically relevant study of the Niris Imaging System by Gallwas *et al*.,[33] biopsies were taken only from suspicious areas, so false-negative results would not be identified.

It is difficult to obtain a definite reference standard for patients with negative index test results; random biopsies are likely to be the most accurate, although they may miss diseased areas. Long-term follow-up may result in high dropout rates and the possibility that disease spotted at long-term follow-up began in the interim period, i.e. may not have been present at initial assessment. The LuViva study (Flowers *et al*., unpublished) followed up around only half of the participants at 2 years, although the reasons for participants not receiving a 2-year follow-up were not explicit.

Outcomes

In order to re-calculate and confirm the reported results, full 2 × 2 data were required. However, these data were reported for only the adjunctive technology and the comparator in the two studies of DySIS.[6,17] Full 2 × 2 data were provided by the study authors for two further studies, on request.[31–32]

All except one of the studies reported results 'per patient'; the study of the Niris Imaging System by Gallwas *et al*.[33] reported results 'per image', meaning that not all of the data were independent observations as some women may have contributed multiple images. Furthermore, in this study it was unclear whether all participants contributed to the analysis.

As discussed earlier, in clinical practice patient management decisions are made based on the colposcopist's diagnosis and the reason for referral for colposcopy from the NHS Cervical Screening Programme. The majority of studies used the cut-off of CIN2+ for determining the sensitivity and specificity of the adjunctive technology. However, management guidelines are different for women with CIN1 from women with no CIN.[5] Therefore, the ability to distinguish between normal, CIN1, CIN2 and CIN3 is important in practice.

Conclusions

The DySIS colposcope is significantly more sensitive than conventional colposcopy for identifying CIN2+ disease, although specificity is significantly lower. The combination of the DSI colour-coded map and conventional colposcopy results in the highest sensitivity, although specificity is lowered further. Based on study quality assessment, these results are likely to be reliable.

The study of the LuViva Advanced Cervical Scan (Flowers *et al*., unpublished) and the clinically relevant study of the Niris Imaging System[33] contain significant biases and uncertainties; therefore, their results can not be relied on. In addition, the authors of the study of LuViva (Flowers *et al*., unpublished) suggest

that the intended use of the technology is to triage women for colposcopy, rather than as an adjunct to colposcopy.

Review of existing economic evaluations

Methods

Systematic searches of the literature were conducted to identify potentially relevant studies for inclusion in the assessment of cost-effectiveness (see *Search strategy*).

Results

The systematic literature search identified no economic evaluation studies of colposcopy or colposcopic adjuncts (DySIS, LuViva Advanced Cervical Scan and Niris Imaging System) that met the inclusion criteria for review. The searches did identify economic evaluations of HPV vaccines, screening strategies, referral strategies to colposcopy and options for managing abnormalities. None of the studies identified were found to be directly relevant to the decision problem addressed in this assessment. The main disadvantage of the studies identified was that each evaluation considered only a small part of the total treatment pathway of concern here. This was particularly evident with studies in which colposcopy was a part of the modelled treatment pathway. The accuracy of colposcopy was either assumed to be 100%[45–46] or combined with the accuracy of biopsy.[47–50] However, those studies undertaking analysis from a UK perspective provided many useful inputs, described in more detail below (see *Model inputs*).

From the review, two UK-based evaluations were identified as potentially relevant. Each was a recent evaluation which used a Markov structure to model the costs and outcomes from a UK perspective.[46,51] The institutions were contacted to discuss the possibility of collaboration. As researchers from the University of Sheffield had recently updated their model and were undertaking updated analyses, an agreement was reached in which their most recent electronic model was provided to the External Assessment Group (EAG). This updated model has been most recently described in a graduate thesis.[52]

Description of decision-analytic model

Overview

A decision-analytic model was developed to assess the cost-effectiveness of the three devices (DySIS, LuViva Advanced Cervical Scan and Niris Imaging System). It compared these with standard colposcopy for examination of the uterine cervix, for the detection of cancerous and precancerous cervical tissue in patients referred for colposcopy through the NHS Cervical Screening Programme. As a result of the weaknesses in the studies of Niris and LuViva (discussed in detail in *Systematic review of clinical effectiveness*), these devices were excluded in the base-case analysis. The analysis adopted the perspective of the UK NHS. The model provides a framework for the synthesis of data from the review of clinical effectiveness (see *Systematic review of clinical effectiveness*) and other relevant parameters.

Outcomes in the model are expressed in terms of quality-adjusted life-years (QALYs). Costs are evaluated from the perspective of the NHS and Personal Social Services, expressed in UK pounds sterling at 2011 prices. Both costs and outcomes are discounted using an annual discount rate of 3.5%, in line with current methods guidelines.[53] All stages of the work were informed by discussion with our clinical advisor and members of the specialist committee to provide feedback on specific aspects of the analysis, such as the modelling approach, data inputs and assumptions.

The following sections outline the structure of the model and provide details of the key assumptions and data sources used to populate the model.

Modelling approach

The decision-analytic model involved two stages. First, a decision tree to model the diagnostic and treatment pathways for patients referred to colposcopy from the NHS Cervical Screening Programme. Second, a Markov model, which simulates the natural history of patients and captures future cytological screening and referrals to colposcopy, to estimate the outcomes of the initial diagnosis and treatment choices. The decision tree has been developed for this appraisal, whereas the Markov model is based on a revised version of the model used by Hadwin *et al*.,[51] henceforth referred to as the Sheffield model.[52]

Diagnostic and treatment decision tree

The diagnostic and treatment decision tree was developed to model the short-term diagnostic and treatment pathways and the outcomes of patients referred to colposcopy from the NHS Cervical Screening Programme. Patients are referred for colposcopy through the NHS Cervical Screening Programme for a variety of reasons (e.g. moderate or severe cytology).[2] For any given referral reason there is a distribution of the true underlying health states (this is discussed in further detail in *Model inputs*). The diagnostic treatment decision tree first allocates patients to their true underlying health state, with the distribution being dependent on their reason for referral, and then sends them down the diagnostic and treatment pathways dependent on probabilities for diagnostic accuracy, treatment and treatment effectiveness. Examples of parts of the decision trees are shown in *Figure 2*, showing the distribution of true underlying health state by reason for referral; *Figure 3*, showing the diagnostic and treatment pathways for a patient with a true underlying health state of CIN1; and *Figure 4*, showing the diagnostic and treatment pathways for a patient with cervical cancer.

The decision tree captures the initial diagnosis of the patient by the colposcopist and any subsequent treatments or screening options based on their diagnosis at colposcopy and the reason for referral from the NHS Cervical Screening Programme. The effectiveness of any treatment is based on the true underlying condition of the patient. Treatment and screening options available include:

1. return to the NHS Cervical Screening Programme
2. refer for rescreen at 6 months: patients can be referred for rescreen with a cytological smear and HPV test, or can be referred for rescreen with colposcopy or adjunct
3. a diagnostic biopsy
4. a treatment biopsy
5. a treatment biopsy followed by cancer treatment.

Figure 3 shows the diagnostic and treatment decision tree for a patient whose true health state is CIN1. The patient receives an initial diagnosis by the colposcopist and can be incorrectly identified as clear, correctly identified as CIN1, incorrectly identified as CIN2/3 or incorrectly identified as having invasive cervical cancer (patients are not diagnosed as HPV+ by the colposcopist). The initial diagnosis is based on the diagnostic accuracy of the device (this is discussed in more detail in *Model inputs*). Following identification, the patient will be assigned to one of the five treatment and screening options discussed above (although, in *Figure 3*, option 5 is excluded as it is assumed that no patient with CIN1 can receive cancer therapy incorrectly, as histology resulting from the treatment biopsy is assumed to be 100% sensitive and specific). The patient's allocation to the treatment/screening option is based on the colposcopist's diagnosis and the reason for their referral for colposcopy from the NHS Cervical Screening Programme (this is discussed in more detail in *Model inputs*).

Patients referred for rescreen at 6 months or returned to the NHS Cervical Screening Programme without receiving treatment enter the Markov model (described in detail in *Description of decision-analytic model*) in the same underlying health state in which they entered the diagnostic and treatment decision tree (in the case of *Figure 3,* CIN1). Patients receiving diagnostic biopsy will then receive a subsequent treatment or screening option (treatment biopsy, referred for rescreen at 6 months or returned to the NHS Cervical Screening Programme) based on their true underlying histology (as diagnostic biopsy and subsequent

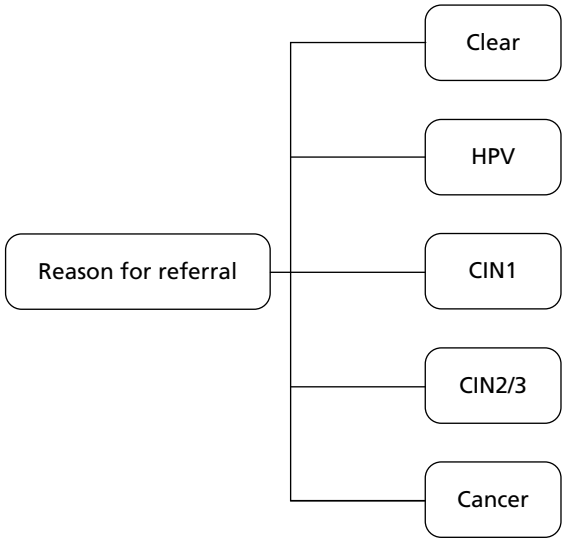


FIGURE 2 Distribution of true underlying health state by reason for referral.

histology is assumed to be 100% sensitive and specific). Patients receiving treatment biopsy, at the initial colposcopy, or at a subsequent colposcopy as the result of a treatment decision based on a diagnostic biopsy, will be either 'cured' or 'not cured', i.e. the treatment biopsy has a failure rate that is described in more detail later in this chapter. Those patients who are cured will be referred for rescreen at 6 months or returned to the NHS Cervical Screening Programme and will enter the Markov model in the 'clear' health state. Those patients who are not cured will be referred for rescreen at 6 months or returned to the NHS Cervical Screening Programme and will enter the Markov model in their original health state, in the case of *Figure 3*, CIN1.

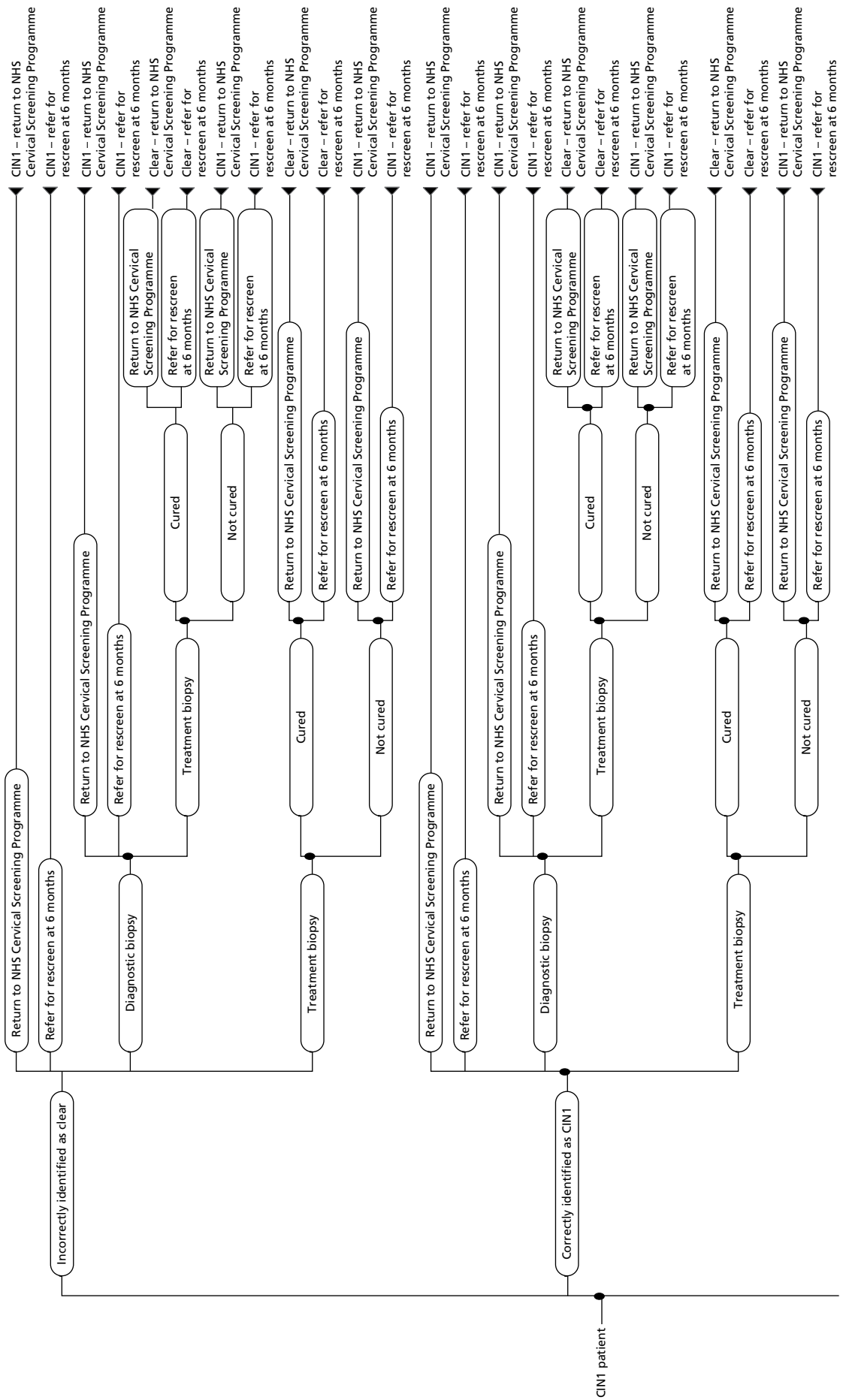
In our model we have split the types of biopsies into treatment and diagnostic biopsies. Different types of biopsies may be used for either reason, but the important distinction in the model is that a diagnostic biopsy is not curative and provides further information on the patient (in the model it is assumed to be perfect information). A treatment biopsy is undertaken with curative intent. Treatment biopsy may be a LLETZ, but in some cases less invasive treatment may be used.

Figure 4 shows the diagnostic decision tree for a patient with invasive cervical cancer. Similarly to *Figure 3* for patients with CIN1, the patient receives an initial diagnosis by the colposcopist and can be incorrectly identified as clear, incorrectly identified as CIN1, incorrectly identified as CIN2/3 or correctly identified as having invasive cervical cancer. In contrast with patients with CIN1, patients with invasive cervical cancer who receive a treatment biopsy will also receive appropriate cancer treatment. As a result of the cancer therapy, they can be cured and returned to the NHS Cervical Screening Programme, or referred for rescreen at 6 months, entering the Markov model as 'clear' but receiving a QALY decrement and cost associated with survival of cervical cancer (this is discussed in detail in *Model inputs*) or they will die of cancer. Those patients who die of cancer do not enter the Markov model but instead receive an expected QALY 'pay-off' and costs associated with dying from cancer (this is discussed in detail in *Model inputs*).

Natural history and screening model

The natural history and screening model is based on the Sheffield model, a revised version of the model used by Hadwin *et al*.[51]

The natural history model consists of nine states: clear, HPV, CIN1, CIN2/3, invasive cancer stages 1, 2, 3 and 4, and death (*Figure 5*). Patients enter the natural history model in the state based on their outcome


CIN1 patient
Incorrectly identified as clear
Correctly identified as CIN1
Return to NHS Cervical Screening Programme
Refer for rescreen at 6 months
Diagnostic biopsy
Return to NHS Cervical Screening Programme
Refer for rescreen at 6 months
Treatment biopsy
Cured
Return to NHS Cervical Screening Programme
Not cured
Return to NHS Cervical Screening Programme
Refer for rescreen at 6 months
Treatment biopsy
Cured
Return to NHS Cervical Screening Programme
Not cured
Return to NHS Cervical Screening Programme
Refer for rescreen at 6 months
Treatment biopsy
Return to NHS Cervical Screening Programme
Refer for rescreen at 6 months
Diagnostic biopsy
Return to NHS Cervical Screening Programme
Refer for rescreen at 6 months
Treatment biopsy
Cured
Return to NHS Cervical Screening Programme
Not cured
Return to NHS Cervical Screening Programme
Refer for rescreen at 6 months
Treatment biopsy
Return to NHS Cervical Screening Programme
Refer for rescreen at 6 months
Return to NHS Cervical Screening Programme
Refer for rescreen at 6 months
CIN1 – return to NHS Cervical Screening Programme
CIN1 – refer for rescreen at 6 months
CIN1 – return to NHS Cervical Screening Programme
CIN1 – refer for rescreen at 6 months
Clear – return to NHS Cervical Screening Programme
Clear – refer for rescreen at 6 months
CIN1 – return to NHS Cervical Screening Programme
CIN1 – refer for rescreen at 6 months
Clear – return to NHS Cervical Screening Programme
Clear – refer for rescreen at 6 months
CIN1 – return to NHS Cervical Screening Programme
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CIN1 – return to NHS Cervical Screening Programme
CIN1 – refer for rescreen at 6 months
Clear – return to NHS Cervical Screening Programme
Clear – refer for rescreen at 6 months
CIN1 – return to NHS Cervical Screening Programme
CIN1 – refer for rescreen at 6 months

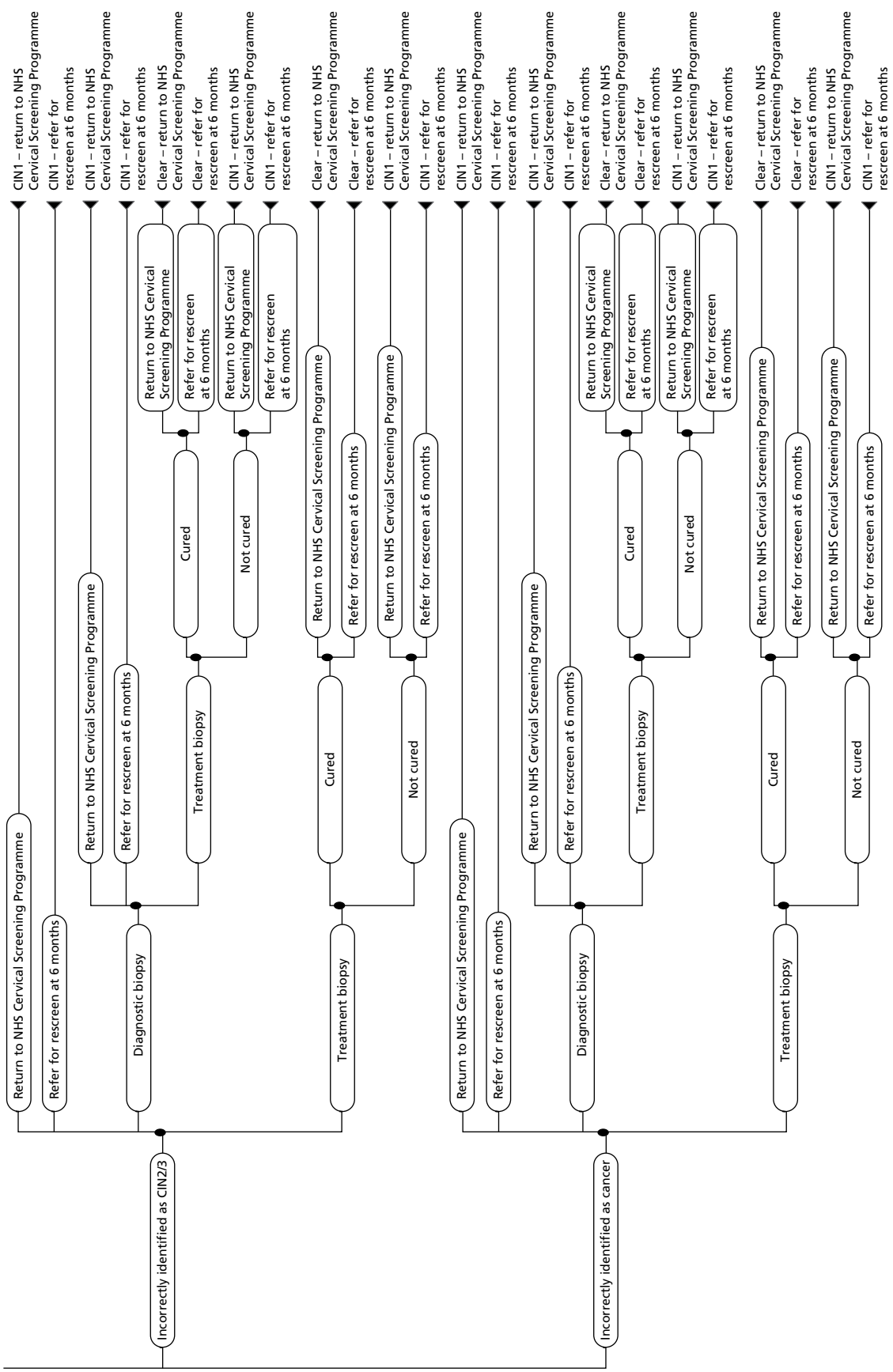
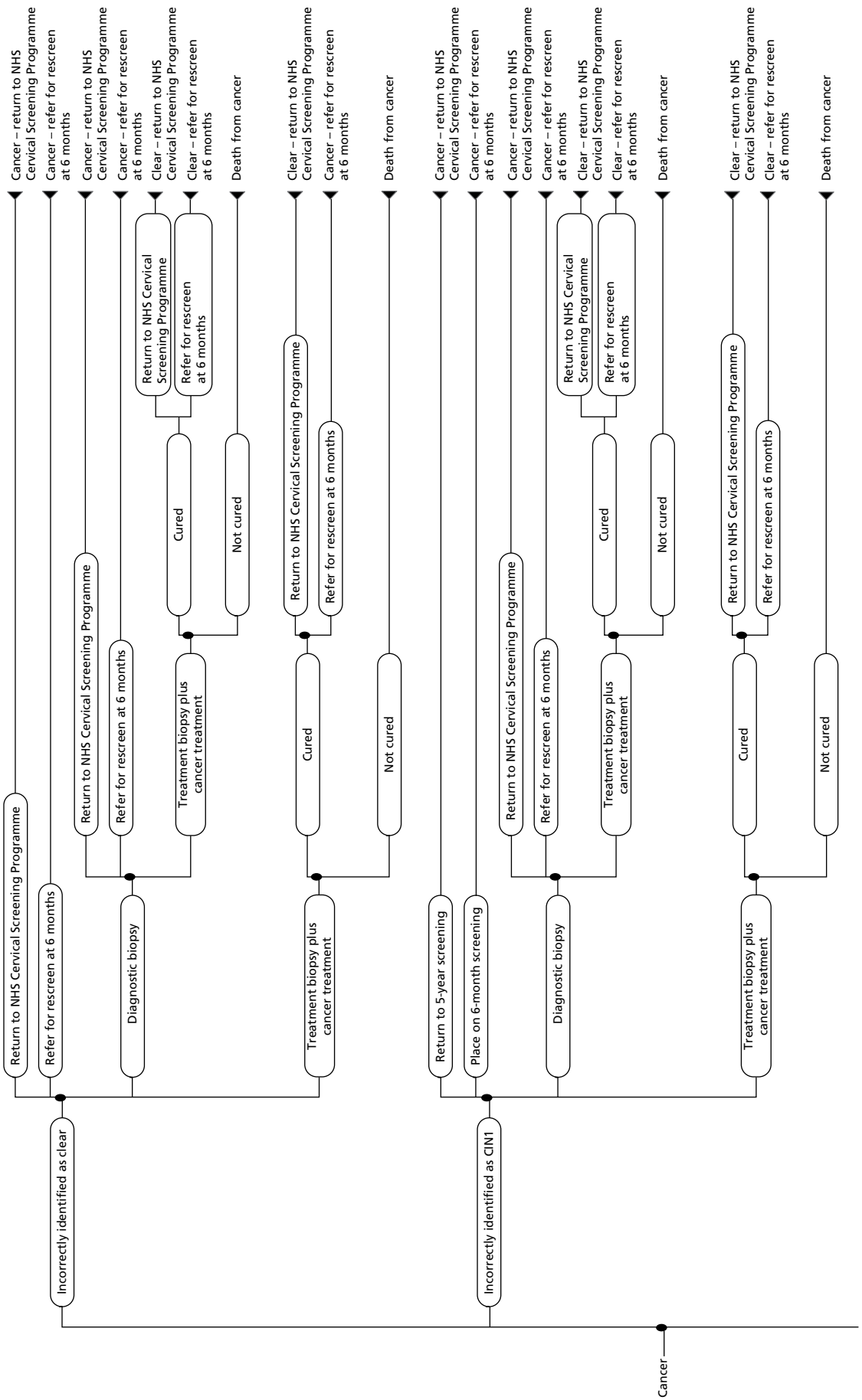


FIGURE 3 Diagnostic decision tree for patients with CIN1.


Cancer
Incorrectly identified as clear
Return to NHS Cervical Screening Programme
Cancer – return to NHS Cervical Screening Programme
Refer for rescreen at 6 months
Cancer – refer for rescreen at 6 months
Diagnostic biopsy
Return to NHS Cervical Screening Programme
Cancer – return to NHS Cervical Screening Programme
Refer for rescreen at 6 months
Cancer – refer for rescreen at 6 months
Treatment biopsy plus cancer treatment
Return to NHS Cervical Screening Programme
Clear – return to NHS Cervical Screening Programme
Refer for rescreen at 6 months
Clear – refer for rescreen at 6 months
Cured
Return to NHS Cervical Screening Programme
Refer for rescreen at 6 months
Not cured
Death from cancer
Incorrectly identified as CIN1
Return to 5-year screening
Cancer – return to NHS Cervical Screening Programme
Place on 6-month screening
Cancer – refer for rescreen at 6 months
Diagnostic biopsy
Return to NHS Cervical Screening Programme
Cancer – return to NHS Cervical Screening Programme
Refer for rescreen at 6 months
Cancer – refer for rescreen at 6 months
Treatment biopsy plus cancer treatment
Return to NHS Cervical Screening Programme
Clear – return to NHS Cervical Screening Programme
Refer for rescreen at 6 months
Clear – refer for rescreen at 6 months
Cured
Return to NHS Cervical Screening Programme
Refer for rescreen at 6 months
Not cured
Death from cancer
Return to NHS Cervical Screening Programme
Clear – return to NHS Cervical Screening Programme
Refer for rescreen at 6 months
Clear – refer for rescreen at 6 months
Treatment biopsy plus cancer treatment
Cured
Return to NHS Cervical Screening Programme
Refer for rescreen at 6 months
Not cured
Death from cancer

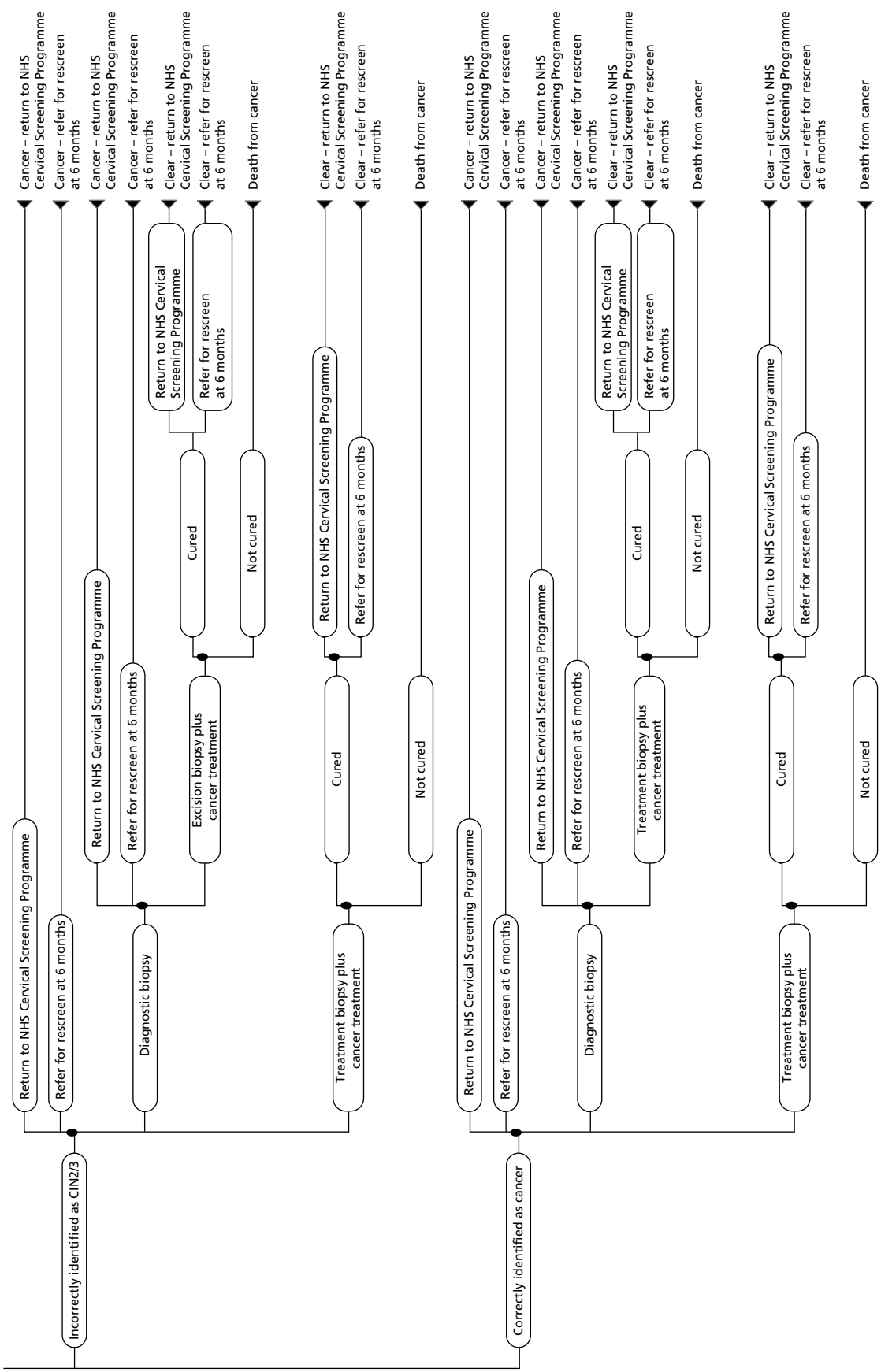


FIGURE 4 Diagnostic decision tree for patients with cancer.

from the diagnostic and treatment decision tree described above. Patients were allowed to progress and regress between these states every 6 months, based on age-related transition probabilities.[47] Possible transitions during any period in the model are represented by the arrows in the figure. Although the transition probabilities in the Hadwin *et al*. paper[51] were largely based on an earlier study,[54] the revised version of the model used the probabilities from Myers *et al*.[47] This model allowed for the regression of CIN2/3 to the less severe states of CIN1 and clear, transitions which were not allowed for in the earlier model.

At different time points during the model, the patients will also enter a screening pathway model (shown in *Figure 6*). For those returned to the NHS Cervical Screening Programme, screening will take place every 3 years between the ages of 25 and 49 years, and every 5 years between the ages of 50 and 64 years. For those referred for rescreen by cytology at 6 months, this will occur 6 months after the initial colposcopy. Following cytological screening, and HPV screening where required, a patient may be re-referred for colposcopy, based on the reasons for referral for colposcopy from the NHS Cervical Screening Programme.[5] When they are re-referred for colposcopy, they re-enter the diagnostic and treatment decision tree described previously.

It should be noted that not all patients with invasive cervical cancer will be identified as a result of cytological screening or colposcopy. These patients will be missed by screening but may subsequently be identified as having cancer, as a result of their cancer becoming symptomatic. These patients would then be treated appropriately, and some will be cured, and will transition to the 'clear' health state in the natural history model but receive an appropriate QALY decrement and cost associated with cancer treatment, whereas some will not be cured and will die of cancer, and will exit the model immediately but receive a QALY pay-off and cost associated with cancer treatment. As previously stated, these pay-offs and decrements associated with cancer are described in detail in *Model inputs*.

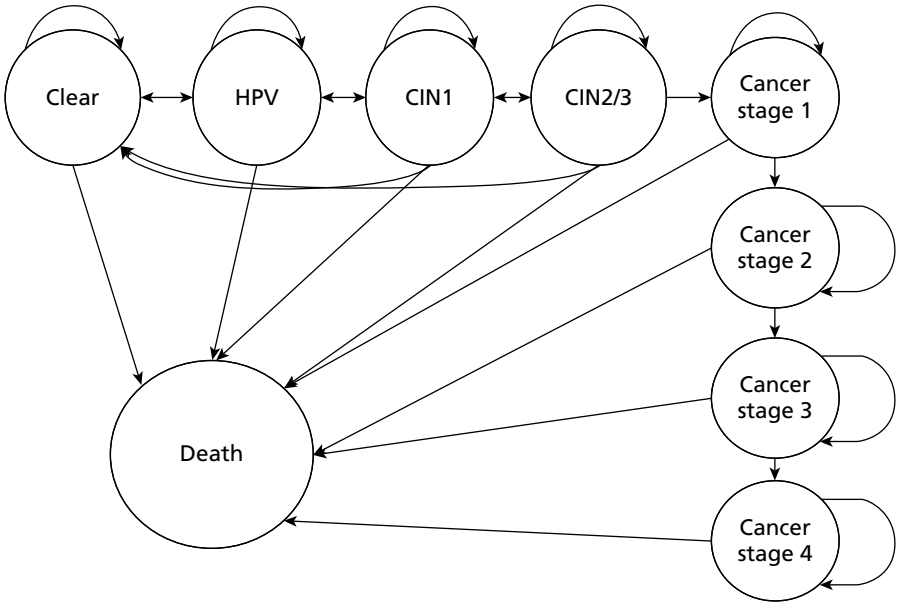


FIGURE 5 Natural history model.[47,51–52]

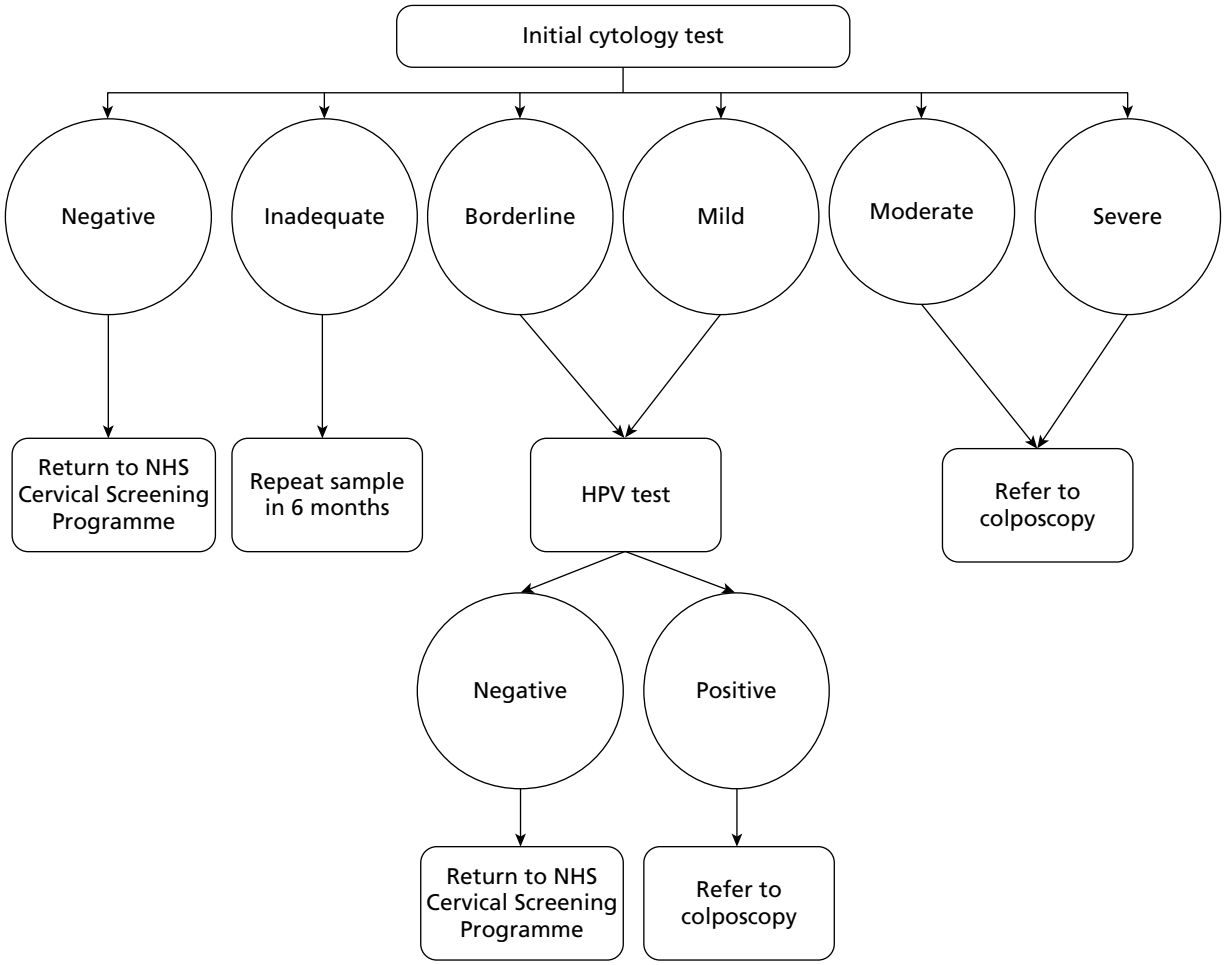


FIGURE 6 Screening pathway model.[52]

Model inputs

Diagnostic accuracy

From the systematic review of clinical effectiveness, sensitivities and specificities for various cut-offs are provided for colposcopy and the various adjuncts (see *Synthesis of the included studies*). However, as discussed in the clinical effectiveness section, the studies relating to the LuViva Advanced Cervical Scan and the Niris Imaging System contain significant biases and uncertainties so their results are not reliable to use in the model. Therefore, for our primary analyses, we compare only DySIS, DySIS plus colposcopy and colposcopy alone. *Table 9* details the sensitivities and specificities used in the cost-effectiveness analyses (based on the CIN2+ cut-off as described in *Synthesis of the included studies*). It should be noted that data here are presented in terms of probabilities rather than in percentages, as in the clinical section.

Although sensitivities and specificities are available, the dichotomous nature of their derivation, based on the use of a CIN2+ cut-off, means these are not sufficient for the model. The model requires the probability of the diagnoses of the different stages of disease made by the new technologies or colposcopy, whether correct or otherwise, conditional on the true underlying disease status. For example, for a patient with CIN1, we need to estimate the probability that they are correctly diagnosed as CIN1, as well as the probabilities that they are incorrectly diagnosed as clear, or found to be 'CIN2/3' or 'cancer'. Therefore, further assumptions are required to convert the sensitivities and specificities into the probabilities required for the model.

TABLE 9 Sensitivities and specificities used in the model

Diagnostic device	Sensitivity	Specificity	Reference
Colposcopy alone	0.519	0.817	Louwers *et al*.[6]
DySIS	0.648	0.702	Louwers *et al*.[6]
DySIS + colposcopy	0.796	0.626	Louwers *et al*.[6]

It should be apparent that just because a true 'clear' patient was found to be below CIN2+, and is therefore defined as a true-negative for the device, it does not mean that they were correctly diagnosed as 'clear', as they could also have been diagnosed as 'CIN1'. Similarly, a 'clear' patient found to be CIN2+, so that they fall into a false-positive for the device, does not necessarily have to be found to be 'CIN2/3', as they could also be found to be 'cancer'. The same issues exist for those who are true 'CIN2/3' or worse. Therefore, to move from sensitivities and specificities based on a CIN2+ cut-off to the probabilities required for the model some information about the distribution of diagnoses conditional on disease status and whether, based on a CIN2+ cut-off, they are true-negative, false-positive, true-positive or false-negative, is required.

Gallwas *et al*.[33] provide information on the probability of a particular diagnosis, based on the device conditional on the true health state as measured by histology (e.g. the probability of being diagnosed CIN1 at colposcopy conditional on being CIN1 or the probability of being diagnosed with cancer conditional on being CIN1). This information can also be used to calculate the probability of being found to be in a particular health state conditional on the true disease state and the result of a diagnostic test. For example, the probability of being found to be CIN1 conditional on the true disease state being CIN1 and the (colposcopic) diagnostic test finding them to be negative at a CIN2+ cut-off. By combining this evidence with the sensitivities and specificities (i.e. the evidence on whether they are true-negative, false-positive, true-positive or false-negative at a cut-off of CIN2+), we can calculate the required probabilities for the model. The probabilities used to convert sensitivities and specificities into model parameters are shown in *Table 10*. Note the assumption here is that, although the data from Gallwas *et al*.[33] are based on the Niris Imaging System, it is assumed that these also apply to colposcopy and the other new technologies being assessed. There are concerns with the Gallwas *et al*.[33] study as histology was undertaken only in patients with a suspicious lesion and thus the table below does not represent the full population. This will have the effect of underestimating the probability of a patient being diagnosed as clear for all negative (clear or CIN1) test results. This has been explored in sensitivity analyses in which we assume that all patients that are found to be negative are diagnosed as clear. Patients considered as inflamed in the study were excluded from the table as it was unclear whether they would be considered clear or CIN1.

For example, a patient with true underlying health state CIN1 has a probability of being found to be CIN1 by colposcopy/new technologies of 0.61. This is calculated by multiplying the probability of her being found to be below the CIN2+ threshold by the diagnostic test, the specificity (0.817), by the probability of her being identified at CIN1, given that she is CIN1 and the diagnostic test found her to be below CIN2+ (0.745).

As stated previously, and in the clinical review section (see *Systematic review of clinical effectiveness*), the evidence on the LuViva Advanced Cervical Scan and the Niris Imaging System contains significant biases and has, therefore, been excluded from the main analyses. Even if the evidence were considered reliable, the heterogeneity between the studies raises issues about their comparability. In the light of the unreliability of the evidence, the heterogeneity and the dearth of formal methods for mixed-treatment comparisons of diagnostic devices, no formal attempt at synthesising the studies has been made.

TABLE 10 Probabilities to convert sensitivities and specificities into model parameters based on data from Gallwas *et al*.[33]

True health state	Result based on CIN2+ cut-off	Diagnosis based on colposcopy or new technology	Probability
Clear	True-negative	Clear	0.935
		CIN1	0.065
	False-positive	CIN2/3	1.000
		Cancer	0.000
CIN1	True-negative	Clear	0.255
		CIN1	0.745
	False-positive	CIN2/3	1.000
		Cancer	0.000
CIN2/3	False-negative	Clear	0.432
		CIN1	0.568
	True-positive	CIN2/3	0.966
		Cancer	0.034
Cancer	False-negative	Clear	0.333
		CIN1	0.667
	True-positive	CIN2/3	0.077
		Cancer	0.923

True health states

The initial model population consists of patients who are referred to colposcopy from the NHS Cervical Screening Programme. To model the underlying progression of the disease and the likelihood of correct diagnoses it is necessary to estimate the true underlying health states of patients entering the model. As the model population is first identified by the reason for referral, we have estimated the true health state by the reason for referral.

Data for this analysis were provided by the Northern Gynaecological Oncology Centre, Queen Elizabeth Hospital, Gateshead (hereafter referred to as the Gateshead data). All patients who visited the colposcopy clinic from 1 January 2006 to 29 November 2011 were included – 4533 patients in total. The percentage of patients in each health state was calculated by the reason for referral as described below. Patients' true health states were estimated, based either on (1) biopsy alone or (2) biopsy if available, otherwise colposcopy. For the case in which only biopsies were used to determine the true health states the population was limited to those who underwent biopsies (*Table 11*).

In the case of using 'biopsy, otherwise colposcopy' to estimate the true health state, biopsy results were used for those that underwent a biopsy and the colposcopy result was used for those who did not have a biopsy (*Table 12*). This provides a larger sample size but the true health state of those added to the sample is determined by the colposcopic finding, which is considered less accurate.

In the data set, some patients had multiple biopsy results from a single visit. In such circumstances, the most severe result was considered the 'true' health state. Furthermore, in the data set the patients were separately identified as having adenocarcinoma or invasive cancer, so these diagnoses were combined to make up the cancer population within the model. The data do not indicate the stage of cancer being diagnosed; in the base case those diagnosed as adenocarcinoma or invasive cancer as a result of the

TABLE 11 True health state, estimated by biopsy only, by the reason for referral based on Gateshead data

	Reasons for referral						
True health state (biopsy result)	Borderline changes (%) (*n* = 1168)	Mild dyskaryosis (%) (*n* = 639)	Moderate dyskaryosis, % (*n* = 576)	Severe dyskaryosis (%) (*n* = 847)	Possible invasion (%) (*n* = 10)	Possible glandular neoplasia (%) (*n* = 122)	Inadequate (%) (*n* = 22)
Normal	22	15	4	2	0	18	64
HPV	40	30	7	2	10	27	32
CIN1	22	32	11	2	0	9	5
CIN2/3	16	22	77	87	50	29	0
Cancer	0	0	1	6	40	17	0

TABLE 12 True health state, estimated by biopsy if available, otherwise colposcopy, by the reason for referral based on Gateshead data

	Reasons for referral						
True health state (biopsy, otherwise colposcopy result)	Borderline changes (%) (*n* = 1360)	Mild dyskaryosis (%) (*n* = 715)	Moderate dyskaryosis (%) (*n* = 633)	Severe dyskaryosis (%) (*n* = 917)	Possible invasion (%) (*n* = 11)	Possible glandular neoplasia (%) (*n* = 151)	Inadequate (%) (*n* = 141)
Normal	28	20	5	3	0	28	88
HPV	37	28	7	2	9	22	11
CIN1	20	31	12	3	0	11	1
CIN2/3	14	20	76	86	45	25	0
Cancer	0	0	0	6	45	14	0

screening were assumed to have stage 1 cancer, based on clinical advice that nearly all cancers identified at screening are stage 1. One limitation of the data is that they do not capture patients who underwent a biopsy under a general anaesthetic, so it is not clear whether these patients would be different from those in the current data set.

Treatment probabilities

Based on clinical advice, treatment decisions are assumed to be based on cytological and colposcopic results (*Table 13*). Two sets of treatment probabilities were tested in the model, the first based on clinical guidelines and clinical advice and the second based on treatment patterns from the Gateshead data. From the Gateshead data we estimated the probabilities of different treatment options for each combination of cytological and colposcopic results. In some cases, multiple cytological and colposcopic results were reported, in these cases we considered the most severe result to be that which was used for decisions.

In the Gateshead data, some of the possible combinations of cytological and colposcopic results did not occur. For instance, in patients with a cytological result of possible invasive cancer there were no cases of colposcopic results of normal or mild in the Gateshead data. Given this lack of data, we were not able to estimate treatment probabilities for some combinations of cytological and colposcopic results. In these cases, we assumed that patients in the Gateshead data would receive the treatment according to guidelines and clinical opinion.

For each combination of cytological and colposcopic results we calculated the percentage of patients receiving a treatment biopsy, diagnostic biopsy, follow-up or 3- to 5-year screening. We assumed follow-up would occur within 6 months and, in the case of cytological results of moderate, severe, possible invasion or possible glandular neoplasia and a normal colposcopic finding, we assumed this follow-up would occur after having a correlation meeting. A correlation meeting is a meeting of colposcopists and pathologists to review the cytological and colposcopic findings and determine the most appropriate next steps of treatment. Following clinical advice we assumed that a correlation meeting for a patient with moderate cytology and a normal colposcopy or severe cytology and normal colposcopy would result in 10%–30% of patients being followed up in 6 months and 70–90% returning for a diagnostic biopsy. We were also advised that a cytological result of possible glandular neoplasia followed by a normal colposcopy would result in the correlation meeting finding the need for additional diagnostic biopsies or possibly a treatment biopsy. Clinical advice suggested that 50% of patients with cytological findings of invasive cancer and normal colposcopy would have an immediate treatment biopsy, and the other 50% would be reviewed during a correlation meeting of which all were likely to result in further diagnostic testing.

Treatment effectiveness

Probability of cure from treatment biopsy

In a 2011 study by Ghaem-Maghami *et al*.,[55] retrospective data on 2455 consecutive women treated for CIN for the first time between 1989 and 2004 using excision were used to examine the failure rates. Failure was measured by the detection of high-grade cervical disease after treatment, defined as cytological findings of moderate dyskaryosis or more severe or histological findings of CIN2+. The median length of follow-up was 238 weeks. The authors reported that the cumulative failure rate at 10 years was 4.9% for CIN1 ($n = 570$), 9.8% for CIN2 ($n = 886$) and 10.3% for CIN3 ($n = 999$). From this we calculated a weighted excision failure rate of CIN2/3 as 10.1% and a total excision failure rate of 8.9% (*Table 14*). This estimate was higher than estimates from a 2007 meta-analysis on failure rates with excision,[56] from which we calculated the total excision failure rate to be 5.78% (915/15,828).

All-cause mortality excluding cervical cancer

Mortality rates from causes other than cervical cancer were calculated using data from the Office for National Statistics (ONS)[57] by subtracting the deaths due to cervical cancer (ICD-10:C53) from the total number of deaths for each age group and dividing by the UK population for each age group also from the ONS data (*Table 15*).[58]

TABLE 13 Treatments by reason for referral and colposcopy results

Reason for referral	Colposcopy or new technology results	Treatment possibilities	Guidelines and clinical advice (%)	Gateshead data (%)
Borderline cytology + HPV positive[a]	Normal	Discharge and return to normal screening	100	10.7
		Follow-up	0	15.1
		Immediate treatment – excision biopsy	0	0.8
		Biopsy, no curative intent (punch or small excision)	0	73.5
	Low grade	Discharge and return to normal screening	0	0.2
		Follow-up	0	2.7
		Immediate treatment – excision biopsy	0	0.9
		Biopsy, no curative intent (punch or small excision)	100	96.2
	High grade	Discharge and return to normal screening	0	0.6
		Follow-up	0	1.2
		Immediate treatment – excision biopsy	0	4.9
		Biopsy, no curative intent (punch or small excision)	100	93.3
	Cancer (I–IV)	Discharge and return to normal screening	0	DNO
		Follow-up	0	DNO
		Immediate treatment – excision biopsy	90	DNO
		Biopsy, no curative intent (punch or small excision)	10	DNO
Mild dyskaryosis + HPV positive[a]	Normal	Discharge and return to normal screening	100	9.4
		Follow-up	0	16.4
		Immediate treatment – excision biopsy	0	0.5
		Biopsy, no curative intent (punch or small excision)	0	73.7
	Low grade	Discharge and return to normal screening	0	0.0
		Follow-up	0	4.1
		Immediate treatment – excision biopsy	0	1.8
		Biopsy, no curative intent (punch or small excision)	100	94.2
	High grade	Discharge and return to normal screening	0	0.0
		Follow-up	0	2.4
		Immediate treatment – excision biopsy	0	13.0
		Biopsy, no curative intent (punch or small excision)	100	84.6
	Cancer (I–IV)	Discharge and return to normal screening	0	DNO
		Follow-up	0	DNO
		Immediate treatment – excision biopsy	90	DNO
		Biopsy, no curative intent (punch or small excision)	10	DNO

TABLE 13 Treatments by reason for referral and colposcopy results (*continued*)

Reason for referral	Colposcopy or new technology results	Treatment possibilities	Guidelines and clinical advice (%)	Gateshead data (%)
Moderate dyskaryosis	Normal	Discharge and return to normal screening	0	8.6
		Follow-up	100	28.6
		Immediate treatment – excision biopsy	0	8.6
		Biopsy, no curative intent (punch or small excision)	0	54.3
	Low grade	Discharge and return to normal screening	0	0.0
		Follow-up	0	7.1
		Immediate treatment – excision biopsy	0	11.1
		Biopsy, no curative intent (punch or small excision)	100	81.7
	High grade	Discharge and return to normal screening	0	1.3
		Follow-up	0	5.4
		Immediate treatment – excision biopsy	80	84.9
		Biopsy, no curative intent (punch or small excision)	20	8.4
	Cancer (I–IV)	Discharge and return to normal screening	0	0.0
		Follow-up	0	0.0
		Immediate treatment – excision biopsy	90	100.0
		Biopsy, no curative intent (punch or small excision)	10	0.0
Severe dyskaryosis	Normal	Discharge and return to normal screening	0	0.0
		Follow-up	100	28.6
		Immediate treatment – excision biopsy	0	33.3
		Biopsy, no curative intent (punch or small excision)	0	38.1
	Low grade	Discharge and return to normal screening	0	1.4
		Follow-up	0	8.1
		Immediate treatment – excision biopsy	70	33.8
		Biopsy, no curative intent (punch or small excision)	30	56.8
	High grade	Discharge and return to normal screening	0	1.4
		Follow-up	0	5.6
		Immediate treatment – excision biopsy	100	88.7
		Biopsy, no curative intent (punch or small excision)	0	4.3
	Cancer (I–IV)	Discharge and return to normal screening	0	0.0
		Follow-up	0	0.0
		Immediate treatment – excision biopsy	90	66.7
		Biopsy, no curative intent (punch or small excision)	10	33.3

continued

TABLE 13 Treatments by reason for referral and colposcopy results (*continued*)

Reason for referral	Colposcopy or new technology results	Treatment possibilities	Guidelines and clinical advice (%)	Gateshead data (%)
Possible glandular neoplasia	Normal	Discharge and return to normal screening	0	5.3
		Follow-up	100	26.3
		Immediate treatment – excision biopsy	0	31.6
		Biopsy, no curative intent (punch or small excision)	0	36.8
	Low grade	Discharge and return to normal screening	0	0.0
		Follow-up	0	12.9
		Immediate treatment – excision biopsy	100	38.7
		Biopsy, no curative intent (punch or small excision)	0	48.4
	High grade	Discharge and return to normal screening	0	3.7
		Follow-up	0	0
		Immediate treatment – excision biopsy	100	88.9
		Biopsy, no curative intent (punch or small excision)	0	7.4
	Cancer (I–IV)	Discharge and return to normal screening	0	0.0
		Follow-up	0	0.0
		Immediate treatment – excision biopsy	90	50.0
		Biopsy, no curative intent (punch or small excision)	10	50.0
Possible invasion	Normal	Discharge and return to normal screening	0	DNO
		Follow-up	50	DNO
		Immediate treatment – excision biopsy	50	DNO
		Biopsy, no curative intent (punch or small excision)	0	DNO
	Low grade	Discharge and return to normal screening	0	DNO
		Follow-up	0	DNO
		Immediate treatment – excision biopsy	100	DNO
		Biopsy, no curative intent (punch or small excision)	0	DNO
	High grade	Discharge and return to normal screening	0	0.0
		Follow-up	0	0.0
		Immediate treatment – excision biopsy	100	100.0
		Biopsy, no curative intent (punch or small excision)	0	0.0
	Cancer (I–IV)	Discharge and return to normal screening	0	0.0
		Follow-up	0	0.0
		Immediate treatment – excision biopsy	90	100.0
		Biopsy, no curative intent (punch or small excision)	10	0.0

DNO, did not occur.

a Gateshead data is pre-HPV triage and therefore refers to all borderline or mild patients.

TABLE 14 The probability of treatment failure with excision

Diagnosis	Failures[a]	*n*	Probability of failure (%)
CIN1	28	570[b]	4.9[b,c]
CIN2	87	886[b]	9.8[b]
CIN3	103	999[b]	10.3[b]
CIN2/3	190	1885[a]	10.1[a,c]
Total	218	2455[a]	8.9[a]

a Calculated.
b Reported in Ghaem-Maghami *et al*.[55]
c Base-case inputs.

TABLE 15 Annual all-cause mortality excluding deaths due to cervical cancer for females by 5-year age groups

Cause of mortality					Annual probability of dying from all other causes (%)
Age groups (years)	All causes	Cervical cancer	Not cervical cancer	Population	
All ages	255,326	816	254,510	28,011,900	0.91
<1	1420	_	1420	346,200	0.41
1–4	229	_	229	1,330,700	0.02
5–9	135	_	135	1,497,900	0.01
10–14	147	_	147	1,542,800	0.000
15–19	342	_	342	1,680,400	0.02
20–24	394	6	388	1,855,700	0.02
25–29	577	25	552	1,844,700	0.03
30–34	772	31	741	1,718,100	0.04
35–39	1363	50	1313	1,882,100	0.07
40–44	2259	56	2203	2,069,800	0.11
45–49	3351	61	3290	2,041,700	0.16
50–54	4807	74	4733	1,770,000	0.27
55–59	6744	58	6686	1,605,100	0.42
60–64	10,786	65	10,721	1,707,800	0.63
65–69	13,347	71	13,276	1,343,700	0.99
70–74	19,352	78	19,274	1,153,800	1.67
75–79	29,015	72	28,943	977,800	2.96
80–84	43,008	73	42,935	786,900	5.46
85–89	54,862	68	54,794	547,300	10.01
90+	62,416	28	62,388	309,200	20.18

Cancer mortality

In the previous versions of the model,[51,52] detected cancer was assumed to have a 100% cure rate. In this version we have relaxed this assumption adding cancer mortality for detected cancer patients as described below, based on data from Cancer Research UK.[59]

Stage 1 cancer is considered to be curable with the prognosis dependent on the depth and width of the cancer. Stage 1a1 is estimated to have a cure rate of 98–99%, stage 1a2 a cure rate of 95–98%, stage 1b1 a cure rate of 90–95% and stage 1b2 a cure rate of 80%. Where stage 1 is generally limited to the cervix, stage 2 cancers have spread outside the neck of the womb into the surrounding tissues, but have not spread into the muscles or ligaments that line the pelvis or to the lower part of the vagina. Stage 2a cancer has spread into the top part of the vagina and the 5-year survival rate is 70–90%; in stage 2b cancer there is further spreading and the 5-year survival rate is 60–70%. In stage 3 cancer it has spread away from the cervix into surrounding structures in the pelvic area and the 5-year survival rate is 30–50%. Stage 4 cancer has spread to other body organs outside the cervix and womb and the 5-year survival rate is 20%.

This analysis assumes that the 1-year cure rate of stage 1 cancer is 95% and that the 5% of patients who progress have the same 5-year outcomes as stage 2 patients. We also assume that patients who live beyond 5 years with higher stages of cancer are cured. The 5-year cure rates of stages 2, 3 and 4 were estimated to be 75%, 50% and 20%, respectively. For stage 3, the high end of the 5-year survival rate was chosen.

Modelling cancer outcomes

As discussed in the diagnostic and treatment decision tree section previously, patients identified with cancer are assumed to either be cured, and re-enter the model as 'clear', or to die as a result of cancer and exit the model immediately. For those patients who are cured, they receive a QALY decrement and cost associated with cancer treatment by cancer stage. This QALY decrement represents the QALYs as a result of cancer symptoms and treatment when compared with full health. This QALY decrement occurs immediately, although the effects that are used to calculate the decrement are assumed to have occurred over 5 years. Those patients who die receive an expected QALY pay-off and cost associated with cancer mortality. The QALY pay-off represents the QALYs that a patient who dies of cancer is expected to receive before their death although they will exit the model at the point it is determined they will die. The methods used to calculate these are described in detail below; first, for patients with cancer stages 2–4, and, second, for patients with cancer stage 1.

Cancer stages 2–4

Five-year mortality rates were identified for cancer stages 2–4.[59] Based on the assumption that mortality is distributed exponentially, survival curves were drawn for patients by stage of cancer. These curves were then separated into those patients who survived until 5 years and those who died within 5 years. For those patients who died as a result of cancer, their survival curve was converted into quality-adjusted survival, by multiplying by the associated health-related quality of life (HRQoL) given cancer stage and treatment. The quality-adjusted survival over 5 years was discounted at a rate of 3.5% to calculate the QALY pay-off for a patient who dies as a result of cancer at the point when they exit the model.

For those patients who survived, the difference between HRQoL based on being in the 'clear' state and HRQoL as a result of treatment of cancer by stage was calculated over 5 years. This was discounted at a rate of 3.5%, to calculate the QALY decrement as a result of cancer and cancer treatment. In the scenario analyses, the length of time a patient experiences a reduction in HRQoL as a result of cancer and cancer treatment was varied.

Cancer stage 1

For cancer stage 1, 5-year survival probabilities were not available as a result of the low mortality associated with the disease if caught at an early stage. Instead, the probability of being cured was

identified. For those patients who are cured, the QALY decrement associated with cancer treatment was calculated in a similar way as for patients with cancer stages 2–4, although the difference was only calculated over 1 year rather than 5 years (i.e. the difference between HRQoL based on being in the 'clear' state and HRQoL as a result of treatment of cancer by stage was calculated over 1 year). Those patients who were not cured were assumed to progress immediately to cancer stage 2 with its associated mortality and HRQoL decrements. Therefore, a proportion who were not cured were assumed to survive cancer stage 2 and receive the HRQoL decrement described above, and the rest were assumed to die as a result of cancer stage 2 and receive the QALY pay-off described above.

Full details of the cancer outcomes are provided in *Table 16*.

Health-related quality of life and quality-adjusted life-year decrements

The QALYs in the current model are those published previously in the Sheffield model,[52] which had been previously used in other models.[60–62] Changes have been made to the HRQoL and QALY inputs as described below. HRQoL refers to the patient's health measured on an interval scale, where '0' represents death and '1' represents perfect health. QALY estimates combine both HRQoL of health states and the time spent in those health states, with 1 QALY representing a year in perfect health. A QALY decrement is the decrease in the HRQoL over a set time period converted into lost QALYs.

Quality-adjusted life-year decrement of colposcopy

Previously the authors used an estimate of 0.03 for the QALY decrement of undergoing a colposcopy and the associated treatment, which may or may not include a biopsy. In the current model it is important to consider the possible health improvements of avoiding biopsies with more accurate colposcopies. We use the following data to separate the QALY decrement associated with a colposcopy and that associated with a biopsy. In a 2003 time trade-off analysis, the authors report the HRQoL of 'three repeat Pap smears' to be 0.958 and the HRQoL of an 'immediate colposcopy with no pathology' to be 0.927, and they estimate the difference to be 0.031 (95% CI 0.007 to 0.055).[63] The difference of 0.031 is, therefore, used in the model as the QALY decrement associated with a colposcopy.

Quality-adjusted life-year decrement of biopsy

The authors also report the HRQoL of a 'cone biopsy after immediate colposcopy' to be 0.922.[63] Therefore, we use the difference between the colposcopy with no pathology and colposcopy with a cone biopsy to estimate the HRQoL decrement of a biopsy, which is 0.005. We assume the HRQoL decrement lasts for 1 year and thus a QALY decrement of 0.005 or 1.8 healthy days associated with biopsy. We use 0.005 in the model as the QALY decrement for both diagnostic and treatment biopsies, as we do not have differential HRQoL estimates. This assumption may be important as it may underestimate the negative health effects of a treatment biopsy. The TOMBOLA (Trial of Management of Borderline and Other Low-Grade Abnormal Smears) study[64] suggests that LLETZ compared with biopsy resulted in more pain (67%

TABLE 16 Cancer outcomes

	Cancer stage			
Outcomes	1	2	3	4
QALY decrement for those who survive[a]	0.0495737	0.3707	0.3707	1.2973
QALY pay-off for those who die[b]	N/A	2.079227	1.953032	1.276931
Cost of cancer treatment (£)	13,920.37	22,930.51	22,779.62	24,244.24

N/A, not applicable.

a The QALYs lost as a result of cancer compared with being in full health.

b The QALYs that a patient receives at the point of detection of cancer before their death.

vs 53%), more discharge (63% vs 46%) and more bleeding (87% vs 79%). Not only did these events occur more often, but also bleeding and discharge were reported to have a significantly longer duration.[64]

In a 2008 meta-analysis of adverse pregnancy outcomes associated with treatment of CIN the authors report that LLETZ was not associated with a significant increase in adverse pregnancy outcomes.[64] Although six out of seven studies suggested a positive but non-significant association with perinatal mortality, five of these compared patients with LLETZ with healthy control subjects, patients without CIN. These studies were also very small and had up to three events. In the one study that compared LLETZ with a population of patients with CIN, the relative risk of adverse pregnancy outcomes was 1.08 (95% CI 0.65 to 1.80), in a study with 2273 events.[65] This result suggests that there is no additional risk of adverse pregnancy outcomes associated with LLETZ. This is an important comparison to help clarify whether there is an additional risk of LLETZ, as the authors report that patients with CIN are known to have an increased risk of adverse obstetric characteristics.[65] As described previously treatment biopsy includes all types of biopsies used for treatment including LLETZ and small excision biopsies.

The QALY decrement associated with biopsy was explored in a sensitivity analysis owing to the uncertainty around this parameter.

Quality-adjusted life-year decrement of cytology

In the previous version of the model the QALY decrement associated with cytology was 0.02. This represents 1 week of life and was much higher than the QALY decrement for biopsy. This seems implausible so we searched other sources for the disutility of cytology. We decided on a QALY decrement of 0.0016 or a disutility of 0.02 over 1 month as was used in other models.[49]

Health-related quality of life of underlying true health states

The previous version of the model also used different HRQoL values for the clear, HPV, CIN1 and CIN2/3 health states, with HRQoL scores of 1 (i.e. perfect health) for those who were clear or had HPV, whereas CIN1 had a score of 0.91 and CIN2/3 a score of 0.87. The model assumes that clear and patients with HPV are in perfect health, whereas the other HRQoL scores are based on the study data of Insinga *et al*.[62] and Chuck.[45] However, given CIN1 and CIN2/3 health states are considered to be asymptomatic, in the base case it was assumed that all patients who were clear, HPV, CIN1 or CIN2/3 would have the same HRQoL (*Table 17*).

TABLE 17 Health-related quality of life (utilities) by health state

Health state	HRQoL score	Source
Clear	0.91	Insinga *et al*.[62] and assumptions
HPV	0.91	Insinga *et al*.[62] and assumptions
CIN1	0.91	Insinga *et al*.[62]
CIN2/3	0.91	Insinga *et al*.[62] and assumptions
Cancer stage 1	0.65	Chuck[45]
Cancer stage 1 with treatment	0.86	Chuck[45]
Cancer stage 2	0.67	Chuck[45]
Cancer stage 2 with treatment	0.83	Chuck[45]
Cancer stage 3	0.56	Chuck[45]
Cancer stage 3 with treatment	0.83	Chuck[45]
Cancer stage 4	0.48	Chuck[45]
Cancer stage 4 with treatment	0.63	Chuck[45]

Costs

An estimate of the average cost per procedure of each of the technologies being assessed is required for a cost-effectiveness analysis. The average cost of a procedure is determined by the set-up cost, annual recurring costs and per patient costs. The set-up costs consist of the capital cost of the machine. The recurring costs consist of the annual maintenance costs and the costs involved in replacing equipment and overheads. Per patient costs consist of the consumables utilised for each procedure and of the cost of staff required.

Information provided by the manufacturers has been used to estimate the costs of each of the technologies being assessed. The purchase price and maintenance costs of colposcopy were provided by clinical advisors (*Table 18*).

The purchase price of each technology was annuitised over the expected lifetime of the technology. Clinical advisors estimated the lifetime of a colposcope to be 15–20 years. The lifetime of the LuViva and DySIS devices were estimated to be 5 years and the Niris device to be 7–10 years by their manufacturers. In the base case we assumed the useful life of the colposcope to be 15 years, DySIS and LuViva to be 5 years, and that of Niris to be 10 years. The equivalent annual cost was calculated from the purchase price of the technology and the useful life of the equipment using the discount rate of costs of 3.5%.

The annual maintenance cost of the colposcope is 10% of the purchase price as suggested by the clinical advisors. The per-patient cost of a speculum was estimated to be £2. The annual maintenance costs and disposable costs of the adjunct technologies were provided by the manufacturers (see *Table 18*).

As the LuViva and Niris trials both used colposcopy to guide the probe or to confirm diagnosis, the cost of the colposcope was also added to their total costs.

To estimate the total cost per patient, it was necessary to know the number of patients expected to be treated each year in order to distribute the fixed costs across the patients. We requested the number of patients managed on a single colposcope from our clinical advisors. The average across available responses from the clinical advisors was 1229 patients per device per year.

To capture the additional costs of a colposcopy visit, treatment costs from the TOMBOLA study were used as provided by a personal communication with Professor Dave Whynes (lead economist in that study) (*Table 19*).[66] These costs were inflated to 2011 prices. The additional cost of a diagnostic biopsy was estimated to be £20.28 and the additional cost of treatment biopsy to be £97.16. As the TOMBOLA cost of a colposcopy examination includes the cost of the colposcope, the colposcopy costs as calculated in *Table 18* were subtracted from the inflated estimates from the TOMBOLA trial (see *Table 19*) to estimate the cost of an examination excluding normal colposcope costs.

To calculate the total cost of each examination by device, the per-patient cost of each device, as calculated in *Table 18*, was added to the cost of an examination excluding normal colposcope costs, £128.90, which is the cost of the colposcopy examination, £132.40, less the cost of the colposcope and disposables, £3.50 (*Table 20*).

The model does not consider the additional cost of a correlation meeting.

Cancer costs by stage were taken from published UK sources and inflated to 2011 prices (*Table 21*).[67]

TABLE 18 Base-case costs (£) of colposcopy and adjunctive technologies

Cost component	Colposcopy	DySIS	DySIS + colposcopy	LuViva	Niris
Assumed useful life of the equipment (years)	15	5	5	5	10
Purchase price (£)	10,000	20,000	20,000	11,500	37,769
Equivalent annual cost (£)[a]	839	4280	4280	2461	4388
Annual maintenance costs (£)	1000	1600	1600	160	0
Other cost (per patient) (£)	0	0	0	3.50	3.50
Disposables (per patient) (£)	2.00	3.50	3.50	17.25	33.19
Total cost per patient (£)[b]	3.50	8.29	8.29	22.88	40.26

a Assumes a 3.5% interest rate.
b Assumes 1229 patients are examined each year per machine.

TABLE 19 Treatment costs from TOMBOLA[66]

Treatment	Unit costs (£)	Costs inflated to 2011 prices (£)
Colposcopy examination only	111.44	132.40
Colposcopy with biopsy[a]	130.19	152.68
Colposcopy with LLETZ[b]	193.22	229.57

a Assumed to be a diagnostic biopsy.
b Assumed cost of any treatment biopsy.

TABLE 20 Total treatment costs by device used in the model

Device	Cost used in model (£)
Colposcopy	132.40 (128.90 + 3.50)
DySIS alone	137.19
DySIS plus colposcopy	137.19
LuViva	151.78
Niris	169.16

TABLE 21 Total treatment costs by cancer stage

Cancer stage	Cost used in model (£)
1	14,304
2	23,562
3	23,407
4	24,912

Analyses

Below, we summarise the analyses undertaken for the report. All analyses are conducted separately for each reason for referral and then a weighted average of cost-effectiveness is reported across all reasons for referral.

The characteristics of the base case are as follows:

- Patients entered the model at the age of 36 years (the average age of those referred for colposcopy from the NHS Cervical Screening Programme).
- Treatment probabilities were based on guidelines and clinical advice.
- The distribution of underlying health states was based on Kelly *et al*.[68] for those referred for borderline plus HPV+ and mild plus HPV+, and on biopsy data from Gateshead for the other reasons for referral.
- HRQoL scores were based on the Eggington study[69] and the assumption that there was no differential HRQoL between clear, HPV, CIN1 and CIN2/3 (see *Health-related quality of life and quality-adjusted life-year decrements*).
- Duration of the HRQoL decrement as a result of cancer was assumed to be 1 year for stage 1 and 5 years for stages 2, 3 and 4.
- No patients were lost to follow-up.

All of the other scenarios considered used the same assumptions and parameter values as the base case unless stated. For the scenario analyses we considered the following variations to our assumptions:

- The patient's age (25 and 45 years old).
- The duration of the HRQoL decrement as a result of cancer for stages 2, 3 and 4 (1 year's and 3 years' duration).
- Cancer treatment costs (50% lower and higher).
- The HRQoL estimates from the Sheffield model were used (i.e. clear and HPV states were assumed to be in perfect health).
- The QALY decrement associated with treatment biopsy was varied (increased by 200%, 500% and 2000%).
- The QALY decrement associated with cytological screening was varied (increased and decreased by 50%).
- Alternative costs of a colposcope were used (£5000 and £20,000).
- Alternative treatment probabilities were used (based on the Gateshead data).
- Patients testing negative by colposcopy or adjuncts would be diagnosed as clear.

Key assumptions for modelling and inputs

A number of key assumptions have been made in the decision-analytic model and these are listed below.

- Treatment and screening decisions are based on the reason for referral for colposcopy and the colposcopist's findings at that examination only (i.e. for those patients re-entering the diagnostic and treatment decision tree, prior history plays no part in the diagnosis and treatment).
- Patients referred to 6-month cytological rescreen after colposcopy require only one inadequate test to be referred again to colposcopy, unlike those on the NHS Cervical Screening Programme who require three inadequate tests.
- Cancer patients with stage 2, 3 or 4 who survive are assumed to receive treatment for 5 years and therefore incur the associated decrements in HRQoL.
- All cancer patients who die as a result of cancer exit the model immediately and receive a QALY pay-off and cost associated with cancer mortality.
- All patients who survive 5 years after cancer treatment are assumed to be cured.

- All patients attend cytology and colposcopy; there is no loss to follow-up.
- Patients who are cured of CIN have the same risk of future CIN as the general population.
- The Gallwas *et al*. study[33] used to convert sensitivities and specificities into the required probabilities of the model is reasonable for all the technologies.

Cost-effectiveness results

The base-case analysis compares only DySIS or DySIS plus colposcopy to colposcopy alone for each reason for referral and for the whole population, because of the lack of reliable evidence for the LuViva and Niris devices. In the sensitivity analyses undertaken on the base case, it was determined that the consequences of treatment biopsy required further exploration.

A secondary analysis was also undertaken assuming a higher QALY decrement and cost for treatment biopsy, as this was shown to be of importance in the model. This secondary analysis was also combined with each of the sensitivity analyses previously described (see *Analyses*).

The whole population was a weighted average of the results of each reason for referral. These estimates were based on data from the NHS Cervical Screening Programme,[2] together with Kelly *et al*.,[68] to account for the reduced numbers of borderline and mild patients as a result of the introduction of HPV triage. The weighted population analyses are 51.3% borderline + HPV, 30.1% mild dyskaryosis + HPV, 8.2% moderate dyskaryosis, 9.3% severe dyskaryosis, 0.4% possible invasion and 0.7% possible glandular neoplasia.

As a result of the unreliable data for Niris and LuViva, an indicative analysis was undertaken to test the needed sensitivity to be considered cost-effective given their reported costs and an assumed specificity.

Results of the base-case analysis

In most instances colposcopy alone was dominated by DySIS or DySIS plus colposcopy (*Table 22*). In other words, colposcopy alone had worse expected outcomes in terms of QALYs and was more costly than either of the DySIS arms. In the case of patients referred for possible invasion, possible neoplasia or inadequate screens, DySIS was more cost-effective than colposcopy alone, as long as the cost-effectiveness threshold was at least £2000 per additional QALY. However, in these cases, colposcopy was still dominated by DySIS plus colposcopy. For all reasons for referral, DySIS alone was more costly and less effective than (dominated by) DySIS plus colposcopy. Therefore, the base case indicates that DySIS plus colposcopy was the cost-effective form of management conditional on the assumptions and evidence used.

The scenario analyses described above were undertaken (see *Appendix 6*). Overall, colposcopy alone had higher costs and lower health outcomes than DySIS or DySIS plus colposcopy for all sensitivity analyses undertaken. The least cost-effective result occurred when colposcopy alone was compared with DySIS alone for patients who were referred because of inadequate cytology. For a population of 25-year-old patients, DySIS alone cost £13,614 per additional QALY compared with colposcopy alone. For all reasons for referral and for all sensitivity analyses, DySIS or DySIS plus colposcopy was cost-effective compared with colposcopy alone as long as the cost-effectiveness threshold was at least £15,000 per QALY.

The base-case results (see *Table 22*) also demonstrated that patients referred with possible invasion had the highest expected costs and worst expected outcomes. Patients referred with inadequate screens had the lowest costs and the best outcomes. Patients referred with borderline/mild cytology and HPV+ had slightly higher costs and worse outcomes than patients referred with moderate/severe cytology. The model suggests this was a result of the difference in treatment patterns between the two groups. More severe patients underwent treatment biopsy which in the model was very effective and had low additional costs (£97) and low QALY decrement (0.005). Less-severe patients returned for multiple treatments, which increased the costs by £132.40 per visit, while they remained at risk of cancers that went undetected. Also, each cytological test and colposcopy visit was associated with a QALY decrement of 0.0016 and 0.03,

TABLE 22 Base-case results by reason for referral and for the whole population

Reasons for referral	Borderline + HPV			Mild + HPV			Moderate			Severe		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	1188.55	20.40278		1223.09	20.39607		1106.85	20.45252		1754.00	20.45968	
DySIS alone	1163.45	20.41037	Dominant	1192.53	20.40468	Dominant	1071.80	20.46103	Dominant	1739.28	20.46442	Dominant
Colposcopy vs DySIS + colposcopy												
Colposcopy	1188.55	20.40278		1223.09	20.39607		1106.85	20.45252		1754.00	20.45968	
DySIS + colposcopy	1131.10	20.41738	Dominant	1155.54	20.41249	Dominant	1031.45	20.46903	Dominant	1716.98	20.46942	Dominant

Reasons for Referral	Possible invasion			Possible neoplasia			3 × inadequate			Whole population[a]		
	Costs	QALYs	ICER	Costs	QALYs	ICER	Costs	QALYs	ICER	Costs	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	6500.85	20.34731		3313.68	20.41361		753.02	20.47523		**1313.59**	**20.41339**	
DySIS alone	6501.71	20.34877	592.59	3316.53	20.41546	1545.34	755.20	20.47653	1687.09	**1287.18**	**20.42098**	**Dominant**
Colposcopy vs DySIS + colposcopy												
Colposcopy	6500.85	20.34731		3313.68	20.41361		753.02	20.47523		**1313.59**	**20.41339**	
DySIS + colposcopy	6496.13	20.35026	Dominant	3312.33	20.41711	Dominant	751.27	20.47768	Dominant	**1254.00**	**20.42805**	**Dominant**

ICER, incremental cost-effectiveness ratio.

a The whole population is a weighted average of the reasons for referral.

respectively. This effect will be further magnified by patients being lost to follow-up, which has not been considered in the model.

Further sensitivity analysis demonstrated that, using the base-case inputs, an increase in a diagnostic device's specificities resulted in worse outcomes. This suggests that it is better to falsely identify patients as CIN2/3 than to find that they are truly CIN1. This occurs because of the difference in treatments for each diagnosis. This result suggests that, as above, given the low additional costs and low QALY decrement of treatment biopsy, it may be a better treatment option for patient with CIN1s than watchful waiting. Further sensitivity analysis was, therefore, undertaken to determine which inputs could be changed in the model to ensure that an increase in specificity resulted in improved outcomes. Three model inputs were identified as important.

1. QALY decrement of treatment biopsy
2. cost of treatment biopsy
3. treatment patterns.

These three inputs were tested to determine the threshold of each input at which an increase in specificity for a given management option would improve outcomes. It was found that the QALY decrement of treatment biopsy would have to be increased from 0.005 (see *Health-related quality of life and quality-adjusted life-year decrements*) to 0.13 (or 47.5 days of healthy life), the cost of treatment biopsy would have to be increased from £97 (see *Costs*) to £2758 or treatment patterns would have to include treatment biopsy of CIN1.

Results of the secondary analyses

Separate secondary analyses were undertaken for the scenarios in which the QALY decrement of treatment biopsy is 0.13 (from 0.005 in the base case) or the cost of treatment biopsy is £2758 (from £97 in the base case). At these values the model generates improved outcomes as the specificity of a given management option is increased.

In the case of increasing the QALY decrement associated with treatment biopsy, the results of the overall analysis suggested that colposcopy alone is more costly and less effective than (i.e. is dominated by) both DySIS alone and DySIS plus colposcopy (*Table 23*) for the overall (weighted) population.

This was also the case for most of the individual referral groups. The only exceptions were that, in the case of colposcopy compared with DySIS alone, DySIS alone was found to be dominated in patients referred with possible neoplasia, possible invasion and three inadequate cytology tests. In the case of colposcopy compared with DySIS plus colposcopy, DySIS plus colposcopy was found to be less costly and less effective than colposcopy in patients referred with possible neoplasia and three inadequate cytology tests. In the former referral group, the incremental cost-effectiveness ratio (ICER) for colposcopy alone was £303, suggesting that colposcopy alone is cost-effective. In the latter referral group, the ICER for colposcopy alone compared with DySIS plus colposcopy was £32,009, which is above NICE's conventional cost-effectiveness threshold (£20,000–£30,000 per QALY gained) and suggests that DySIS plus colposcopy is the cost-effective option.

The sensitivity analyses of this secondary analysis show that although both DySIS comparators are not always cost-effective in the possible invasion and possible neoplasia referral groups and, in some scenarios are dominated, in the overall weighted population both DySIS comparators were found to be less costly and more effective than colposcopy alone (see *Appendix 6*). The intuition for this is discussed further below (see *Discussion*).

A further sensitivity analysis was conducted to establish the QALY decrement with treatment biopsy, which would result in DySIS plus colposcopy having an ICER compared with colposcopy alone of £20,000 and £30,000, respectively (i.e. the QALY decrements at which the combined form of management would

TABLE 23 Secondary analysis results with treatment biopsy QALY decrement 0.13 by reason for referral and for the whole population

Reasons for referral	Borderline + HPV			Mild + HPV			Moderate			Severe		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	1188.55	20.35130		1223.09	20.33886		1106.85	20.32422		1754.00	20.31718	
DySIS alone	1163.45	20.35538	Dominant	1192.53	20.34380	Dominant	1071.80	20.32932	Dominant	1739.28	20.32049	Dominant
Colposcopy vs DySIS + colposcopy												
Colposcopy	1188.55	20.35130		1223.09	20.33886		1106.85	20.32422		1754.00	20.31718	
DySIS + colposcopy	1131.10	20.35991	Dominant	1155.54	20.34901	Dominant	1031.45	20.33499	Dominant	1716.98	20.32451	Dominant

Reasons for Referral	Possible invasion			Possible neoplasia			3 × inadequate			Whole population[a]		
	Costs	QALYs	ICER	Costs	QALYs	ICER	Costs	QALYs	ICER	Costs	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	6500.85	20.20776		3313.68	20.29134		753.02	20.46303		**1313.59**	**20.33799**	
DySIS alone	6501.71	20.20771	Dominated	3316.53	20.28840	Dominated	755.20	20.46282	Dominated	**1287.18**	**20.34230**	**Dominant**
Colposcopy vs DySIS + colposcopy												
Colposcopy	6500.85	20.20776		3313.68	20.29134		753.02	20.46303		**1313.59**	**20.33799**	
DySIS + Colposcopy	6496.13	20.20819	Dominant	3312.33	20.28688	303.35	751.27	20.46297	32,008.73	**1254.00**	**20.34705**	**Dominant**

a The whole population is a weighted average of the reasons for referral.

potentially no longer be cost-effective). It was established that the QALY decrement would have to be 0.38 or 139 healthy days (rather than 0.005 or 1.8 healthy days in the base case, and 0.13 or 47 healthy days in the secondary analysis) for DySIS alone not to be cost-effective compared with colposcopy alone at a £20,000 per QALY threshold. If the QALY decrement is 0.42 or 153 healthy days then DySIS plus colposcopy is not cost-effective compared with colposcopy alone at the £20,000 per QALY threshold.

In the case of increasing the cost of treatment biopsy to £2758 (from £97 in the base case) the results of the overall (weighted) analysis suggested that colposcopy alone was less costly and less effective than both DySIS alone and DySIS plus colposcopy (*Table 24*). DySIS alone resulted in £13,808 per additional QALY compared with colposcopy alone and DySIS plus colposcopy resulted in £12,761 per additional QALY, suggesting that both DySIS-based strategies were cost-effective compared with colposcopy at standard cost-effectiveness thresholds. The cost-effectiveness between referral groups varied widely with DySIS alone costing £74,876 per additional QALY compared with colposcopy alone in those patients referred for possible neoplasia. All comparisons with colposcopy alone in referral groups of moderate, severe, possible invasion, possible neoplasia and inadequate cytology produced cost-effectiveness results greater than £25,000 per additional QALY. However, both DySIS-based strategies were cost-effective in the referral groups borderline + HPV and mild + HPV, which comprise 51.3% and 30.1% of the modelled population, respectively.

The sensitivity analyses of this secondary analysis shows that both DySIS comparators are cost-effective in the overall weighted population in all sensitivity analyses undertaken at a threshold of £10,000 per QALY. Although the DySIS comparators were not always cost-effective in each of the individual referral groups, they were always more effective than colposcopy alone (see *Appendix 7*).

A further sensitivity analysis was conducted to establish the cost of treatment biopsy which would result in DySIS plus colposcopy having an ICER compared with colposcopy alone of £20,000 and £30,000, respectively (i.e. the cost at which the combined form of management would potentially no longer be cost-effective). It was established that the cost would have to be £7698 (rather than £97 in the base case and £2758 in the secondary analysis) for DySIS alone not to be cost-effective compared with colposcopy alone at a £20,000 per QALY threshold, and £8912 for DySIS plus colposcopy not to be cost-effective at a £20,000 per QALY threshold. The cost of treatment biopsy would have to be £11,068 to find DySIS alone compared with colposcopy alone not cost-effective at a £30,000 per QALY threshold and £12,695 to find DySIS plus colposcopy not cost-effective compared with colposcopy alone at a £30,000 per QALY threshold.

Indicative analysis of LuViva and Niris

Two further analyses were undertaken based only on the costs of the LuViva Advanced Cervical Scan and the Niris Imaging System. Owing to the unreliability of the evidence on these devices, these analyses are indicative only and should be interpreted with caution. Given the costs of LuViva and assuming the same specificity as DySIS plus colposcopy, the sensitivity of LuViva would have to be 83% to be considered cost-effective at £20,000 per QALY compared with DySIS plus colposcopy. Given the costs of Niris and assuming the same specificity as DySIS plus colposcopy, the sensitivity of Niris would have to be 86% to be considered cost-effective at £20,000 per QALY compared with DySIS plus colposcopy. DySIS plus colposcopy was chosen as the comparator, as it was found to be the cost-effective option at a £20,000 per QALY threshold in the base case.

It should be emphasised that this evaluation is not comparable to the sensitivities reported above (see *Synthesis of the included studies*). The evaluation provides the sensitivities of Niris and LuViva needed to be cost-effective assuming that they are being used in a population similar to that used for the DySIS studies. The previous quality assessments reported above (see *Quality of research available*) make it clear that these studies are not comparable. Similarly, issues exist for the specificities thus in this analysis we have assumed that it will be the same as DySIS plus colposcopy. It is unclear how reasonable this assumption is.

TABLE 24 Secondary analysis results with treatment biopsy cost of £2758 by reason for referral and for the whole population

Reasons for referral	Borderline + HPV			Mild + HPV			Moderate			Severe		
	Costs	QALYs	ICER	Costs	QALYs	ICER	Costs	QALYs	ICER	Costs	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	1686.37	20.40278		1781.46	20.39607		2432.19	20.45252		3829.41	20.45968	
DySIS alone	1747.22	20.41037	8023.00	1841.51	20.40468	6977.35	2692.37	20.46103	30,568.11	4046.35	20.46442	45,852.74
Colposcopy vs DySIS + colposcopy												
Colposcopy	1686.37	20.40278		1781.46	20.39607		2432.19	20.45252		3829.41	20.45968	
DySIS + colposcopy	1776.64	20.41738	6181.54	1869.32	20.41249	5351.36	2951.27	20.46903	31,437.41	4274.52	20.46942	45,714.04

Reasons for referral	Possible invasion			Possible neoplasia			3 × inadequate			Whole population[a]		
	Costs	QALYs	ICER	Costs	QALYs	ICER	Costs	QALYs	ICER	Costs	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	8957.49	20.34731		5553.71	20.41361		933.31	20.47523		**2161.56**	**20.41339**	
DySIS alone	9049.45	20.34877	63,055.50	5691.59	20.41546	74,876.31	975.73	20.47653	32,725.11	**2266.39**	**20.42098**	**13,807.91**
Colposcopy vs DySIS + colposcopy												
Colposcopy	8957.49	20.34731		5553.71	20.41361		933.31	20.47523		**2161.56**	**20.41339**	
DySIS + colposcopy	9133.52	20.35026	59,664.66	5794.90	20.41711	68,952.75	1002.11	20.47768	28,090.58	**2348.62**	**20.42805**	**12,760.81**

a The whole population is a weighted average of the reasons for referral.

Discussion

The literature review did not identify any cost-effectiveness analyses of colposcopy or of any of the adjunctive technologies. However, economic evaluations of other parts of the management pathway did inform the current evaluation. In particular, an economic model developed at the University of Sheffield, which evaluated the cost-effectiveness of HPV testing triage of women with low-grade abnormal cervical smears, was available for adaptation and was further developed by the EAG. The new model allowed for the comparison of colposcopy with other similar diagnostics and was based on the sensitivity and specificity of each device, as well as the costs of the device and its consumables. Given current practice, treatment was determined by the reason for referral and the results of the colposcopy or adjunct. In the diagnosis of CIN1, watchful waiting was practiced but in the case of CIN2/3 the patients were more likely to receive a treatment biopsy. The results of treatment and the future chances of detection, whether from colposcopic follow-up or from routine screening, determined the future risk of cervical cancer.

The underlying progression in the model along with many of the model inputs were used in the previous economic analyses. However, the EAG updated the model to incorporate treatment decisions based on cytological and colposcopic findings, the effectiveness of cancer treatment, the QALY decrement of biopsy, and the fixed and variable costs of colposcopy and the new technologies. Data were lacking for the long-term costs and consequences of a treatment biopsy, and the model did not incorporate the long-term costs of treatment biopsy; this was considered an important variable, as it influenced the direction of effect of the specificities of the diagnostic technologies.

Sufficient data were available to compare DySIS alone and DySIS plus colposcopy with colposcopy alone. The base-case analysis suggests that both DySIS management options dominate (i.e. are less costly and more effective than) colposcopy alone in the overall weighted population. In the few instances where DySIS alone did not dominate colposcopy alone, the ICERs were £593, £1545 or £1687 per QALY for the referral groups ‘possible invasion’, ‘possible glandular neoplasia’ or ‘inadequate cytology’, respectively. For all reasons for referral, DySIS plus colposcopy is less costly and more effective than DySIS alone. The results of the overall weighted population were robust to the ranges tested in the sensitivity analysis; the highest ICER was £13,614 per QALY in the inadequate cytology referral group in a 25-year-old population comparing DySIS alone with colposcopy alone.

In the base-case analysis, increasing the specificity of a given technology had the effect of lowering its predicted health outcomes and worsening its cost-effectiveness. Three important variables were identified as influencing the direction of effect of specificity:

1. QALY decrement of treatment biopsy
2. costs of treatment biopsy
3. treatment patterns of CIN1.

All of these inputs worked on the same premise that watchful waiting of CIN1 is only appropriate if the costs and health outcomes of a treatment biopsy outweigh the additional costs of follow-up and the risk of developing cancer from being misdiagnosed in the future. In the base case, the QALY decrement and the costs associated with treatment biopsy suggested that it was better to treat CIN1 with a treatment biopsy. This may be a genuine insight of the model but it may also reflect that the cost and QALY decrement in the model were too low. Scenario analyses were undertaken to determine the QALY decrement or cost of treatment biopsy necessary for specificity to have a positive effect on health outcomes and cost-effectiveness. In both cases these values were much higher than those used in the model. The QALY decrement of the treatment biopsy would have to increase to 0.13 from 0.005 and the cost of the treatment biopsy would have to increase to £2758 from £97. These parameter values are much larger than those used in the base case and may be implausible (a 2500% increase in the QALY decrement of the treatment biopsy or a 2700% increase in the cost of treatment biopsy). These parameters suggest that treatment biopsy would result in a loss of 45 days of life. However, it is possible

that both the QALY decrement and the cost of treatment biopsy are simultaneously higher in which case they would both work in the same direction, and there are multiple combinations that would change the effect of specificity. More accurate estimates of both of these inputs would allow us to make more precise estimates of the cost-effectiveness of the alternative technologies, but only at extreme values would either of these inputs in isolation change the conclusion of the modelling that DySIS is cost-effective compared with colposcopy.

In the secondary analyses, colposcopy was more costly and less effective than either DySIS option in the overall weighted population. However, under some assumptions, neither DySIS option was cost-effective for some of the referral groups. This was the case when the cost of treatment biopsy was increased to £2758. Under this assumption, only borderline-plus-HPV and mild-plus-HPV groups were considered cost-effective. DySIS alone compared with colposcopy alone was £8023 and £6977 per QALY in the borderline-plus-HPV and mild-plus-HPV groups, respectively. DySIS plus colposcopy compared with colposcopy alone was £6182 and £5351 per QALY in the borderline-plus-HPV and mild-plus-HPV groups, respectively. As these groups constituted >80% of the population overall, both DySIS comparators can still be considered cost-effective even under the assumptions of the secondary analysis. Although not cost-effective in the more severe reasons for referral, the DySIS comparators were still more effective in these groups.

For this secondary analysis, DySIS and DySIS plus colposcopy appear less favourable in patients with more serious reasons for referral, whereas they remain favourable in the other groups. This is true when either the QALY decrement or cost associated with treatment biopsy is increased. There is a combination of factors that contribute to this. First, the lower specificity of the devices and the more intensive treatment patterns as a result of the more severe cytology will result in more patients who are truly 'clear', 'HPV' or 'CIN1' receiving invasive treatment in the more serious referral groups. Second, as the treatment biopsies become more costly, either in terms of increased costs or lost health as a result of increased QALY decrement, then it is possible that capturing more patients with CIN2/3 as a result of the higher sensitivity of the devices will not prove beneficial, i.e. it might be better to miss such patients as the costs associated with treating them exceed the health benefits as a result of assuming a very high cost and QALY decrement for treatment biopsy. These issues are likely to affect the more serious referral groups more as a result of the split between the underlying true health states in these groups.

The differential cost-effectiveness between referral groups in the secondary analysis suggests that it may be more cost-effective to use different diagnostic devices in different groups. However, if the device is funded for one or more referral groups then the additional cost of using it in other referral groups is zero, with the exception of any differential in the cost of disposables. This suggests that although it may not be cost-effective to fund a device for each referral group separately, it still may be cost-effective to use it in all groups if it is cost-effective to fund it for a single group. To determine if it is cost-effective in a single group would require changing the expected throughput to that of the referral group being considered and will change the per-patient costs of each device. This is not expected to make an important difference in the case of DySIS, as it was found that DySIS was cost-effective in the borderline-plus-HPV and mild-plus-HPV groups that account for >80% of those referred.

Only indicative sensitivity analyses based on the costs of the LuViva Advanced Cervical Scan and the Niris Imaging System were undertaken, and these do not allow us to draw any conclusions on their potential cost-effectiveness. This sensitivity analysis does allow us to say that given their costs, and assuming that they could obtain a specificity equal to DySIS plus colposcopy, their sensitivity would have to be 83% for LuViva and 86% for Niris to be considered cost-effective at £20,000 per QALY threshold compared with the most cost-effective option in our model – DySIS plus colposcopy. These results are not comparable to the sensitivities reported above (see *Synthesis of the included studies*) because of the differences in patient populations and the quality issues of the studies as described above.

Conclusions

From the economic analysis the EAG concludes that the effectiveness evidence on LuViva and Niris is too unreliable to be included in the analysis. The results of the analysis suggest that DySIS plus colposcopy is less costly and more effective than both DySIS alone or colposcopy alone, and that these results are robust to the numerous sensitivity analyses that were undertaken.

Chapter 3 Discussion

Statement of principal findings

The systematic review of the clinical effectiveness of adjunctive colposcopy technologies found a limited amount of data on three adjunctive technologies: two studies of the DySIS colposcope, one study of the LuViva Advanced Cervical Scan, and three studies of the Niris Imaging System.

The two studies of the DySIS colposcope were well reported and had a low risk of bias; they found statistically significantly higher sensitivity with DySIS (both alone and in combination with colposcopy) than conventional colposcopy alone for identifying CIN2+ disease, although specificity was significantly lower with DySIS.

The study of LuViva and those of Niris were all poorly reported and so the risk of bias in these studies was often unclear; where study methodology was reported there were a number of limitations that led to a high risk of bias. Consequently, the results of these studies cannot be considered reliable.

The base-case cost-effectiveness analysis suggests that both DySIS treatment options (DySIS alone and DySIS plus colposcopy) are less costly and more effective than (dominate) colposcopy alone in the overall weighted population. In the few instances where DySIS alone was more costly and more effective than colposcopy alone, the ICERs were £593, £1545 or £1687 per QALY for the referral groups 'possible invasion', 'possible neoplasia' or 'inadequate cytology', respectively. For all reasons for referral DySIS plus colposcopy is less costly and more effective than DySIS alone. The results of the overall weighted population were robust to the ranges tested in the sensitivity analysis; the highest ICER was £13,614 per QALY in the inadequate cytology referral group in a 25-year-old population comparing DySIS alone with colposcopy alone.

A finding of the base-case analysis was that immediate treatment of women with CIN1 was more effective and cost-effective than watchful waiting. This finding was sensitive to the parameter values for the QALY decrement and cost of treatment biopsy and assumed treatment patterns. In the secondary analyses the DySIS comparators were less costly and more effective in the scenario when the QALY decrement of treatment biopsy was increased to 0.13 (from 0.005) and cost-effective when the cost of treatment biopsy was increased to £2758 (from £97) with ICERs of £13,808 and £12,761 per QALY for DySIS alone and DySIS plus colposcopy, respectively, compared with colposcopy alone.

Only indicative sensitivity analyses based on the costs of the LuViva Advanced Cervical Scan and the Niris Imaging System were undertaken, which do not allow us to draw any conclusions on their potential cost-effectiveness.

When comparing the clinical effectiveness results with the cost-effectiveness results, a noticeable contrast is evident: although DySIS plus colposcopy had a very similar overall accuracy to colposcopy alone, it appears cost-effective. This disparity is as a result of several reasons. First, measures of diagnostic accuracy do not necessarily capture what is of importance when it comes to determining patient outcomes. When treating patients with suspected cancerous or precancerous lesions, simply knowing whether a patient is above or below a CIN2+ cut-off is not sufficient for determining treatment, which will in turn affect a patient's outcomes. Secondly, accuracy combines both the effects of sensitivity and specificity in a defined way that does not reflect the same values from the model that are determined by treatment patterns.

In the model the effects of sensitivity and specificity depend on the consequences of treatment. In the case where the treatment consequences (costs and adverse effects) are lower than the risk and consequences

of missing treatment (cancer progression), but current practice does not treat, then it is better for a diagnostic technology to have lower specificity. If, however, the treatment consequences are more severe than the consequences of missing treatment, but current practice undertakes treatment, then it is better for a diagnostic technology to have lower sensitivity. This balance becomes particularly difficult using a binary cut-off (sensitivity and specificity at CIN2+) when actual diagnosis will decide treatment across more than two diagnoses (clear, CIN1, CIN2, CIN3, cancer). For increased sensitivity and specificity to be cost-effective, the treatment patterns for all diagnosed patients must also be cost-effective.

Strengths and limitations of the assessment

Strengths

We conducted a rigorous systematic review of the clinical effectiveness of adjunctive colposcopy technologies, which addressed a clear research question using predefined inclusion criteria. Comprehensive literature searches were performed to locate all relevant published and unpublished studies without any language restrictions. Hand-searching and contact with the manufacturers further reduced the potential for missing relevant studies. Therefore, we are confident that all relevant studies were included in the review. Study selection was undertaken independently by two reviewers and data extraction and quality assessment were checked by a second reviewer to minimise the potential for reviewer bias or error. Validity assessment was undertaken using a validated checklist for diagnostic studies, with additional review-specific quality assessment items added.

To model the decision problem, the adjunct technologies need to be located in the diagnostic and treatment pathway. The model captures the full complexity of this pathway and is also driven by an underlying natural history component that captures the progression of the disease. A previously validated economic model was made available from the University of Sheffield and updated to fit the current decision problem. The clinical experts were very involved in the model development and helped verify treatment patterns and other model inputs. The model facilitates a careful assessment of the uncertainties in the evidence available and assumptions underlying its structure. The cost-effectiveness results for DySIS are robust to most uncertainties in the model.

Limitations

The main limitation of the systematic review of the clinical effectiveness of adjunctive colposcopy technologies was the limited amount and quality of the evidence available. Some of the earlier studies assessed precommercial versions of the technologies, so are not comparable to the later studies, after technologies had been developed further.

Owing to potential biases in the studies of the LuViva Advanced Cervical Scan and the Niris Imaging System, only the results of the studies of the DySIS colposcope are likely to be reliable. Only one of the studies of the Niris Imaging System used clinically relevant cut-offs for classifying images; however, the lack of reference standard assessment for patients with no suspicious areas in this study means that the results are unreliable. The study of the LuViva Advanced Cervical Scan appeared to use a different reference standard for patients with no suspicious areas, thus reducing the reliability of the results of the study. In addition, the authors suggest that the intended use of LuViva is to triage women for colposcopy, rather than as an adjunct to colposcopy.

The findings of the economic analysis are limited by the effectiveness data available. These data were reported as sensitivity and specificity at a CIN2+ threshold. In practice, decisions are not made on whether a patient is CIN2+ or not, and more detailed information about how accurately patients were identified would be more appropriate. To compensate for this lack of data we assumed that DySIS would diagnose across the possible health states clear, CIN1, CIN2, CIN3 or cancer, similarly to Niris in the study by

Gallwas *et al*.[32] The QALY decrement and costs associated with treatment biopsy may not fully take into account the long-term consequences of the procedure. When modelling the outcomes of cancer patients simplifying assumptions have been made.

The Sheffield model on which this model was based was not probabilistic and we were unable to make the complete model probabilistic within the time frame of the assessment. We did consider the inclusion of probabilistic analysis in the diagnostic model but were unaware of methods for capturing the bivariate distribution of sensitivity and specificity from single trial estimates, which is needed for the probabilistic analysis.

Uncertainties

The studies included in this assessment were based on populations of women primarily referred with abnormal cervical cytology. There is uncertainty about how generalisable the results of these studies are to the population of women referred for colposcopy in the future.

The recent introduction of the HPV triage test will alter the population of women referred for colposcopy through the NHS Cervical Screening Programme (women with low-grade abnormalities on screening will be referred for colposcopy only if they are positive for hrHPV).[5] In addition, the screening population is likely to change as females who have received the HPV vaccine reach screening age.

There is uncertainty associated with the method and data used to convert sensitivities and specificities to the required probabilities for the model. This is true, in particular, because of the use of data from a single technology to inform this parameter for all technologies. It is possible that this will be different across technologies. There is a lack of data available on the costs and QALY decrement of treatment biopsy and it is unclear whether the estimates used are robust. It is unclear how 'see and treat' and loss to follow-up might influence the cost-effectiveness of the adjunct devices.

These analyses consider the cost-effectiveness of purchasing a DySIS device rather than purchasing a new colposcope. A separate analysis might consider the cost-effectiveness of replacing a colposcope that has already been purchased. In this case, the per-patient costs of colposcope would exclude the annuitised cost of the colposcope (£1.50). It is expected that this difference will not change the decision being made, particularly if the replaced colposcope has value and can be sold to contribute to the purchase of the new device.

These analyses assume the average use of a colposcope or adjunct as indicated by our clinical advisors. In clinics where colposcopes would be used much less frequently, such as GP clinics, it is unclear whether DySIS would be cost-effective.

It is possible that the introduction of a new device will change treatment patterns. The cost-effectiveness results provided in this report are based on treatment patterns from current clinical opinion or from the Gateshead data, which are both based on the use of standard colposcopy.

Other relevant factors

Currently the economic model does not take account of patients with previous cancerous or precancerous lesions being at higher risk of recurrence than the general population.

The cost-effectiveness of each device may be affected by the level of 'see and treat' used and the amount of loss to follow-up; however, neither of these factors have been evaluated in the economic model.

These results depend on the use of current guidelines and clinical advice to determine treatment probabilities. Any changes to the guidelines will result in different cost-effectiveness.

Chapter 4 Conclusions

DySIS, particularly when combined with colposcopy, has higher sensitivity than conventional colposcopy alone. There is no reliable evidence on the clinical effectiveness of the other adjunctive colposcopy technologies: the LuViva Advanced Cervical Scan and the Niris Imaging System.

From the economic analysis, the EAG concludes that the results of the analysis suggest that DySIS plus colposcopy is less costly and more effective than both DySIS alone and colposcopy alone, and that these results are robust to the numerous sensitivity analyses that were undertaken. The effectiveness evidence on LuViva and Niris is not considered sufficiently reliable to be included in the economic analysis.

Implications for service provision

The introduction of any of these new devices may require additional staff training, which may result in additional upfront costs that were not considered in the analysis. These costs may be actual training costs paid to the manufacturer but might also be costs associated with the additional time or initial accuracy of staff as they learn to use the new device.

Suggested research priorities

In light of the risk of bias affecting the results of the studies of the LuViva Advanced Cervical Scan and the Niris Imaging System, further studies are necessary to reliably evaluate their diagnostic accuracy. The bias risk was a result of the reference standard methodologies used, with further uncertainty about study reliability stemming from the unclear reporting in relation to other possible sources of bias.

The findings of the current model suggest that treatment of CIN1 is cost-effective. However, current treatment guidelines suggest that watchful waiting is preferred for these patients. Further research is needed to assess the robustness of the current model findings to inform the appropriate management of CIN1.

Future studies on the diagnostic accuracy of such technologies should provide results for each diagnostic category (clear, CIN1, CIN2, CIN3, possible invasion and possible neoplasia) rather than sensitivity and specificity at a single cut-off. This could be done by completing *Table 25*.

TABLE 25 Preferred accuracy data

	Findings of new device					
Histological result	Clear	CIN1	CIN2	CIN3	Possible invasion	Possible neoplasia
Clear						
CIN1						
CIN2						
CIN3						
Possible invasion						
Possible neoplasia						

With the information from this table we would not be required to use additional data or assumptions to convert the sensitivities and specificities into the required probabilities for the model.

Future studies should consider assessing interobserver agreement between colposcopists.

Given that a new device may change treatment patterns, further research could also consider collecting data on 'see and treat' rates and the number of biopsies performed.

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Contributions of authors

Ros Wade (Research Fellow) was responsible for the clinical effectiveness section, writing the protocol, study selection, data extraction, validity assessment and writing the final report.

Eldon Spackman (Research Fellow) was responsible for the cost-effectiveness section, writing the protocol, study selection, data extraction, development of the economic model and writing the final report.

Mark Corbett (Research Fellow) was involved in the clinical effectiveness section, writing the protocol, study selection, data extraction, validity assessment and writing the final report.

Simon Walker (Research Fellow) was involved in the cost-effectiveness section, study selection, data extraction, development of the economic model and writing the final report.

Kate Light (Information Specialist) devised the search strategy, carried out the literature searches and wrote the search methodology sections of the final report.

Raj Naik (Consultant Gynaecological Oncologist) provided clinical advice and commented on drafts of the final report.

Mark Sculpher (Professor of Health Economics) provided input at all stages, was involved in the development of the economic model, commented on drafts of the report and had overall responsibility for the cost-effectiveness section of the report.

Alison Eastwood (Senior Research Fellow) provided input at all stages, commented on drafts of the report and had overall responsibility for the clinical effectiveness section of the report.

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Appendix 1 Literature search strategies

The base search strategy was constructed using MEDLINE and then adapted to the other resources searched.

MEDLINE

Via OvidSP, using the segment 1948 to week 2 September 2011, searched on 22 September 2011.

Key

/ = indexing term (MeSH heading)
exp = exploded MeSH heading
sh = subject heading (MeSH) field
$ = truncation
? = embedded truncation or single character truncation
pt = publication type
.ti,ab. = terms in either title or abstract fields
adj = terms adjacent to each other (same order)
adj1 = terms within one word of each other (any order)
adj2 = terms within two words of each other (any order)

1. Cervix Uteri/ (20,005)
2. cervix.ti,ab. (33,049)
3. cervic$.ti,ab. (142,264)
4. endocervix.ti,ab. (910)
5. endocervic$.ti,ab. (3889)
6. ectocervix.ti,ab. (268)
7. ectocervic$.ti,ab. (413)
8. squamocolumnar junction.ti,ab. (317)
9. or/1-8 (168,551)

Line 9 captures terms for the cervix

10. Colposcopy/ (4780)
11. Spectrum Analysis/ (36,398)
12. Tomography, Optical Coherence/ (8286)
13. Spectrometry, Fluorescence/ (50,960)
14. colposcop$.ti,ab. (5529)
15. (reflectance adj2 spectroscop$).ti,ab. (1048)
16. (impedance adj2 spectroscop$).ti,ab. (1394)
17. (fluoresence adj2 spectroscop$).ti,ab. (3)
18. (fluorescence adj2 spectroscop$).ti,ab. (8665)
19. (Dielectric adj2 Spectroscop$).ti,ab. (344)
20. (reflectance adj2 spectrometr$).ti,ab. (64)
21. (impedance adj2 spectrometr$).ti,ab. (21)
22. (fluoresence adj2 spectrometr$).ti,ab. (0)
23. (fluorescence adj2 spectrometr$).ti,ab. (856)
24. (Dielectric adj2 Spectrometr$).ti,ab. (4)
25. (reflectance adj2 spectrum analys$).ti,ab. (0)
26. (fluorescence adj2 spectrum analys$).ti,ab. (18)

27. (fluoresence adj2 spectrum analys$).ti,ab. (0)
28. (impedance adj2 spectrum analys$).ti,ab. (4)
29. (Dielectric adj2 Spectrum analys$).ti,ab. (0)
30. telecolposcopy.ti,ab. (12)
31. optical coherence tomography.ti,ab. (7291)
32. (multispectral adj2 fluorescence).ti,ab. (31)
33. microcolposcopy.ti,ab. (14)
34. dysis.ti,ab. (6)
35. dynamic spectral imaging system.ti,ab. (0)
36. Zilico.ti,ab. (0)
37. apx 100.ti,ab. (0)
38. luviva.ti,ab. (0)
39. Advanced Cervical Scan.ti,ab. (0)
40. multimodal hyperspectral imaging.ti,ab. (0)
41. niris.ti,ab. (13)
42. guided therapeutics.ti,ab. (2)
43. imalux.ti,ab. (8)
44. spectrx.ti,ab. (8)
45. trimodal.ti,ab. (462)
46. or/10-45 (109,432)

Line 46 captures terms for colposcopy

47. 9 and 46 (5618)

Line 47 combines terms for the cervix and colposcopy

48. limit 47 to yr = "2000 -Current" (2371)

Line 48 applies a date limit

Allied and Complementary Medicine Database

Via OvidSP, using the segment 1985 to September 2011, searched on 22 September 2011.

Key

/ = indexing term
exp = exploded indexing term
sh = subject heading field
$ = truncation
? = embedded truncation or single character truncation
pt = publication type
.ti,ab. = terms in either title or abstract fields
adj = terms adjacent to each other (same order)
adj1 = terms within one word of each other (any order)
adj2 = terms within two words of each other (any order)

1. uterine cervical neoplasms/ (17)
2. cervix.ti,ab. (53)
3. cervic$.ti,ab. (2882)
4. endocervix.ti,ab. (0)
5. endocervic$.ti,ab. (0)
6. ectocervix.ti,ab. (0)
7. ectocervic$.ti,ab. (0)
8. squamocolumnar junction.ti,ab. (0)
9. or/1-8 (2925)
10. Spectrum Analysis/ (842)
11. colposcop$.ti,ab. (3)
12. (reflectance adj2 spectroscop$).ti,ab. (1)
13. (impedance adj2 spectroscop$).ti,ab. (2)
14. (fluoresence adj2 spectroscop$).ti,ab. (0)
15. (fluorescence adj2 spectroscop$).ti,ab. (11)
16. (Dielectric adj2 Spectroscop$).ti,ab. (0)
17. (reflectance adj2 spectrometr$).ti,ab. (0)
18. (impedance adj2 spectrometr$).ti,ab. (0)
19. (fluoresence adj2 spectrometr$).ti,ab. (0)
20. (fluorescence adj2 spectrometr$).ti,ab. (1)
21. (Dielectric adj2 Spectrometr$).ti,ab. (0)
22. (reflectance adj2 spectrum analys$).ti,ab. (0)
23. (fluorescence adj2 spectrum analys$).ti,ab. (0)
24. (fluoresence adj2 spectrum analys$).ti,ab. (0)
25. (impedance adj2 spectrum analys$).ti,ab. (0)
26. (Dielectric adj2 Spectrum analys$).ti,ab. (0)
27. telecolposcopy.ti,ab. (0)
28. optical coherence tomography.ti,ab. (4)
29. (multispectral adj2 fluorescence).ti,ab. (0)
30. microcolposcopy.ti,ab. (0)
31. dysis.ti,ab. (0)
32. dynamic spectral imaging system.ti,ab. (0)
33. Zilico.ti,ab. (0)
34. apx 100.ti,ab. (0)
35. luviva.ti,ab. (0)
36. Advanced Cervical Scan.ti,ab. (0)
37. multimodal hyperspectral imaging.ti,ab. (0)

38. niris.ti,ab. (0)
39. guided therapeutics.ti,ab. (0)
40. imalux.ti,ab. (0)
41. spectrx.ti,ab. (0)
42. trimodal.ti,ab. (1)
43. or/10-42 (863)
44. 9 and 43 (5)
45. 44 (5)
46. limit 45 to yr = "2000 -Current" (3)

BIOSIS Previews

Via Dialog, using the segment 1993 to week 2 October 2011, searched on 19 October 2011.

Key

? = truncation
/ti,ab,de = terms in title, abstract, or descriptor fields
(w) = terms adjacent to each other (same order)
py = publication year
: = range e.g. py = 2008:2011 means year = 2008 or 2009 or 2010 or 2011
(n) = terms adjacent to each other (any order)
(2n) = terms within two words of each other (any order)
cc = concept code (for subject area limitation)
s s10/2008:2010 – limits set 10 to records published between 2008 and 2010 (inclusive)

Set	Items	Description
1	35,051	cervix/ti,ab,de
2	82,846	cervic?/ti,ab,de
3	491	endocervix/ti,ab,de
4	2343	endocervic?/ti,ab,de
5	151	ectocervix/ti,ab,de
6	298	ectocervic?/ti,ab,de
7	262	squamocolumnar(w)junction/ti,ab,de
8	97,536	s1:s7
9	2413	colposcop?/ti,ab,de
10	2211	reflectance(2w)spectroscop?/ti,ab,de
11	1453	impedance(2w)spectroscop?/ti,ab,de
12	26	fluoresence(2w)spectroscop?/ti,ab,de
13	12,743	fluorescence(2w)spectroscop?/ti,ab,de
14	349	dielectric(2w)spectroscop?/ti,ab,de
15	142	reflectance(2w)spectrometr?/ti,ab,de
16	19	impedance(2w)spectrometr?/ti,ab,de
17	5	fluoresence(2w)spectrometr?/ti,ab,de
18	1716	fluorescence(2w)spectrometr?/ti,ab,de
19	4	dielectric(2w)spectrometr?/ti,ab,de
20	6	reflectance(2w)spectrum(w)analys?/ti,ab,de
21	36	fluorescence(2w)spectrum(w)analys?/ti,ab,de
22	0	fluoresence(2w)spectrum(w)analys?/ti,ab,de
23	0	impedance(2w)spectrum(w)analys?/ti,ab,de
24	1	dielectric(2w)spectrum(w)analys?/ti,ab,de
25	2	telecolposcopy/ti,ab,de
26	6201	optical(w)coherence(w)tomography/ti,ab,de

Set	Items	Description
27	30	multispectral(2w)fluorescence/ti,ab,de
28	4	microcolposcopy/ti,ab,de
29	8	dysis/ti,ab,de
30	0	dynamic(w)spectral(w)imaging(w)system/ti,ab,de
31	0	zilico/ti,ab,de
32	0	apx((w)100/ti,ab,de
33	0	luviva/ti,ab,de
34	0	advanced(w)cervical(w)scan/ti,ab,de
35	0	multimodal(w)hyperspectral(w)imaging/ti,ab,de
36	12	niris/ti,ab,de
37	2	guided(w)therapeutics/ti,ab,de
38	5	imalux/ti,ab,de
39	8	spectrx/ti,ab,de
40	307	trimodal/ti,ab,de
41	27,309	s9:s40
42	2241	s8 and s41
43	1476	s42/2000:2011

Cochrane Database of Systematic Reviews (CDSR; Issue 9 of 12, September 2011) and Cochrane Central Register of Controlled Trials (CENTRAL; Issue 3 of 4, July 2011)

Via the Wiley Cochrane Library website, searched on 22 September 2011.

Key

MeSH descriptor = indexing term (MeSH heading)
* = truncation
" " = phrase search
:ti,ab = terms in either title or abstract fields
near/1 = terms within one word of each other (any order)
near/2 = terms within two words of each other (any order)
next = terms are next to each other

(Note: The hits for each line refer to the whole of The Cochrane Library, not just the databases specified here.)

#1	MeSH descriptor **Cervix Uteri**, this term only	864
#2	(cervix):ti or (cervix):ab	1690
#3	(cervic*):ti or (cervic*):ab	6441
#4	(endocervix):ti or (endocervix):ab	34
#5	(endocervic*):ti or (endocervic*):ab	222
#6	(ectocervix):ti or (ectocervix):ab	15
#7	(ectocervic*):ti or (ectocervic*):ab	16
#8	(squamocolumnar junction):ti or (squamocolumnar junction):ab	13
#9	(#1 OR #2 OR #3 OR #5 OR #6 OR #7 OR #8)	7481
#10	MeSH descriptor **Colposcopy**, this term only	276
#11	MeSH descriptor **Spectrum Analysis**, this term only	66
#12	MeSH descriptor **Tomography, Optical Coherence**, this term only	257
#13	MeSH descriptor **Spectrometry, Fluorescence**, this term only	93
#14	(colposcop*):ti or (colposcop*):ab	393
#15	(reflectance NEAR/2 spectroscop*):ti or (reflectance NEAR/2 spectroscop*):ab	25
#16	(impedance NEAR/2 spectroscop*):ti or (impedance NEAR/2 spectroscop*):ab	10
#17	(fluoresence NEAR/2 spectroscop*):ti or (fluoresence NEAR/2 spectroscop*):ab	0
#18	(fluorescence NEAR/2 spectroscop*):ti or (fluorescence NEAR/2 spectroscop*):ab	19
#19	(dielectric NEAR/2 spectroscop*):ti or (dielectric NEAR/2 spectroscop*):ab	0
#20	(reflectance NEAR/2 spectrometr*):ti or (reflectance NEAR/2 spectrometr*):ab	3
#21	(impedance NEAR/2 spectrometr*):ti or (impedance NEAR/2 spectrometr*):ab	0
#22	(fluoresence NEAR/2 spectrometr*):ti or (fluoresence NEAR/2 spectrometr*):ab	0
#23	(fluorescence NEAR/2 spectrometr*):ti or (fluorescence NEAR/2 spectrometr*):ab	6
#24	(dielectric NEAR/2 spectrometr*):ti or (dielectric NEAR/2 spectrometr*):ab	0
#25	(reflectance AND (spectrum NEXT analys*)):ti or (reflectance AND (spectrum NEXT analys*)):ab	0

#26	(fluorescence AND (spectrum NEXT analys*)):ti or (fluorescence AND (spectrum NEXT analys*)):ab	0
#27	(fluoresence AND (spectrum NEXT analys*)):ti or (fluoresence AND (spectrum NEXT analys*)):ab	0
#28	(impedance AND (spectrum NEXT analys*)):ti or (impedance AND (spectrum NEXT analys*)):ab	0
#29	(dielectric AND (spectrum NEXT analys*)):ti or (dielectric AND (spectrum NEXT analys*)):ab	0
#30	(telecolposcopy):ti or (telecolposcopy):ab	1
#31	(optical coherence tomography):ti or (optical coherence tomography):ab	429
#32	(multispectral NEAR/2 fluorescence):ti or (multispectral NEAR/2 fluorescence):ab	1
#33	(microcolposcopy):ti or (microcolposcopy):ab	1
#34	(dysis):ti or (dysis):ab	0
#35	"dynamic spectral imaging system":ti or "dynamic spectral imaging system":ab	0
#36	(Zilico):ti or (Zilico):ab	0
#37	"apx 100":ti or "apx 100":ab	0
#38	(luviva):ti or (luviva):ab	0
#39	"Advanced Cervical Scan":ti or "Advanced Cervical Scan":ab	0
#40	"multimodal hyperspectral imaging":ti or "multimodal hyperspectral imaging":ab	0
#41	(niris):ti or (niris):ab	0
#42	(guided therapeutics):ti or (guided therapeutics):ab	1
#43	(imalux):ti or (imalux):ab	0
#44	(spectrx):ti or (spectrx):ab	0
#45	(trimodal):ti or (trimodal):ab	6
#46	(#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45)	1171
#47	(#46), from 2000 to 2011	891

Cumulative Index to Nursing and Allied Health Literature

Via EBSCO*host*, using the segment 1981 to 16 September 2011, searched on 22 September 2011.

Key

MH = indexing term (CINAHL heading)
+ = exploded CINAHL heading
* = truncation
? = embedded truncation
" " = phrase search
ZT = publication type
n1 = terms within one word of each other (any order)
n2 = terms within two words of each other (any order)

#	Query	Limiters/expanders	Last run via	Results
S47	S46	Limiters – published date from: 20000101-20111231 Search modes –Boolean/phrase	Interface: EBSCO*host* Search screen: Advanced search Database: CINAHL	378
S46	S9 and S45	Search modes – Boolean/phrase	Interface: EBSCO*host* Search screen: Advanced search Database: CINAHL	467
S45	(S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32 or S33 or S34 or S35 or S36 or S37 or S38 or S39 or S40 or S41 or S42 or S43 or S44)	Search modes – Boolean/phrase	Interface: EBSCO*host* Search screen: Advanced search Database: CINAHL	2011
S44	TI trimodal OR AB trimodal	Search modes – Boolean/phrase	Interface: EBSCO*host* Search screen: Advanced search Database: CINAHL	22
S43	TI spectrx OR AB spectrx	Search modes – Boolean/phrase	Interface: EBSCO*host* Search screen: Advanced search Database: CINAHL	3
S42	TI imalux OR AB imalux	Search modes – Boolean/phrase	Interface: EBSCO*host* Search screen: Advanced search Database: CINAHL	0
S41	TI "guided therapeutics" OR AB "guided therapeutics"	Search modes – Boolean/phrase	Interface: EBSCO*host* Search screen: Advanced search Database: CINAHL	0
S40	TI niris OR AB niris	Search modes – Boolean/phrase	Interface – EBSCO*host* Search screen: Advanced search Database: CINAHL	1

APPENDIX 1

#	Query	Limiters/expanders	Last run via	Results
S39	TI "multimodal hyperspectral imaging" OR AB "multimodal hyperspectral imaging"	Search modes – Boolean/phrase	Interface – EBSCO*host* Search screen: Advanced search Database: CINAHL	0
S38	TI "Advanced Cervical Scan" OR AB "Advanced Cervical Scan"	Search modes – Boolean/phrase	Interface: EBSCO*host* Search screen: Advanced search Database: CINAHL	0
S37	TI luviva OR AB luviva	Search modes – Boolean/phrase	Interface: EBSCO*host* Search screen: Advanced search Database: CINAHL	0
S36	TI "apx 100" OR AB "apx 100"	Search modes – Boolean/phrase	Interface: EBSCO*host* Search screen: Advanced search Database: CINAHL	0
S35	TI Zilico OR AB Zilico	Search modes – Boolean/phrase	Interface: EBSCO*host* Search screen: Advanced search Database: CINAHL	0
S34	TI "dynamic spectral imaging system" OR AB "dynamic spectral imaging system"	Search modes – Boolean/phrase	Interface: EBSCO*host* Search screen: Advanced search Database: CINAHL	0
S33	TI dysis OR AB dysis	Search modes – Boolean/phrase	Interface: EBSCO*host* Search screen: Advanced search Database: CINAHL	0
S32	TI microcolposcopy OR AB microcolposcopy	Search modes – Boolean/phrase	Interface: EBSCO*host* Search screen: Advanced search Database: CINAHL	0
S31	TI multispectral w2 fluorescence OR AB multispectral w2 fluorescence	Search modes – Boolean/phrase	Interface: EBSCO*host* Search screen: Advanced search Database: CINAHL	1
S30	TI "optical coherence tomography" OR AB "optical coherence tomography"	Search modes – Boolean/phrase	Interface: EBSCO*host* Search screen: Advanced search Database: CINAHL	279
S29	TI telecolposcopy OR AB telecolposcopy	Search modes – Boolean/phrase	Interface: EBSCO*host* Search screen: Advanced search Database: CINAHL	3
S28	TI dielectric w2 "spectrum analys*" OR AB dielectric w2 "spectrum analys*"	Search modes – Boolean/phrase	Interface: EBSCO*host* Search screen: Advanced search Database: CINAHL	0

#	Query	Limiters/expanders	Last run via	Results
S27	TI impedance w2 "spectrum analys*" OR AB impedance w2 "spectrum analys*"	Search modes – Boolean/phrase	Interface: EBSCO*host* Search screen: Advanced search Database: CINAHL	0
S26	TI fluoresence w2 "spectrum analys*" OR AB fluoresence w2 "spectrum analys*"	Search modes – Boolean/phrase	Interface: EBSCO*host* Search screen: Advanced search Database: CINAHL	0
S25	TI fluorescence w2 "spectrum analys*" OR AB fluorescence w2 "spectrum analys*"	Search modes – Boolean/phrase	Interface: EBSCO*host* Search screen: Advanced search Database: CINAHL	0
S24	TI reflectance w2 "spectrum analys*" OR AB reflectance w2 "spectrum analys*"	Search modes – Boolean/phrase	Interface: EBSCO*host* Search screen: Advanced search Database: CINAHL	0
S23	TI dielectric w2 spectrometr* OR AB dielectric w2 spectrometr*	Search modes – Boolean/phrase	Interface: EBSCO*host* Search screen: Advanced search Database: CINAHL	0
S22	TI fluorescence w2 spectrometr* OR AB fluorescence w2 spectrometr*	Search modes – Boolean/phrase	Interface: EBSCO*host* Search screen: Advanced search Database: CINAHL	5
S21	TI fluoresence w2 spectrometr* OR AB fluoresence w2 spectrometr*	Search modes – Boolean/phrase	Interface: EBSCO*host* Search screen: Advanced search Database: CINAHL	0
S20	TI impedance w2 spectrometr* OR AB impedance w2 spectrometr*	Search modes – Boolean/phrase	Interface: EBSCO*host* Search screen: Advanced search Database: CINAHL	3
S19	TI reflectance w2 spectrometr* OR AB reflectance w2 spectrometr*	Search modes – Boolean/phrase	Interface: EBSCO*host* Search screen: Advanced search Database: CINAHL	0
S18	TI dielectric w2 spectroscop* OR AB dielectric w2 spectroscop*	Search modes – Boolean/phrase	Interface: EBSCO*host* Search screen: Advanced search Database: CINAHL	3
S17	TI fluorescence w2 spectroscop* OR AB fluorescence w2 spectroscop*	Search modes – Boolean/phrase	Interface: EBSCO*host* Search screen: Advanced search Database: CINAHL	25
S16	TI fluoresence w2 spectroscop* OR AB fluoresence w2 spectroscop*	Search modes – Boolean/phrase	Interface: EBSCO*host* Search screen: Advanced search Database: CINAHL	0

#	Query	Limiters/expanders	Last run via	Results
S15	TI impedance w2 spectroscop* OR AB impedance w2 spectroscop*	Search modes – Boolean/phrase	Interface: EBSCO*host* Search screen: Advanced search Database: CINAHL	27
S14	TI reflectance w2 spectroscop* OR AB reflectance w2 spectroscop*	Search modes – Boolean/phrase	Interface: EBSCO*host* Search screen: Advanced search Database: CINAHL	15
S13	TI colposcop* OR AB colposcop*	Search modes – Boolean/phrase	Interface: EBSCO*host* Search screen: Advanced search Database: CINAHL	422
S12	(MH "Spectrometry, Fluorescence")	Search modes – Boolean/phrase	Interface: EBSCO*host* Search screen: Advanced search Database: CINAHL	90
S11	(MH "Spectrum Analysis")	Search modes – Boolean/phrase	Interface: EBSCO*host* Search screen: Advanced search Database: CINAHL	847
S10	(MH "Colposcopy")	Search modes – Boolean/phrase	Interface: EBSCO*host* Search screen: Advanced search Database: CINAHL	621
S9	S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8	Search modes – Boolean/phrase	Interface: EBSCO*host* Search screen: Advanced search Database: CINAHL	13,984
S8	TI "squamocolumnar junction" OR AB "squamocolumnar junction"	Search modes – Boolean/phrase	Interface: EBSCO*host* Search screen: Advanced search Database: CINAHL	10
S7	TI ectocervic* OR AB ectocervic*	Search modes – Boolean/phrase	Interface: EBSCO*host* Search screen: Advanced search Database: CINAHL	9
S6	TI ectocervix OR AB ectocervix	Search modes – Boolean/phrase	Interface: EBSCO*host* Search screen: Advanced search Database: CINAHL	5
S5	TI endocervic* OR AB endocervic*	Search modes – Boolean/phrase	Interface: EBSCO*host* Search screen: Advanced search Database: CINAHL	110
S4	TI endocervix OR AB endocervix	Search modes – Boolean/phrase	Interface: EBSCO*host* Search screen: Advanced search Database: CINAHL	8

#	Query	Limiters/expanders	Last run via	Results
S3	TI cervic* OR AB cervic*	Search modes – Boolean/phrase	Interface: EBSCO*host* Search screen: Advanced search Database: CINAHL	13,193
S2	TI cervix OR AB cervix	Search modes – Boolean/phrase	Interface: EBSCO*host* Search screen: Advanced search Database: CINAHL	961
S1	(MH "Cervix")	Search modes – Boolean/phrase	Interface: EBSCO*host* Search screen: Advanced search Database: CINAHL	863

ClinicalTrials.gov

Via website www.clinicaltrials.gov/, using the segment to September 2011, searched on 28 September 2011.

Advanced screen

Search terms = (Cervix OR cervical) AND (Colposcopy OR spectroscopy OR spectrometry OR spectrum analysis) [Performs a general search in all sections of the study record, including title, description, conditions, interventions, locations, etc.] (61 results).

Search terms (searching all fields as above) = dysis OR zilico OR apx 100 OR niris OR imalux OR spectrx OR luviva (4 results).

Current Controlled Trials

Via website www.controlled-trials.com/, using the segment to September 2011, searched on 28 September 2011.

Selected active ISRCTN Register only.

cervical AND Colposcopy	9
cervix AND Colposcopy	3 – all duplicates of the 9
cervical AND spectroscopy	0
cervix AND spectroscopy	0
cervical AND spectrometry	0
cervix AND spectrometry	0
cervical AND spectrum analysis	0
cervix AND spectrum analysis	0
dysis OR zilico OR apx 100 OR niris OR imalux OR spectrx OR luviva 0	0

Database of Abstracts of Reviews of Effects (Issue 3 of 4 2011), Health Technology Assessment Database (Issue 3 of 4 2011), and the NHS Economic Evaluation Database (Issue 3 of 4 2011)

Via the Wiley Cochrane Library website searched on 22 September 2011.

Key

MeSH descriptor = indexing term (MeSH heading)
* = truncation
" " = phrase search
:ti,ab = terms in either title or abstract fields
near/1 = terms within one word of each other (any order)
near/2 = terms within two words of each other (any order)
next = terms are next to each other

(Note: The hits for each line refer to the whole of The Cochrane Library, not just the databases specified here.)

#1	MeSH descriptor **Cervix Uteri**, this term only	864
#2	(cervic*)	7989
#3	(cervix)	2899
#4	(endocervix)	43
#5	(endocervic*)	263
#6	(ectocervix)	18
#7	(ectocervic*)	21
#8	(squamocolumnar junction)	14
#9	(**#1** OR **#2** OR **#3** OR **#4** OR **#5** OR **#6** OR **#7** OR **#8**)	8969
#10	MeSH descriptor **Colposcopy**, this term only	276
#11	MeSH descriptor **Spectrum Analysis**, this term only	66
#12	MeSH descriptor **Tomography, Optical Coherence**, this term only	257
#13	MeSH descriptor **Spectrometry, Fluorescence**, this term only	93
#14	(colposcop*)	563
#15	reflectance NEAR/2 spectroscop*	26
#16	impedance NEAR/2 spectroscop*	10
#17	fluoresence NEAR/2 spectroscop*	0
#18	fluorescence NEAR/2 spectroscop*	21
#19	dielectric NEAR/2 spectroscop*	0
#20	reflectance NEAR/2 spectrometr*	3
#21	impedance NEAR/2 spectrometr*	0
#22	fluoresence NEAR/2 spectrometr*	0
#23	fluorescence NEAR/2 spectrometr*	105
#24	dielectric NEAR/2 spectrometr*	0
#25	reflectance AND (spectrum NEXT analys*)	5

#26	fluorescence AND (spectrum NEXT analys*)	3
#27	fluoresence AND (spectrum NEXT analys*)	0
#28	impedance AND (spectrum NEXT analys*)	7
#29	dielectric AND (spectrum NEXT analys*)	0
#30	telecolposcopy	1
#31	"optical coherence tomography"	454
#32	multispectral NEAR/2 fluorescence	1
#33	microcolposcopy	1
#34	dysis	0
#35	"dynamic spectral imaging system"	0
#36	zilico	0
#37	"apx 100"	0
#38	luviva	0
#39	"Advanced Cervical Scan"	0
#40	"multimodal hyperspectral imaging"	0
#41	niris	0
#42	"guided therapeutics"	0
#43	imalux	0
#44	spectrx	2
#45	trimodal	12
#46	(#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45)	1297
#47	(#9 AND #46)	467
#48	(#47), from 2000 to 2011	293

EMBASE

Via OvidSP, using the segment 1996 to week 37 2011, searched on 22 September 2011.

Key

/ = indexing term (EMTREE heading)
* = focused EMTREE heading
exp = exploded EMTREE heading
$ = truncation
? = embedded truncation
.ti,ab. = terms in either title or abstract fields
adj = terms adjacent to each other (same order)
adj1 = terms within one word of each other (any order)
adj2 = terms within two words of each other (any order)

1. exp uterine cervix/ (7607)
2. cervix.ti,ab. (15,941)
3. cervic$.ti,ab. (97,305)
4. endocervix.ti,ab. (453)
5. endocervic$.ti,ab. (2516)
6. ectocervix.ti,ab. (157)
7. ectocervic$.ti,ab. (267)
8. squamocolumnar junction.ti,ab. (290)
9. or/1-8 (106,929)
10. Colposcopy/ (4510)
11. spectroscopy/ (33,388)
12. reflectometry/ (1840)
13. electrochemical impedance spectroscopy/ (900)
14. spectrofluorometry/ (11,789)
15. optical coherence tomography/ (10,884)
16. colposcop$.ti,ab. (3912)
17. (reflectance adj2 spectroscop$).ti,ab. (1212)
18. (impedance adj2 spectroscop$).ti,ab. (1772)
19. (fluoresence adj2 spectroscop$).ti,ab. (2)
20. (fluorescence adj2 spectroscop$).ti,ab. (8382)
21. (Dielectric adj2 Spectroscop$).ti,ab. (412)
22. (reflectance adj2 spectrometr$).ti,ab. (77)
23. (impedance adj2 spectrometr$).ti,ab. (23)
24. (fluoresence adj2 spectrometr$).ti,ab. (0)
25. (fluorescence adj2 spectrometr$).ti,ab. (989)
26. (Dielectric adj2 Spectrometr$).ti,ab. (6)
27. (reflectance adj2 spectrum analys$).ti,ab. (0)
28. (fluorescence adj2 spectrum analys$).ti,ab. (12)
29. (fluoresence adj2 spectrum analys$).ti,ab. (0)
30. (impedance adj2 spectrum analys$).ti,ab. (4)
31. (Dielectric adj2 Spectrum analys$).ti,ab. (0)
32. optical coherence tomography.ti,ab. (8250)
33. (multispectral adj2 fluorescence).ti,ab. (33)
34. microcolposcopy.ti,ab. (8)
35. dysis.ti,ab. (33)
36. dynamic spectral imaging system.ti,ab. (0)
37. Zilico.ti,ab. (0)

38. apx 100.ti,ab. (0)
39. luviva.ti,ab. (0)
40. Advanced Cervical Scan.ti,ab. (0)
41. multimodal hyperspectral imaging.ti,ab. (1)
42. niris.ti,ab. (17)
43. guided therapeutics.ti,ab. (10)
44. imalux.ti,ab. (11)
45. spectrx.ti,ab. (10)
46. trimodal.ti,ab. (347)
47. or/10-46 (73,182)
48. 9 and 47 (4355)
49. 48 (4355)
50. limit 49 to yr = "2000 -Current" (3637)

Health Management Information Consortium

Via OvidSP, using the segment 1985 to September 2011, searched on 22 September 2011.

Key

$ = truncation
? = embedded truncation
.ti,ab. = terms in either title or abstract fields
adj = terms adjacent to each other (same order)
adj1 = terms within one word of each other (any order)
adj2 = terms within two words of each other (any order)

1. Cervix Uteri/ (0)
2. cervix.ti,ab. (53)
3. cervic$.ti,ab. (2882)
4. endocervix.ti,ab. (0)
5. endocervic$.ti,ab. (0)
6. ectocervix.ti,ab. (0)
7. ectocervic$.ti,ab. (0)
8. squamocolumnar junction.ti,ab. (0)
9. or/1-8 (2925)
10. Colposcopy/ (0)
11. colposcop$.ti,ab. (3)
12. (reflectance adj2 spectroscop$).ti,ab. (1)
13. (impedance adj2 spectroscop$).ti,ab. (2)
14. (fluoresence adj2 spectroscop$).ti,ab. (0)
15. (fluorescence adj2 spectroscop$).ti,ab. (11)
16. (Dielectric adj2 Spectroscop$).ti,ab. (0)
17. (reflectance adj2 spectrometr$).ti,ab. (0)
18. (impedance adj2 spectrometr$).ti,ab. (0)
19. (fluoresence adj2 spectrometr$).ti,ab. (0)
20. (fluorescence adj2 spectrometr$).ti,ab. (1)
21. (Dielectric adj2 Spectrometr$).ti,ab. (0)
22. (reflectance adj2 spectrum analys$).ti,ab. (0)
23. (fluorescence adj2 spectrum analys$).ti,ab. (0)
24. (fluoresence adj2 spectrum analys$).ti,ab. (0)
25. (impedance adj2 spectrum analys$).ti,ab. (0)
26. (Dielectric adj2 Spectrum analys$).ti,ab. (0)
27. telecolposcopy.ti,ab. (0)
28. optical coherence tomography.ti,ab. (4)
29. (multispectral adj2 fluorescence).ti,ab. (0)
30. microcolposcopy.ti,ab. (0)
31. dysis.ti,ab. (0)
32. dynamic spectral imaging system.ti,ab. (0)
33. Zilico.ti,ab. (0)
34. apx 100.ti,ab. (0)
35. luviva.ti,ab. (0)
36. Advanced Cervical Scan.ti,ab. (0)
37. multimodal hyperspectral imaging.ti,ab. (0)
38. niris.ti,ab. (0)
39. guided therapeutics.ti,ab. (0)
40. imalux.ti,ab. (0)

41. spectrx.ti,ab. (0)
42. trimodal.ti,ab. (1)
43. or/10-42 (23)
44. 9 and 43 (2)
45. 44 (2)
46. limit 45 to yr = "2000 -Current" (0)

Inspec

Via OvidSP, using the segment 1969 to week 36 2011, searched on 22 September 2011.

Key

/ = subject heading
exp = exploded EMTREE heading
$ = truncation
? = embedded truncation
.ti,ab. = terms in either title or abstract fields
adj = terms adjacent to each other (same order)
adj1 = terms within one word of each other (any order)
adj2 = terms within two words of each other (any order)

1. gynaecology/ (2663)
2. ervix.ti,ab. (654)
3. cervic$.ti,ab. (2546)
4. endocervix.ti,ab. (1)
5. endocervic$.ti,ab. (11)
6. ectocervix.ti,ab. (4)
7. ectocervic$.ti,ab. (7)
8. squamocolumnar junction.ti,ab. (2)
9. or/1-8 (5219)
10. biomedical optical imaging/ (15,871)
11. spectroscopy/ (8228)
12. electrochemical impedance spectroscopy/ (6857)
13. fluorescence spectroscopy/ (3208)
14. optical tomography/ (8916)
15. spectral analysis/ (28,390)
16. colposcop$.ti,ab. (102)
17. (reflectance adj2 spectroscop$).ti,ab. (3176)
18. (impedance adj2 spectroscop$).ti,ab. (11,183)
19. (fluoresence adj2 spectroscop$).ti,ab. (0)
20. (fluorescence adj2 spectroscop$).ti,ab. (7047)
21. (Dielectric adj2 Spectroscop$).ti,ab. (3161)
22. (reflectance adj2 spectrometr$).ti,ab. (89)
23. (impedance adj2 spectrometr$).ti,ab. (52)
24. (fluoresence adj2 spectrometr$).ti,ab. (0)
25. (fluorescence adj2 spectrometr$).ti,ab. (760)
26. (Dielectric adj2 Spectrometr$).ti,ab. (46)
27. (reflectance adj2 spectrum analys$).ti,ab. (6)
28. (fluorescence adj2 spectrum analys$).ti,ab. (20)
29. (fluoresence adj2 spectrum analys$).ti,ab. (0)
30. (impedance adj2 spectrum analys$).ti,ab. (20)
31. (Dielectric adj2 Spectrum analys$).ti,ab. (6)
32. telecolposcopy.ti,ab. (6)
33. optical coherence tomography.ti,ab. (4417)
34. (multispectral adj2 fluorescence).ti,ab. (49)
35. microcolposcopy.ti,ab. (0)
36. dysis.ti,ab. (0)
37. dynamic spectral imaging system.ti,ab. (2)
38. Zilico.ti,ab. (0)
39. apx 100.ti,ab. (1)

40. luviva.ti,ab. (0)
41. Advanced Cervical Scan.ti,ab. (0)
42. multimodal hyperspectral imaging.ti,ab. (0)
43. niris.ti,ab. (5)
44. guided therapeutics.ti,ab. (3)
45. imalux.ti,ab. (3)
46. spectrx.ti,ab. (2)
47. trimodal.ti,ab. (271)
48. or/10-47 (85,075)
49. 9 and 48 (603)
50. limit 49 to yr = "2000 -Current" (574)

Inside Conferences

Via Dialog, using the segment 1993 to 2011 18 October, searched on 19 October 2011.

Key

? = truncation
/ti,ab,de = terms in title, abstract, or descriptor fields
(w) = terms adjacent to each other (same order)
py = publication year
: = range e.g. py = 2008:2011 means year = 2008 or 2009 or 2010 or 2011
(n) = terms adjacent to each other (any order)
(2n) = terms within two words of each other (any order)
cc = concept code (for subject area limitation)
s s10/2008:2010 – limits set 10 to records published between 2008 and 2010 (inclusive)

Set	Items	Description
1	600	cervix/ti,ab,de
2	6600	cervic?/ti,ab,de
3	3	endocervix/ti,ab,de
4	50	endocervic?/ti,ab,de
5	1	ectocervix/ti,ab,de
6	4	ectocervic?/ti,ab,de
7	3	squamocolumnar(w)junction/ti,ab,de
8	7186	s1:s7
9	450	colposcop?/ti,ab,de
10	650	reflectance(2w)spectroscop?/ti,ab,de
11	1468	impedance(2w)spectroscop?/ti,ab,de
12	3	fluoresence(2w)spectroscop?/ti,ab,de
13	1970	fluorescence(2w)spectroscop?/ti,ab,de
14	600	dielectric(2w)spectroscop?/ti,ab,de
15	8	reflectance(2w)spectrometr?/ti,ab,de
16	4	impedance(2w)spectrometr?/ti,ab,de
17	1	fluoresence(2w)spectrometr?/ti,ab,de
18	217	fluorescence(2w)spectrometr?/ti,ab,de
19	4	dielectric(2w)spectrometr?/ti,ab,de
20	0	reflectance(2w)spectrum(w)analys?/ti,ab,de
21	46	fluorescence(2w)spectrum(w)analys?/ti,ab,de
22	0	fluoresence(2w)spectrum(w)analys?/ti,ab,de
23	1	impedance(2w)spectrum(w)analys?/ti,ab,de
24	1	dielectric(2w)spectrum(w)analys?/ti,ab,de
25	1	telecolposcopy/ti,ab,de

Set	Items	Description
26	2049	optical(w)coherence(w)tomography/ti,ab,de
27	21	multispectral(2w)fluorescence/ti,ab,de
28	0	microcolposcopy/ti,ab,de
29	0	dysis/ti,ab,de
30	0	dynamic(w)spectral(w)imaging(w)system/ti,ab,de
31	0	zilico/ti,ab,de
32	0	apx((w)100/ti,ab,de
33	0	luviva/ti,ab,de
34	0	advanced(w)cervical(w)scan/ti,ab,de
35	0	multimodal(w)hyperspectral(w)imaging/ti,ab,de
36	2	niris/ti,ab,de
37	0	guided(w)therapeutics/ti,ab,de
38	0	imalux/ti,ab,de
39	0	spectrx/ti,ab,de
40	21	trimodal/ti,ab,de
41	7425	s9:s40
42	398	s8 and s41
43	260	s42/2000:2011

PASCAL

Via Dialog, using the segment 1973 to week 2 October 2011, searched on 19 October 2011.

Key

? = truncation
/ti,ab,de = terms in title, abstract, or descriptor fields
(w) = terms adjacent to each other (same order)
py = publication year
: = range e.g. py = 2008:2011 means year = 2008 or 2009 or 2010 or 2011
(n) = terms adjacent to each other (any order)
(2n) = terms within two words of each other (any order)
cc = concept code (for subject area limitation)
s s10/2008:2010 – limits set 10 to records published between 2008 and 2010 (inclusive)

Set	Items	Description
1	26,102	cervix/ti,ab,de
2	64,544	cervic?/ti,ab,de
3	646	endocervix/ti,ab,de
4	1640	endocervic?/ti,ab,de
5	140	ectocervix/ti,ab,de
6	178	ectocervic?/ti,ab,de
7	144	squamocolumnar(w)junction/ti,ab,de
8	74,958	s1:s7
9	2306	colposcop?/ti,ab,de
10	4587	reflectance(2w)spectroscop?/ti,ab,de
11	10,846	impedance(2w)spectroscop?/ti,ab,de
12	4	fluoresence(2w)spectroscop?/ti,ab,de
13	10,255	fluorescence(2w)spectroscop?/ti,ab,de
14	2593	dielectric(2w)spectroscop?/ti,ab,de
15	627	reflectance(2w)spectrometr?/ti,ab,de
16	657	impedance(2w)spectrometr?/ti,ab,de
17	2	fluoresence(2w)spectrometr?/ti,ab,de
18	34,891	fluorescence(2w)spectrometr?/ti,ab,de
19	604	dielectric(2w)spectrometr?/ti,ab,de
20	9	reflectance(2w)spectrum(w)analys?/ti,ab,de
21	25	fluorescence(2w)spectrum(w)analys?/ti,ab,de
22	0	fluoresence(2w)spectrum(w)analys?/ti,ab,de
23	29	impedance(2w)spectrum(w)analys?/ti,ab,de
24	12	dielectric(2w)spectrum(w)analys?/ti,ab,de
25	2	telecolposcopy/ti,ab,de
26	3940	optical(w)coherence(w)tomography/ti,ab,de

Set	Items	Description
27	31	multispectral(2w)fluorescence/ti,ab,de
28	9	microcolposcopy/ti,ab,de
29	3	dysis/ti,ab,de
30	1	dynamic(w)spectral(w)imaging(w)system/ti,ab,de
31	0	zilico/ti,ab,de
32	0	apx((w)100/ti,ab,de
33	0	luviva/ti,ab,de
34	0	advanced(w)cervical(w)scan/ti,ab,de
35	0	multimodal(w)hyperspectral(w)imaging/ti,ab,de
36	6	niris/ti,ab,de
37	0	guided(w)therapeutics/ti,ab,de
38	1	imalux/ti,ab,de
39	7	spectrx/ti,ab,de
40	437	trimodal/ti,ab,de
41	67,761	s9:s40
42	2044	s8 and s41
43	1002	s42/2000:2011

Science Citation Index Expanded

Via Web of Knowledge, using the segment 2000 to 22 September 2011, searched on 23 September 2011.

Key

TS = topic tag; searches terms in title, abstract, author keywords and keywords plus fields
* = truncation
? = embedded truncation
" " = phrase search
near/1 = terms within one word of each other (any order)
near/2 = terms within two words of each other (any order)
same = terms within same sentence

#42	1,997	#41 AND #8 *Databases = SCIE, Time span = 2000–11* *Lemmatisation = On*
#41	**64,814**	#40 OR #39 OR #38 OR #37 OR #36 OR #35 OR #34 OR #33 OR #32 OR #31 OR #30 OR #29 OR #28 OR #27 OR #26 OR #25 OR #24 OR #23 OR #22 OR #21 OR #20 OR #19 OR #18 OR #17 OR #16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 *Databases = SCIE, Time span = 2000–11* *Lemmatisation = On*
#40	**499**	Topic = (trimodal) *Databases = SCIE, Time span = 2000–11* *Lemmatisation = On*
#39	**16**	Topic = (spectrx) *Databases = SCIE, Time span = 2000–11* *Lemmatisation = On*
#38	**6**	Topic = (imalux) *Databases = SCIE, Time span = 2000–11* *Lemmatisation = On*
#37	**5**	Topic = ("guided therapeutics") *Databases = SCIE, Time span = 2000–11* *Lemmatisation = On*
#36	**15**	Topic = (niris) *Databases = SCIE, Time span = 2000–11* *Lemmatisation = On*
#35	**0**	Topic = ("multimodal hyperspectral imaging") *Databases = SCIE, Time span = 2000–11* *Lemmatisation = On*
#34	**0**	Topic = ("Advanced Cervical Scan") *Databases = SCIE, Time span = 2000–11* *Lemmatisation = On*
#33	**0**	Topic = (luviva) *Databases = SCIE, Time span = 2000–11* *Lemmatisation = On*
#32	**0**	Topic = ("apx 100") *Databases = SCIE, Time span = 2000–11* *Lemmatisation = On*

#31	**0**	Topic = (Zilico) *Databases = SCIE, Time span = 2000–11* *Lemmatisation = On*
#30	**1**	Topic = ("dynamic spectral imaging system") *Databases = SCIE, Time span = 2000–11* *Lemmatisation = On*
#29	**23**	Topic = (dysis) *Databases = SCIE, Time span = 2000–11* *Lemmatisation = On*
#28	**3**	Topic = (microcolposcopy) *Databases = SCIE, Time span = 2000–11* *Lemmatisation = On*
#27	**71**	Topic = (multispectral NEAR/2 fluorescence) *Databases = SCIE, Time span = 2000–11* *Lemmatisation = On*
#26	**10,214**	Topic = ("optical coherence tomography") *Databases = SCIE, Time span = 2000–11* *Lemmatisation = On*
#25	**16**	Topic = (telecolposcopy) *Databases = SCIE, Time span = 2000–11* *Lemmatisation = On*
#24	**4**	Topic = (dielectric NEAR/2 "spectrum analys*") *Databases = SCIE, Time span = 2000–11* *Lemmatisation = On*
#23	**20**	Topic = (impedance NEAR/2 "spectrum analys*") *Databases = SCIE, Time span = 2000–11* *Lemmatisation = On*
#22	**0**	Topic = (fluoresence NEAR/2 "spectrum analys*") *Databases = SCIE, Time span = 2000–11* *Lemmatisation = On*
#21	**25**	Topic = (fluorescence NEAR/2 "spectrum analys*") *Databases = SCIE, Time span = 2000–11* *Lemmatisation = On*
#20	**4**	Topic = (reflectance NEAR/2 "spectrum analys*") *Databases = SCIE, Time span = 2000–11* *Lemmatisation = On*
#19	**54**	Topic = (dielectric NEAR/2 spectrometr*) *Databases = SCIE, Time span = 2000–11* *Lemmatisation = On*
#18	**3305**	Topic = (fluorescence NEAR/2 spectrometr*) *Databases = SCIE, Time span = 2000–11* *Lemmatisation = On*
#17	**1**	Topic = (fluoresence NEAR/2 spectrometr*) *Databases = SCIE, Time span = 2000–11* *Lemmatisation = On*

#16	**89**	Topic = (impedance NEAR/2 spectrometr*) *Databases = SCIE, Time span = 2000–11* *Lemmatisation = On*
#15	**304**	Topic = (reflectance NEAR/2 spectrometr*) *Databases = SCIE, Time span = 2000–11* *Lemmatisation = On*
#14	**4193**	Topic = (dielectric NEAR/2 spectroscop*) *Databases = SCIE, Time span = 2000–11* *Lemmatisation = On*
#13	**19,430**	Topic = (fluorescence NEAR/2 spectroscop*) *Databases = SCIE, Time span = 2000–11* *Lemmatisation = On*
#12	**16**	Topic = (fluoresence NEAR/2 spectroscop*) *Databases = SCIE, Time span = 2000–11* *Lemmatisation = On*
#11	**17,914**	Topic = (impedance NEAR/2 spectroscop*) *Databases = SCIE, Time span = 2000–11* *Lemmatisation = On*
#10	**7715**	Topic = (reflectance NEAR/2 spectroscop*) *Databases = SCIE, Time span = 2000–11* *Lemmatisation = On*
#9	**2095**	Topic = (colposcop*) *Databases = SCIE, Time span = 2000–11* *Lemmatisation = On*
#8	**75,249**	#7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1 *Databases = SCIE, Time span = 2000–11* *Lemmatisation = On*
#7	**203**	Topic = ("squamocolumnar junction") *Databases = SCIE, Time span = 2000–11* *Lemmatisation = On*
#6	**157**	Topic = (ectocervic*) *Databases = SCIE, Time span = 2000–11* *Lemmatisation = On*
#5	**75**	Topic = (ectocervix) *Databases = SCIE, Time span = 2000–11* *Lemmatisation = On*
#4	**1589**	Topic = (endocervic*) *Databases = SCIE, Time span = 2000–11* *Lemmatisation = On*
#3	**265**	Topic = (endocervix) *Databases = SCIE, Time span = 2000–11* *Lemmatisation = On*
#2	**69,399**	Topic = (cervic*) *Databases = SCIE, Time span = 2000–11* *Lemmatisation = On*
#1	**12,399**	Topic = (cervix) *Databases = SCIE, Time span = 2000–11* *Lemmatisation = On*

Science Citation Index – Conference Proceedings

Via Web of Knowledge, using the segment 1990 to 22 September 2011, searched on 23 September 2011.

Key

TS = topic tag; searches terms in Title, Abstract, Author Keywords and Keywords Plus fields
* = truncation
? = embedded truncation
" " = phrase search
near/1 = terms within one word of each other (any order)
near/2 = terms within two words of each other (any order)
same = terms within same sentence

#42	**263**	#41 AND #8 *Databases = CPCI-S, Time span = 2000–11* *Lemmatisation = On*
#41	**13,448**	#40 OR #39 OR #38 OR #37 OR #36 OR #35 OR #34 OR #33 OR #32 OR #31 OR #30 OR #29 OR #28 OR #27 OR #26 OR #25 OR #24 OR #23 OR #22 OR #21 OR #20 OR #19 OR #18 OR #17 OR #16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 *Databases = CPCI-S, Time span = 2000–11* *Lemmatisation = On*
#40	**54**	Topic = (trimodal) *Databases = CPCI-S, Time span = 2000–11* *Lemmatisation = On*
#39	**1**	Topic = (spectrx) *Databases = CPCI-S, Time span = 2000–11* *Lemmatisation = On*
#38	**5**	Topic = (imalux) *Databases = CPCI-S, Time span = 2000–11* *Lemmatisation = On*
#37	**1**	Topic = ("guided therapeutics") *Databases = CPCI-S, Time span = 2000–11* *Lemmatisation = On*
#36	**6**	Topic = (niris) *Databases = CPCI-S, Time span = 2000–11* *Lemmatisation = On*
#35	**0**	Topic = ("multimodal hyperspectral imaging") *Databases = CPCI-S, Time span = 2000–11* *Lemmatisation = On*
#34	**0**	Topic = ("Advanced Cervical Scan") *Databases = CPCI-S, Time span = 2000–11* *Lemmatisation = On*
#33	**0**	Topic = (luviva) *Databases = CPCI-S, Time span = 2000–11* *Lemmatisation = On*
#32	**0**	Topic = ("apx 100") *Databases = CPCI-S, Time span = 2000–11* *Lemmatisation = On*

#31	**0**	Topic = (Zilico) *Databases = CPCI-S, Time span = 2000–11* *Lemmatisation = On*
#30	**1**	Topic = ("dynamic spectral imaging system") *Databases = CPCI-S, Time span = 2000–11* *Lemmatisation = On*
#29	**10**	Topic = (dysis) *Databases = CPCI-S, Time span = 2000–11* *Lemmatisation = On*
#28	**0**	Topic = (microcolposcopy) *Databases = CPCI-S, Time span = 2000–11* *Lemmatisation = On*
#27	**35**	Topic = (multispectral NEAR/2 fluorescence) *Databases = CPCI-S, Time span = 2000–11* *Lemmatisation = On*
#26	**3738**	Topic = ("optical coherence tomography") *Databases = CPCI-S, Time span = 2000–11* *Lemmatisation = On*
#25	**3**	Topic = (telecolposcopy) *Databases = CPCI-S, Time span = 2000–11* *Lemmatisation = On*
#24	**3**	Topic = (dielectric NEAR/2 "spectrum analys*") *Databases = CPCI-S, Time span = 2000–11* *Lemmatisation = On*
#23	**9**	Topic = (impedance NEAR/2 "spectrum analys*") *Databases = CPCI-S, Time span = 2000–11* *Lemmatisation = On*
#22	**0**	Topic = (fluoresence NEAR/2 "spectrum analys*") *Databases = CPCI-S, Time span = 2000–11* *Lemmatisation = On*
#21	**4**	Topic = (fluorescence NEAR/2 "spectrum analys*") *Databases = CPCI-S, Time span = 2000–11* *Lemmatisation = On*
#20	**3**	Topic = (reflectance NEAR/2 "spectrum analys*") *Databases = CPCI-S, Time span = 2000–11* *Lemmatisation = On*
#19	**10**	Topic = (dielectric NEAR/2 spectrometr*) *Databases = CPCI-S, Time span = 2000–11* *Lemmatisation = On*
#18	**438**	Topic = (fluorescence NEAR/2 spectrometr*) *Databases = CPCI-S, Time span = 2000–11* *Lemmatisation = On*
#17	**0**	Topic = (fluoresence NEAR/2 spectrometr*) *Databases = CPCI-S, Time span = 2000–11* *Lemmatisation = On*
#16	**16**	Topic = (impedance NEAR/2 spectrometr*) *Databases = CPCI-S, Time span = 2000–11* *Lemmatisation = On*

#15	**36**	Topic = (reflectance NEAR/2 spectrometr*) *Databases = CPCI-S, Time span = 2000–11* *Lemmatisation = On*
#14	**1343**	Topic = (dielectric NEAR/2 spectroscop*) *Databases = CPCI-S, Time span = 2000–11* *Lemmatisation = On*
#13	**2638**	Topic = (fluorescence NEAR/2 spectroscop*) *Databases = CPCI-S, Time span = 2000–11* *Lemmatisation = On*
#12	**2**	Topic = (fluoresence NEAR/2 spectroscop*) *Databases = CPCI-S, Time span = 2000–11* *Lemmatisation = On*
#11	**3644**	Topic = (impedance NEAR/2 spectroscop*) *Databases = CPCI-S, Time span = 2000–11* *Lemmatisation = On*
#10	**1494**	Topic = (reflectance NEAR/2 spectroscop*) *Databases = CPCI-S, Time span = 2000–11* *Lemmatisation = On*
#9	**266**	Topic = (colposcop*) *Databases = CPCI-S, Time span = 2000–11* *Lemmatisation = On*
#8	**9112**	#7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1 *Databases = CPCI-S, Time span = 2000–11* *Lemmatisation = On*
#7	**31**	Topic = ("squamocolumnar junction") *Databases = CPCI-S, Time span = 2000–11* *Lemmatisation = On*
#6	**18**	Topic = (ectocervic*) *Databases = CPCI-S, Time span = 2000–11* *Lemmatisation = On*
#5	**8**	Topic = (ectocervix) *Databases = CPCI-S, Time span = 2000–11* *Lemmatisation = On*
#4	**219**	Topic = (endocervic*) *Databases = CPCI-S, Time span = 2000–11* *Lemmatisation = On*
#3	**30**	Topic = (endocervix) *Databases = CPCI-S, Time span = 2000–11* *Lemmatisation = On*
#2	**7972**	Topic = (cervic*) *Databases = CPCI-S, Time span = 2000–11* *Lemmatisation = On*
#1	**1686**	Topic = (cervix) *Databases = CPCI-S, Time span = 2000–11* *Lemmatisation = On*

Additional searches were conducted to identify systematic reviews of colposcopy. In order to capture as many relevant reviews as possible, these searches consisted only of colposcopy-related terms.

Cochrane Database of Systematic Reviews

Via Wiley Cochrane Library website Issue 10 of 12, October 2011, searched on 25 October 2011.

Key

Medical subject heading (MeSH) descriptor = indexing term (MeSH heading)
* = truncation
" " = phrase search
:ti,ab = terms in either title or abstract fields
near/1 = terms within one word of each other (any order)
near/2 = terms within two words of each other (any order)
next = terms are next to each other

(Note: The hits for each line refer to the whole of The Cochrane Library, not just CDSR. The total number of hits retrieved for CDSR was 6.)

MeSH descriptor **Colposcopy**, this term only	280
MeSH descriptor **Spectrum Analysis**, this term only	66
MeSH descriptor **Tomography, Optical Coherence**, this term only	274
MeSH descriptor **Spectrometry, Fluorescence**, this term only	94
(colposcop*):ti or (colposcop*):ab	395
(reflectance NEAR/2 spectroscop*):ti or (reflectance NEAR/2 spectroscop*):ab	25
(impedance NEAR/2 spectroscop*):ti or (impedance NEAR/2 spectroscop*):ab	10
(fluoresence NEAR/2 spectroscop*):ti or (fluoresence NEAR/2 spectroscop*):ab	0
(fluorescence NEAR/2 spectroscop*):ti or (fluorescence NEAR/2 spectroscop*):ab	20
(dielectric NEAR/2 spectroscop*):ti or (dielectric NEAR/2 spectroscop*):ab	0
(reflectance NEAR/2 spectrometr*):ti or (reflectance NEAR/2 spectrometr*):ab	3
(impedance NEAR/2 spectrometr*):ti or (impedance NEAR/2 spectrometr*):ab	1
(fluoresence NEAR/2 spectrometr*):ti or (fluoresence NEAR/2 spectrometr*):ab	0
(fluorescence NEAR/2 spectrometr*):ti or (fluorescence NEAR/2 spectrometr*):ab	6
(dielectric NEAR/2 spectrometr*):ti or (dielectric NEAR/2 spectrometr*):ab	0
(reflectance AND (spectrum NEXT analys*)):ti or (reflectance AND (spectrum NEXT analys*)):ab	0
(fluorescence AND (spectrum NEXT analys*)):ti or (fluorescence AND (spectrum NEXT analys*)):ab	0
(fluoresence AND (spectrum NEXT analys*)):ti or (fluoresence AND (spectrum NEXT analys*)):ab	0
(impedance AND (spectrum NEXT analys*)):ti or (impedance AND (spectrum NEXT analys*)):ab	0
(dielectric AND (spectrum NEXT analys*)):ti or (dielectric AND (spectrum NEXT analys*)):ab	0
(telecolposcopy):ti or (telecolposcopy):ab	1
(optical coherence tomography):ti or (optical coherence tomography):ab	456
(multispectral NEAR/2 fluorescence):ti or (multispectral NEAR/2 fluorescence):ab	1
(microcolposcopy):ti or (microcolposcopy):ab	1
(dysis):ti or (dysis):ab	0
"dynamic spectral imaging system":ti or "dynamic spectral imaging system":ab	0
(Zilico):ti or (Zilico):ab	1

"apx 100":ti or "apx 100":ab	0
(luviva):ti or (luviva):ab	0
"Advanced Cervical Scan":ti or "Advanced Cervical Scan":ab	0
"multimodal hyperspectral imaging":ti or "multimodal hyperspectral imaging":ab	0
(niris):ti or (niris):ab	0
(guided therapeutics):ti or (guided therapeutics):ab	1
(imalux):ti or (imalux):ab	0
(spectrx):ti or (spectrx):ab	0
(trimodal):ti or (trimodal):ab	8
(**#1** OR **#2** OR **#3** OR **#4** OR **#5** OR **#6** OR **#7** OR **#8** OR **#9** OR **#10** OR **#11** OR **#12** OR **#13** OR **#14** OR **#15** OR **#16** OR **#17** OR **#18** OR **#19** OR **#20** OR **#21** OR **#22** OR **#23** OR **#24** OR **#25** OR **#26** OR **#27** OR **#28** OR **#29** OR **#30** OR **#31** OR **#32** OR **#33** OR **#34** OR **#35** OR **#36**)	1215

Database of Abstracts of Reviews of Effects

Via Wiley Cochrane Library website Issue 4 of 4, October 2011, searched on 25 October 2011.

Key

MeSH descriptor = indexing term (MeSH heading)
* = truncation
" " = phrase search
:ti,ab = terms in either title or abstract fields
near/1 = terms within one word of each other (any order)
near/2 = terms within two words of each other (any order)
next = terms are next to each other

(Note: The hits for each line refer to the whole of The Cochrane Library, not just DARE. The total number of hits retrieved for DARE was 31.)

#1	MeSH descriptor **Colposcopy**, this term only	280
#2	MeSH descriptor **Spectrum Analysis**, this term only	66
#3	MeSH descriptor **Tomography, Optical Coherence**, this term only	274
#4	MeSH descriptor **Spectrometry, Fluorescence**, this term only	94
#5	(colposcop*)	570
#6	reflectance NEAR/2 spectroscop*	26
#7	impedance NEAR/2 spectroscop*	10
#8	fluoresence NEAR/2 spectroscop*	0
#9	fluorescence NEAR/2 spectroscop*	22
#10	dielectric NEAR/2 spectroscop*	1
#11	reflectance NEAR/2 spectrometr*	3
#12	impedance NEAR/2 spectrometr*	1
#13	fluoresence NEAR/2 spectrometr*	0
#14	fluorescence NEAR/2 spectrometr*	107
#15	dielectric NEAR/2 spectrometr*	0
#16	reflectance AND (spectrum NEXT analys*)	5
#17	fluorescence AND (spectrum NEXT analys*)	3
#18	fluoresence AND (spectrum NEXT analys*)	0
#19	impedance AND (spectrum NEXT analys*)	7
#20	dielectric AND (spectrum NEXT analys*)	0
#21	telecolposcopy	1
#22	"optical coherence tomography"	481
#23	multispectral NEAR/2 fluorescence	1
#24	microcolposcopy	1
#25	dysis	0
#26	"dynamic spectral imaging system"	0

#27	zilico	1
#28	"apx 100"	0
#29	luviva	0
#30	"Advanced Cervical Scan"	0
#31	"multimodal hyperspectral imaging"	0
#32	niris	0
#33	"guided therapeutics"	0
#34	imalux	0
#35	spectrx	2
#36	trimodal	14
#37	(**#1** OR **#2** OR **#3** OR **#4** OR **#5** OR **#6** OR **#7** OR **#8** OR **#9** OR **#10** OR **#11** OR **#12** OR **#13** OR **#14** OR **#15** OR **#16** O **#17** OR **#18** OR **#19** OR **#20** OR **#21** OR **#22** OR **#23** OR **#24** OR **#25** OR **#26** OR **#27** OR **#28** OR **#29** OR **#30** OR **#31** OR **#32** OR **#33** OR **#34** OR **#35** OR **#36**)	1344

Database of Abstracts of Reviews of Effects

This database was searched using the CRD DARE administrative database on 25 October 2011.

Key

* = truncation
" " = phrase search

1 colposcop* (73)
2 "Spectrum analys*" (4)
3 spectroscop* (128)
4 spectrometr (38)
5 spectrometr (38)
6 telecolposcop* (1)
7 "optical coherence tomography*" (27)
8 microcolposcop* (1)
9 dysis (0)
10 "dynamic spectral imaging system*" (0)
11 Zilico (0)
12 "apx 100" (0)
13 luviva (0)
14 "Advanced Cervical Scan*" (0)
15 "multimodal hyperspectral imaging" (0)
16 niris (0)
17 "guided therapeutrics" (0)
18 imalux (0)
19 spectrx (0)
20 trimodal (3)
21 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 (256)

Guidelines and treatment pathways

The following websites were searched to identify treatment guidelines and pathways:

- **Scottish Intercollegiate Guidelines Network (SIGN) (www.sign.ac.uk/, searched on 16 June 2011)** using the onsite search engine with the single search term "colposcopy". In addition, the website was scanned. This dual approach identified two relevant guidelines.
- **National Institute for Health and Clinical Excellence (NICE) (www.nice.org.uk/, searched on 16 June 2011)** using the onsite search engine with single search terms: "colposcopy", "dysis". The section of the website labelled "Cervical Cancer" was scanned in detail. This dual approach identified four items.
- **National Guideline Clearinghouse (www.guidelines.gov/, searched on 16 June 2011)** using the onsite search engine with single search terms: "dysis", "colposcopy". The following limits were applied: "treatment or intervention", date of publication was limited to 2005 or later. This produced four hits.
- **NIHR Health Technology Assessment programme (www.hta.ac.uk/, searched on 16 June 2011)** using the onsite search engine with the single search terms: "dysis", "colposcopy". Ten items were retrieved, none of which was a guideline.
- **NHS Evidence (www.evidence.nhs.uk/, searched on 16 June 2011)** using the onsite search engine with the single search terms: "dysis", "colposcopy". The following limit was applied: "Types of information: guidelines".

- **Trip database (www.tripdatabase.com/, searched on 16 June 2011)** using the onsite search engine with the single search terms: “dysis”, “colposcopy”. The following limit was applied: “guidelines”. Ninety-three items were retrieved and scanned for relevance.

Appendix 2 Data extraction tables

Louwers *et al.*, 2011[6]

Study details and design	Participant details	Intervention/comparators	Outcomes/analyses	Results
Linked references: Zaal *et al.*, unpublished **Type of report:** Full publication **Funding:** The VU University Medical Centre, Amsterdam and Forth Photonics Ltd, UK. Forth Photonics had a role in the study design and critically appraised the manuscript, but they had no role in data collection or final data analysis **Study design:** Diagnostic cohort study **Setting:** Outpatient colposcopy clinics at the VU University Medical Centre, Amsterdam, the Reinier de Graaf Hospital, Voorburg, and the Sint Antonius Hospital, Nieuwegein, the Netherlands **Duration of recruitment:** 1 July 2008 to 1 September 2009	**Inclusion/exclusion criteria:** Women aged ≥18 years referred for colposcopy with abnormal cervical cytology (at least borderline nuclear abnormalities) or for follow-up of a CIN1 or CIN2 lesion Exclusion criteria were previous surgery on the cervix, pelvic radiotherapy, current pregnancy or pregnancy in the last 3 months Substudy by Zaal *et al.*, unpublished: Women from the ATP cohort who had an adequate HPV test result were included **Number recruited:** 275 consecutive women were recruited, of which 36 (13.1%) were excluded owing to unsaved examination data (9), no colour-coded map available (9), DSI colposcope did not start (7), no available histology (5), no abnormal referral cytology (3), no DSI colposcopy after signing informed consent (3)	**Intervention:** DSI colposcope – DySIS v2.1. Digital video camera resolution 1024 × 768 pixels; white bright LED illumination; field of view (approx.) 25 × 35 mm; ×10 to ×27 magnification; polarised glare-free images; green and blue digital filter Additionally, there is the option to measure and map the dynamics (i.e. rise time, intensity and persistence) of the acetowhitening effect, for every point of the cervix. Modelling of the measured dynamic curves provides a per-point analysis of the acetowhitening effect. Once acetic acid has been applied, DySIS starts automatically with the measurement of the acetowhitening effect; this data acquisition phase lasts approximately 3 minutes. At the end of the examination the DySIS information is concisely presented in the form of a colour-coded map, which can be overlaid on to the colour image of the tissue. DySIS and the measurement principles and procedures have been described previously (including study by Soutter *et al.*)[17]	**Outcome measures:** The primary outcome was histologically confirmed high-grade cervical disease (CIN2+) Patients were also given a questionnaire to evaluate patient satisfaction **Details of assessment:** All clinical data were analysed using 2 × 2 tables, chi-squared tests, asymptotic McNemar's tests and 95% CIs Substudy by Zaal *et al.*, unpublished: Difference in colposcopic impression and histological outcome in women positive for HPV16 (HPV16+) vs women negative for HPV16 but positive for at least one hrHPV type (non-16 hrHPV+) was calculated using two-sided Fisher's exact test The MWW test was performed to assess whether the number of high-grade pixels in the DSI map (a reflection of lesion size) was related to the HPV16 status and the ability to correctly classify a lesion as high grade	**Analyses presented:** per patient **ITT cohort – DySIS** Sensitivity = 65% (95% CI 56% to 74%), specificity = 70% (95% CI 62% to 78%), PPV = 64% (95% CI 55% to 73%), NPV = 71% (95% CI 63% to 79%) ***Calculated by EAG*:** *Sensitivity = 64.8% (95% CI 55.4% to 73.2%), specificity = 70.2% (95% CI 61.9% to 77.4%), PPV = 64.2% (95% CI 54.9% to 72.6%), NPV = 70.8% (95% CI 62.4% to 77.9%), accuracy = 67.8%, LR+ = 2.18 (95% CI 1.62 to 2.93), LR– = 0.50 (95% CI 0.38 to 0.66), prevalence = 45.2%* **ITT cohort – conventional colposcopy (using DSI colposcope)** Sensitivity = 52% (95% CI 42% to 61%), specificity = 82% (95% CI 75% to 88%), PPV = 70% (95% CI 60% to 80%), NPV = 67% (95% CI 60% to 75%)

Study details and design	Participant details	Intervention/comparators	Outcomes/analyses	Results
	Number analysed: 239 women were included in the ITT cohort 183 women were included in the ATP cohort, as the management of 56 women did not strictly adhere to the protocol: the transformation zone was not completely visible with DSI (19), no biopsy was taken from the DSI colposcope high-grade location (14), image quality was unsatisfactory (7), hardware failed (6), DSI colposcope started too late (2), too much blood (3) or miscellaneous (5) Substudy by Zaal *et al.*, unpublished: 177 **Mean age (range):** ITT cohort = 36.7 (18.7–62.6) years ATP cohort = 36.6 (18.7–62.6) years Substudy by Zaal *et al.*, unpublished: median age 33.6 (18.7–62.6) years	After DySIS had been used as a regular video colposcope, the colour-coded map was then revealed and overlaid on the image of the cervix, but not before the entry of the colposcopist's final predictions. Using the same thresholds as the study by Soutter *et al.*,[17] the colour-coded map provided a prediction for the presence and grade of neoplasia, and indication of the most atypical site for biopsy sampling accordingly **Type of speculum:** NR **Comparator:** Colposcopic examination using DySIS as a regular video colposcope. The colposcopic impression was then digitally recorded by the colposcopist with annotation of the most atypical location and predicted severity of the lesion. Up to this point, the colposcopist was blinded to the DySIS analysis of the images **Type of speculum:** NR		***Calculated by EAG*:** *Sensitivity = 51.9% (95% CI 42.5% to 61.0%), specificity = 81.7% (95% CI 74.2% to 87.4%), PPV = 70% (95% CI 59.2% to 78.9%), NPV = 67.3% (95% CI 59.7% to 74.1%), accuracy = 68.2%, LR+ = 2.83 (95% CI 1.89 to 4.24), LR– = 0.59 (95% CI 0.48 to 0.73), prevalence = 45.2%* The difference between sensitivity of 65% and 52% is statistically significant ($p = 0.039$). The difference between specificity of 70% and 82% is statistically significant ($p = 0.011$) **ITT cohort – DySIS and conventional colposcopy combined** Sensitivity = 80% (95% CI 72% to 87%), specificity = 63% (95% CI 54% to 71%), PPV = 64% (95% CI 56% to 72%), NPV = 79% (95% CI 71% to 87%). ***Calculated by EAG*:** *Sensitivity = 79.6% (95% CI 71.1% to 86.1%), specificity = 62.6% (95% CI 54.1% to 70.4%), PPV = 63.7% (95% CI 55.3% to 71.3%), NPV = 78.8% (95% CI 70.0% to 85.6%), accuracy = 70.3%, LR+ = 2.13 (95% CI 1.67 to 2.71), LR– = 0.33 (95% CI 0.22 to 0.48), prevalence = 45.2%*

Study details and design	Participant details	Intervention/comparators	Outcomes/analyses	Results
	Indication for colposcopy: ITT cohort = 219 (91.6%) abnormal cytology; 20 (8.4%) follow-up CIN1–2 ATP cohort = 166 (90.7%) abnormal cytology; 17 (9.3%) follow-up CIN1–2 Substudy by Zaal *et al.*, unpublished: 129 (72.9%) abnormal cytology; 31 (17.5%) abnormal cytology and HPV+; 15 (8.5%) follow-up CIN1; 2 (1.1%) follow-up CIN2 **Other relevant participant information:** Substudy by Zaal *et al.*, unpublished: 152 (85.9%) patients were premenopausal/perimenopausal, 13 (7.3%) were postmenopausal and 12 (6.8%) had unknown menopausal status **Result of last smear:** ITT cohort: normal = 5 (2.1%), borderline or mild dyskaryosis = 153 (64.0%), worse than borderline/mild dyskaryosis = 81 (33.9%) ATP cohort: normal = 4 (2.2%), borderline or mild dyskaryosis = 118 (64.5%), worse than borderline/mild dyskaryosis = 61 (33.3%) Substudy by Zaal *et al.*, unpublished: normal = 4 (2.3%), borderline or mild dyskaryosis = 113 (63.8%), worse than borderline/mild dyskaryosis = 60 (33.9%)	**Reference standard:** Histology result. The colour-coded map produced by DySIS was compared with the colposcopist's own impression (when using DySIS as a regular video colposcope) and punch biopsies were taken from all identified suspicious areas, including those indicated by the colposcopist, DySIS and one additional control biopsy of apparently normal cervical tissue on the opposite side of the lesion(s). If the colposcopist and DySIS evaluated the cervix as normal, one biopsy was taken from the transformation zone at the 12 o'clock position. For patients having a 'see and treat' loop electrosurgical excision procedure, no punch biopsies were taken. The biopsy sampling procedure was recorded on video and later reviewed to check whether the tissue sample was collected from the annotated area All histology was independently reviewed by a pathologist specialising in gynaecological pathology. In case of disagreement between original assessment and review, a third expert reviewer graded the lesion (19% of all samples), blinded to all previous results, and final diagnosis was determined by the majority decision		**ATP cohort – DySIS** Sensitivity = 79% (95% CI 70% to 88%), specificity = 77% (95% CI 69% to 86%), PPV = 76% (95% CI 67% to 84%), NPV = 81% (95% CI 73% to 89%) ***Calculated by EAG*:** *Sensitivity = 79.1% (95% CI 69.3% to 86.3%), specificity = 77.3% (95% CI 68.0% to 84.5%), PPV = 75.6% (95% CI 65.8% to 83.3%), NPV = 80.6% (95% CI 71.5% to 87.4%), accuracy = 78.1%, LR+ = 3.49 (95% CI 2.38 to 5.11), LR– = 0.27 (95% CI 0.18 to 0.41), prevalence = 47.0%* **ATP cohort – conventional colposcopy (using DSI colposcope)** Sensitivity = 55% (95% CI 44% to 65%), specificity = 85% (95% CI 77% to 92%), PPV = 76% (95% CI 65% to 86%), NPV = 68% (95% CI 59% to 76%)

Study details and design	Participant details	Intervention/comparators	Outcomes/analyses	Results
	hrHPV test: ITT cohort: negative = 73 (30.5%), positive = 158 (66.1%), not performed = 8 (3.3%) ATP cohort: negative 54 (29.5%), positive = 123 (67.2%), not performed = 6 (3.3%) Substudy by Zaal *et al.*, unpublished: HPV test was positive in 133 women; 10 lrHPV+, 80 non-16 hrHPV+, 42 hrHPV16+, in one case the typing was inconclusive	High-risk HPV and viral load were also tested in the cervical sample		***Calculated by EAG*:** *Sensitivity = 54.7% (95% CI 44.2% to 64.7%), specificity = 84.5% (95% CI 76.0% to 90.4%), PPV = 75.8% (95% CI 63.8% to 84.8%), NPV = 67.8% (95% CI 59.0% to 75.4%), accuracy = 70.5%, LR+ = 3.53 (95% CI 2.14 to 5.85), LR– = 0.54 (95% CI 0.42 to 0.69), prevalence = 47.0%* The difference between sensitivity of 79% and 55% is statistically significant ($p = 0.0006$). The difference between specificity of 77% and 85% is not statistically significant ($p = 0.144$) **ATP cohort – DySIS and conventional colposcopy combined** Sensitivity = 88% (95% CI 82% to 95%), specificity = 69% (95% CI 60% to 78%), PPV = 72% (95% CI 63% to 80%), NPV = 87% (95% CI 80% to 95%) ***Calculated by EAG*:** *Sensitivity = 88.4% (95% CI 79.9% to 93.6%), specificity = 69.1% (95% CI 59.3% to 77.4%), PPV = 71.7% (95% CI 62.5% to 79.4%), NPV = 87.0% (95% CI 77.7% to 92.8%), accuracy = 78.1%, LR+ = 2.86 (95% CI 2.10 to 3.89), LR– = 0.17 (95% CI 0.09 to 0.31), prevalence = 47.0%* **Adverse events** No adverse events were reported during the study period

Study details and design	Participant details	Intervention/comparators	Outcomes/analyses	Results
				Patient satisfaction 178/183 (97.3%) women in the ATP cohort completed the patient satisfaction questionnaire; the main result was that DSI colposcopy was no extra burden for the majority of women, compared with conventional colposcopy Substudy by Zaal *et al.*, unpublished: Final histology was normal or low grade in 92 (52%) and high grade in 85 (48%) women Among all women, DySIS indicated a higher percentage of lesions as being severe in HPV16+ women than among non-16 hrHPV+ women (73.8% vs 52.5%, $p = 0.032$). CIN2+ threshold: Total population: *DySIS*: sensitivity = 80% (95% CI 70% to 88%), specificity = 77% (95% CI 67% to 85%) *Conventional colposcopy*: sensitivity = 55% (95% CI 44% to 66%), specificity = 85% (95% CI 76% to 91%). Non-16 hrHPV+ population: *DySIS*: Sensitivity = 74% (95% CI 57% to 87%), specificity = 67% (95% CI 50% to 80%) *Conventional colposcopy*: Sensitivity = 61% (95% CI 43% to 76%), specificity = 83% (95% CI 69% to 93%). HPV16+ population: *DySIS*: Sensitivity = 97% (95% CI 84% to 100%), specificity = 100% (95% CI 69% to 100%);

Study details and design	Participant details	Intervention/comparators	Outcomes/analyses	Results
				Conventional colposcopy: Sensitivity = 53% (95% CI 35% to 71%), specificity = 90% (95% CI 55% to 100%) The sensitivity of DySIS to detect CIN2+ lesions was better among HPV16+ women than among non-16 hrHPV+ women (97% vs 74%; $p = 0.009$). The sensitivity of DySIS to detect CIN3+ lesions was better among HPV16+ women than among non-16 hrHPV+ women (96% vs 79%, p = not significant). No significant differences were observed in the visual impression of the colposcopist between HPV16+ and non-16 hrHPV+ women There were no differences in the mean number of high-grade pixels according to HPV16 status. However, among the CIN2+ lesions that were appointed as high grade by DySIS, those lesions that were also appointed as high grade by the colposcopist were significantly larger than those that were appointed as negative/low grade by the colposcopist (mean rank 35.74 vs 21.02, $p = 0.001$)

lrHPV, low-risk human papillomavirus; MWW, Mann–Whitney–Wilcoxon.

Soutter *et al.*, 2009[17]

Study details and design	Participant details	Intervention/comparators	Outcomes/analyses	Results
Linked references: Soutter *et al.*, conference abstract[18] **Type of report:** Full publication **Funding:** UK SMART program LOT/031/428 and Forth Photonics **Study design:** Diagnostic cohort study **Setting:** Outpatient colposcopy clinics at Hammersmith Hospital and St Mary's Hospital, London, and the Alexandra Hospital, Athens, Greece **Duration of recruitment:** May 2004 to July 2005	**Inclusion/exclusion criteria:** Women with abnormal cervical cytology (showing squamous or glandular cell dyskaryosis or borderline nuclear change) or symptoms suggesting the possibility of cervical neoplasia (postcoital bleeding, postmenopausal bleeding or intermenstrual bleeding) Exclusion criteria were self-referring women without an abnormal cervical cytology result, an inadequate or inflammatory cytology result, any other clinical indication for referral for colposcopy, pregnancy, previous pelvic radiotherapy or any woman for whom any prolongation of the examination was thought to be inadvisable **Number recruited:** 529 consecutive women were recruited; 82 women were recruited to the training group (May to July 2004) and 447 women were recruited to the test group (August 2004 to July 2005), of which 139 were excluded owing to software problems (15), no biopsy taken (23), unsatisfactory view of the cervix owing to the size and design of the speculum (45), problems with the application of acetic acid (37) owing to a batch of faulty disposable nozzles, other reasons (19)	**Intervention:** Precommercial DySIS model (FPC-03) 1024 × 768, 8-bit/channel digital colour CCD camera. The optical head captures images from a 23 mm × 20 mm area, including the transformation zone of the cervix. In this precommercial version, the optical head was mounted on a mechanical arm to position and stabilise it, and locked on to an extension shaft attached to the speculum, to ensure a stable field of view during image acquisition. A syringe was used to spray 2 ml of 3% acetic acid on to the cervix through a nozzle mounted on the extension shaft. After application of the acetic acid, a series of images is captured automatically every 5 seconds for 240 seconds and stored in the computer. Changes in the diffuse reflectance vs time integral are calculated through curve modelling and fitting (CB parameter – diffuse reflectance vs time curves and their interval value) and their spatial distribution is displayed as a PCM	**Outcome measures:** The primary outcome was the incremental DySIS test characteristics over conventional colposcopy, using histology as a reference **Details of assessment:** A ROC curve analysis of the training group data was used to choose an appropriate cut-off value to identify high-grade disease in the test group (553 CB units) A ROC curve analysis was used to evaluate the overall performance of DySIS in the test group. Fisher's exact test with two-sided *p*-values was used to evaluate the differences in the number of cases correctly identified by the different tests *Subgroup assessment by Soutter et al., conference abstract*:[18] For 299 patients the grade of the abnormal smear was known. The sensitivities and specificities of DySIS and conventional colposcopy were calculated separately for patients referred with low-grade smears and patients referred with high-grade smears	**Analyses presented:** per patient 72/308 (23.4%) women had high-grade disease or worse, of which 43 had CIN3, one had adenocarcinoma in situ, two had microinvasive squamous cell carcinoma **DySIS** Sensitivity = 79% (68% to 88%), specificity = 76% (70% to 81%) ***Calculated by EAG*:** *Sensitivity = 79.2% (95% CI 68.4% to 86.9%), specificity = 75.8% (95% CI 70.0% to 80.9%), PPV = 50.0% (95% CI 41.0% to 59.0%), NPV = 92.3% (95% CI 87.6% to 95.3%), accuracy = 76.6%, LR+ = 3.28 (95% CI 2.54 to 4.23), LR– = 0.28 (95% CI 0.17 to 0.43), prevalence = 23.4%*

Study details and design	Participant details	Intervention/comparators	Outcomes/analyses	Results
	Number analysed: 308 women (the test group). 603 punch biopsies were suitable for comparison with the DySIS data, of which 102 (in 72 women) were high-grade disease or worse. Treatment biopsies from 86 women and follow-up biopsies from 15 women were included, two review visit biopsies and three treatment biopsies were excluded because they were not reviewed **Median age (upper and lower quartiles):** 37 (29–46) years 28 women were >50 years, of which nine were >60 years **Indication for colposcopy:** 296 had abnormal cytology; 12 had symptoms **Other relevant participant information:** No women with clinically apparent cancer were included Four women were referred with AGUS cervical cytology result	The DySIS user was guided by the PCM and marked the areas with the highest CB values with a coloured circle **Type of speculum:** NR **Comparator:** While the DySIS examination was being conducted by one colposcopist, a second colposcopist did a colposcopic assessment using a separate video monitor displaying the images of the cervix captured by DySIS. The second colposcopist completed a colposcopy form and indicated on a diagram the areas for biopsy **Type of speculum:** NR		**Conventional colposcopy** Sensitivity = 49% (37% to 61%), specificity = 89% (85% to 93%) ***Calculated by EAG*:** *Sensitivity = 48.6% (95% CI 37.4% to 59.9%), specificity = 89.4% (95% CI 84.8% to 92.7%), PPV = 58.3% (95% CI 45.7% to 69.9%), NPV = 85.1% (95% CI 80.1% to 89.0%), accuracy = 79.9%, LR+ = 4.59 (95% CI 2.96 to 7.13), LR– = 0.58 (95% CI 0.46 to 0.72), prevalence = 23.4%* **ROC curve analysis:** Area under the curve = 0.844 (95% CI 0.797 to 0.892) Subgroup results: Of the four women who were referred with AGUS cervical cytology result, one had adenocarcinoma in situ and one CIN3; both of these had abnormal DySIS. The remaining two had CIN1, neither had abnormal DySIS results Of the 28 women who were aged >50 years, eight had high-grade disease, seven of which were detected by DySIS. Of the 20 without high-grade disease, 16 were correctly categorised by DySIS

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Study details and design	Participant details	Intervention/comparators	Outcomes/analyses	Results
		Reference standard: Histology result. Both colposcopists selected areas for biopsy and also selected sites that did not seem to contain CIN in order to reduce verification bias. The DySIS user took biopsies from all the points identified by both colposcopists (a single biopsy was taken when selected sites coincided) The initial histological report was provided by institutional pathologists. All diagnostic biopsies and any subsequent treatment or follow-up biopsies were evaluated independently by two accredited histopathologists not associated with the hospital in which the biopsies were taken or originally assessed. Disagreements were resolved by a third histopathologist; 16.5% biopsies needed to be sent for a third opinion. Histopathologists were unaware of the DySIS result and the histopathology reports of the other pathologists. The final diagnosis was determined by the majority opinion		Although women with only inflammatory changes on cervical cytology were excluded, many had inflammatory changes on the cervix but a more marked cytological picture. Cervicitis did not affect the interpretation as areas of high-grade CIN were clearly seen as distinct areas with high CB values **Unsatisfactory examination:** Colposcopy was described as unsatisfactory in 65 cases because the squamocolumnar junction was not clearly visible; however, these women were not excluded from the study **Adverse events:** No adverse events were reported **Subgroup assessment by grade of referral smear:** Subgroup assessment by Soutter *et al.*, conference abstract:[18] Among 224 women referred with a low-grade smear, 31 (13.8%) had a high-grade or invasive lesion, whereas in 75 women referred with a high-grade smear, 40 (53.3%) had a high-grade or invasive lesion *Patients referred for a low-grade smear*: DySIS: Sensitivity: 77.4%, specificity: 77.2% Colposcopy: Sensitivity: 19.4%, specificity: 93.3% *Patients referred for a high-grade smear*: DySIS: Sensitivity: 80.0%, specificity: 74.3% Colposcopy: Sensitivity: 72.5%, specificity: 68.6% The difference in DySIS sensitivity between low- and high-grade smear referrals was 2.6% (95% CI –22.9% to 16.5%; $p > 0.999$) The difference in DySIS specificity between low-grade and high-grade smear referrals was 2.9% (95% CI –10.5% to 20.2%; $p = 0.532$) The difference in colposcopy sensitivity between low- and high-grade smear referrals was 53.1% (95% CI 30.8% to 69.8%; $p < 0.0001$) The difference in colposcopy specificity between low- and high-grade smear referrals was 24.7% (95% CI 11.1% to 41.6%; $p < 0.0001$)

AGUS, atypical glandular cells of undetermined significance; CCD, charged, coupled device; NR, not reported; PCM, pseudocolour map; ROC, receiver operator characteristic.

Flowers *et al.*, unpublished

Study details and design	Participant details	Intervention/comparators	Outcomes/analyses	Results
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Gallwas *et al.*, 2011[32]

Study details and design	Participant details	Intervention/comparators	Outcomes/analyses	Results
Linked papers: Gallwas *et al.*, 2010[34] **Type of report:** Full publication **Funding:** Grants from Friedrich-Baur-Stiftung and Muenchener Medizinische Wochenschrift. A Niris Imaging System was loaned by Imalux **Study design:** Diagnostic cohort study **Setting:** Outpatient Munich, Germany **Duration of recruitment:** July 2008 to May 2010	**Inclusion/exclusion criteria:** All women were referred for colposcopy. Women aged <18 years, and pregnant women, were excluded **Number recruited:** Unclear, although 1375 images were taken from 120 women (1165 images were from unsuspicious areas, and 210 were compared with histology) **Number analysed:** 210 images (number of women unknown) **Mean age (range):** 31.1 years (18–46) **Indication for colposcopy:** All women had abnormal cytology **Other relevant participant information:** All participants were pre-menopausal **Result of last smear:** PAP II, 19; PAP IIW, 14; PAP III, 5; PAP IIID, 44; PAP IVA, 32; PAP IVB, 5; PAP V, 1 hrHPV test: 93 women tested positive	**Intervention:** Colposcopy-guided OCT using the Niris Imaging system (consisting of an imaging console, a keyboard, a touchpad for data entry, and a detachable fibre optic probe). The console produces near-infrared light ($\lambda = 1310$ nm) through a 2.7-mm diameter probe. Light is back-scattered from the patient's tissue, collected by the probe and combined with an internal reference signal to produce a high-spatial resolution image of the superficial tissue microstructure with a depth scanning range of 1–2 mm (10-to 20-μm resolution) a lateral scanning range of approximately 2 mm at (approximately 25-μm resolution) acquiring a 200×200 pixel image in 1.5 seconds Images were evaluated by two investigators, blinded to colposcopic and histological findings, as being normal, inflammation, CIN1, CIN2, CIN3 or squamous carcinoma **Type of speculum:** NR **Details of cleaning/sheath:** Niris probe sheath was used **Comparator:** Conventional colposcopy **Type of speculum:** NR **Details of cleaning/sheath:** NR	**Outcome measures:** CIN using cut offs at CIN1+, CIN2+ and CIN3+ **Details of assessment:** Clinical data were analysed using 2×2 tables with 95% CIs reported	In this paper, similar results were presented separately for two investigators. Presented here are the results for the first investigator: **Analyses presented:** per image Nine images were confirmed by histology to be cancerous (no details on grade were reported) **Colposcopy-guided Niris Imaging system: CIN1+ threshold:** Sensitivity = 98% (95% CI 96% to 100%), specificity = 39% (95% CI 27% to 51%), PPV = 79% (95% CI 73% to 85%), NPV = 89% (95% CI 78% to 101*%), LR+ = 1.61 (95% CI 1.31 to 2.05), LR– = 0.05 (95% CI 0.00 to 0.16) **sic* ***Calculated by EAG*:** *Sensitivity = 97.9% (95% CI 94.1% to 99.3%), specificity = 39.1% (95% CI 28.1% to 51.3%), PPV = 78.6% (95% CI 72.1% to 83.9%), NPV = 89.3% (95% CI 72.8% to 96.3%), accuracy = 80.0%, LR+ = 1.61 (95% CI 1.32 to 1.96), LR– = 0.05 (95% CI 0.02 to 0.17), prevalence = 69.5%*

Study details and design	Participant details	Intervention/comparators	Outcomes/analyses	Results
		Reference standard: Histology result. Biopsies taken from suspicious areas identified using OCT. Details of when biopsies were taken as a result of colposcopic examination were not reported		**Colposcopy-guided Niris Imaging system: CIN2+ threshold:** Sensitivity = 86% (95% CI 80% to 93%), specificity = 64% (95% CI 54% to 73%), PPV = 73% (95% CI 65% to 80%), NPV = 81% (95% CI 72% to 90%), LR+ = 2.38 (95% CI 1.75 to 3.45), LR– = 0.21 (95% CI 0.10 to 0.37) ***Calculated by EAG*:** *Sensitivity = 86.5% (95% CI 78.9% to 91.6%), specificity = 63.6% (95% CI 53.8% to 72.4%), PPV = 72.7% (95% CI 64.6% to 79.6%), NPV = 80.8% (95% CI 70.7% to 88.0%), accuracy = 75.7%, LR+ = 2.38 (95% CI 1.81 to 3.12), LR– = 0.21 (95% CI 0.13 to 0.35), prevalence = 52.9%*

Study details and design	Participant details	Intervention/comparators	Outcomes/analyses	Results
				Colposcopy-guided Niris Imaging system: CIN3+ threshold:
				Sensitivity = 87% (95% CI 80% to 95%, specificity = 81% (95% CI 74% to 88%), PPV = 73% (95% CI 64% to 82%), NPV = 91% (95% CI 86% to 97%), LR+ = 4.60 (95% CI 3.11 to 7.72), LR– = 0.16 (95% CI 0.06 to 0.27)
				***Calculated by EAG*:**
				Sensitivity = 87.2% (95% CI 78.0% to 92.9%), specificity = 81.1% (95% CI 73.5% to 86.8%), PPV = 73.1% (95% CI 63.3% to 81.1%), NPV = 91.5% (95% CI 85.0% to 95.3%), accuracy = 83.3%, LR+ = 4.60 (95% CI 3.20 to 6.62), LR– = 0.16 (95% CI 0.09 to 0.28), prevalence = 37.1%
				Colposcopy alone:
				Sensitivity: CIN1+ = 99%, CIN2+ = 99%, CIN3+ = 78%
				Specificity:CIN1+ = 19%, CIN2+ = 61%, CIN3+ = 74%
				Adverse events:
				NR as an outcome

NR, not reported.

Liu *et al.*, 2010[32]

Study details and design	Participant details	Intervention/comparators	Outcomes/analyses	Results
Linked references: Wulan *et al.*,[35] Liu *et al.*,[32] Rasool[36] **Type of report:** Full publication **Funding:** NR **Study design:** Diagnostic cohort study **Setting:** Outpatient, Peking University Shenzhen Hospital, Shenzhen, China **Duration of recruitment:** NR	**Inclusion/exclusion criteria:** Non-pregnant women aged ≥ 18 years referred for colposcopy Participants had to have abnormal cervical cytological findings or a positive test for one of the high-risk types of HPV **Number recruited:** Unclear Number analysed: 299 women (1237 paired diagnoses) **Median age (range):** 36.7 (19.2–67.9) years **Indication for colposcopy:** NR Other relevant participant information: 10% of women were menopausal **Result of last smear:** NR **hrHPV test:** NR	**Intervention:** Niris Imaging System (consisting of an imaging console, a keyboard, a touchpad for data entry, and a detachable fibre optic probe). The console produces near-infrared light ($\lambda = 1310$ nm) directed through a 2.7-mm diameter probe. Light is back-scattered from the patient's tissue, collected by the probe and combined with an internal reference signal to produce a high-spatial resolution image of the superficial tissue microstructure with a 10- to 20-μm depth resolution and 15- to 25-μm lateral resolution, acquiring a 200×200 pixel image in 1.5 seconds Niris images were read at the time of image capture by the operator and impressions were rated as being normal, indeterminate or abnormal **Type of speculum:** NR Details of cleaning/sheath: Disposable OCT probe sheath Comparator: Conventional colposcopy. The cervix was divided into quadrants for examination. Impressions were rated as being normal, low grade, high grade, or cancer. Type of speculum: NR Details of cleaning/sheath: NR	**Outcome measures:** CIN using cut-offs at indeterminate or abnormal **Details of assessment:** Sensitivities and specificities were presented with 95% CI	**Analyses presented:** By lesion, by woman, and by a woman's worst quadrant biopsy result 53 women (18%) had CIN2+, 28 (9%) had CIN3+ **Colposcopy-directed Niris Imaging System** Sensitivity and specificity results were also reported in the paper using the proportion of patients with a histology result of CIN3+

Study details and design	Participant details	Intervention/comparators	Outcomes/analyses	Results
		Reference standard: Histology result from a team of pathologists. One gynaecologic pathologist served as the final reference and quality control All patients had a minimum of 5 biopsies, one in each quadrant, and endocervical curettage. In normal quadrants biopsies were taken at the 2, 4, 8 and 10 o'clock positions at the squamocolumnar junction		***Selected 2 × 2 data provided following personal correspondence with an author*:** **Colposcopy-directed Niris Imaging System, by woman** Device: Colposcopy-directed Niris Indeterminate/abnormal: CIN2+ 24, <CIN2 34, Total 58 Normal: CIN2+ 29, <CIN2 211, Total 240 Total: CIN2+ 53, <CIN2 245, Total 298 ***Calculated by EAG*:** *Sensitivity = 45.3% (95% CI 32.7% to 58.5%), specificity = 86.1% (95% CI 81.2% to 89.9%), PPV = 41.4% (95% CI 29.6% to 54.2%), NPV = 87.9% (95% CI 83.2% to 91.5%), accuracy = 78.9%, LR+ = 3.26 (95% CI 2.12 to 5.02), LR− = 0.64 (95% CI 0.50 to 0.82), prevalence = 17.8%* **Colposcopy-directed Niris Imaging System, by woman** Device: Colposcopy-directed Niris Abnormal: CIN2+ 17, <CIN2 17, Total 34 Normal/indeterminate: CIN2+ 36, <CIN2 228, Total 264 Total: CIN2+ 53, <CIN2 245, Total 298 *Calculated by EAG*: *Sensitivity = 32.1% (95% CI 21.1% to 45.5%), specificity = 93.1% (95% CI 89.2% to 95.6%), PPV = 50.0% (95% CI 34.1% to 65.9%), NPV = 86.4% (95% CI 81.7% to 90.0%), accuracy = 82.2%, LR+ = 4.62 (95% CI 2.53 to 8.45), LR− = 0.73 (95% CI 0.61 to 0.88), prevalence = 17.8%*

Study details and design	Participant details	Intervention/comparators	Outcomes/analyses	Results

Colposcopy alone

Type of analysis	Sensitivity (95% CI)	Specificity (95% CI)
By lesion		
Colpo low grade pos	60 (48 to 72)	83 (86 to 80)
Colpo high grade pos	NR in paper *Calculated by EAG*: *29 (21 to 39)*	98 (97 to 99)
By woman		
Colpo low grade pos	74 (60 to 84)	67 (73 to 61)
Colpo high grade pos	23 (13 to 36)	96 (91 to 93[a])
By worst quadrant biopsy		
Colpo low grade pos	58 (45 to 71)	81 (76 to 86)
Colpo high grade pos	19 (10 to 32)	99 (96 to 100)

Colpo, colposcopy; pos, positive.
a *sic* (EAG calculation below).

Sensitivity and specificity results were also reported in the paper using the proportion of patients with a histology result of CIN3+

Study details and design	Participant details	Intervention/comparators	Outcomes/analyses	Results

***Selected 2 × 2 data provided following personal correspondence with an author*:**

Colposcopy alone, by woman

Device		Histology		
		CIN2+	<CIN2	Total
Colposcopy	High grade	12	9	21
	Normal/low grade	41	237	278
Total		53	246	299

Calculated by EAG:

Sensitivity = 22.6% (95% CI 13.5% to 35.5%), specificity = 96.3% (95% CI 93.2% to 98.1%), PPV = 57.1% (95% CI 36.5% to 75.5%), NPV = 85.3% (95% CI 80.6% to 88.9%), accuracy = 83.3%, LR+ = 6.19 (95% CI 2.75 to 13.94), LR– = 0.80 (95% CI 0.69 to 0.93), prevalence = 17.7%

Adverse events:

NR as an outcome

NR, not reported.

Escobar *et al.*, 2006[31]

Study details and design	Participant details	Intervention/comparators	Outcomes/analyses	Results
Linked references: Kuznetsova *et al.*[39] (*AiC information has been removed*) Rojas-Espaillat *et al.*[38] Rasool *et al.*[36] Apisdorf *et al.*[37] **Type of report:** Full publication **Funding:** NR **Study design:** Diagnostic cohort study **Setting:** Outpatient. Cleveland Clinic Foundation, USA, and Hospital Maternidad Nuestra Senora de la Altagracia, Dominican Republic **Duration of recruitment:** June to November 2004	**Inclusion/exclusion criteria:** Women aged 18–80 years referred with abnormal cervical cytology (≥ atypical squamous cells of undetermined significance) or with suspicious lesions of the uterine cervix were eligible **Exclusion criteria:** Previous hysterectomy, previous treatment for pre-invasive or invasive cervical cancer, pregnancy or being a prisoner **Number recruited:** 220 patients of which eight were excluded owing to age (1), heavy bleeding (2), normal Pap (1), recent cone biopsies (2), blank form (1) and unknown reason (1) **Number analysed:** 212 (1215 images) **Mean age (range):** 35.5 (18–80) years	**Intervention:** *Imalux OCT device*: Operating at a 980-nm wavelength, with a lateral resolution of 25 μm and in-depth resolution of 11 μm in tissue Three investigators independently interpreted the OCT images, which were graded as 'normal' if a well-organised, simple two-layer structure with a sharp interface between the surface epithelium and underlying stromal layer was seen, 'abnormal' if the tissue was unstructured with no apparent interface present, and 'indeterminate' if irregularities on the images suggested artefacts or physiological alterations and did not meet criteria for normal or abnormal Image readings were made three separate times (after the examination) for each patient: knowing only the patient's age; knowing the visual inspection results (including access to an image); and knowing referral Pap results, the colposcopic diagnosis by quadrant, and viewing the magnified digital photograph of the cervix **Type of speculum:** NR **Details of cleaning/sheath:** Disposable OCT probe sheath	**Outcome measures:** CIN using cut-offs at indeterminate or abnormal **Details of assessment:** Sensitivities and specificities were presented with 95% CI. ROC curves were also generated for the three sets of OCT readings	179 women had ≤CIN1 and 33 women had ≥CIN2 **Analyses per person:** *Colposcopy (and visual inspection) plus Niris, using abnormal as cut-off*: Sensitivity = 46% (95% CI 30% to 64%), specificity = 69% (95% CI 62% to 75%) *Colposcopy, using CIN2+ as cut-off*: Sensitivity = 39% (95% CI 24% to 57%), specificity = 71% (95% CI 64% to 77%) *Analyses per lesion*: *Colposcopy (and visual inspection) plus Niris, cut-off not stated*: Sensitivity = 33% (95% CI 14% to 60%), specificity = 91% (95% CI 86% to 94%) ***2 × 2 data provided following personal correspondence with an author*:** **Analyses per person:** **Niris Imaging System alone** Histology: CIN2+ / <CIN2 / Total Niris alone — Indeterminate/abnormal: 30 / 158 / 188 Normal: 2 / 19 / 21 Total: 32 / 177 / 209 *Calculated by EAG*: *Sensitivity = 93.8% (95% CI 79.9% to 98.3%), specificity = 10.7% (95% CI 7.0% to 16.2%), PPV = 16% (95% CI 11.4% to 21.9%), NPV = 90.5% (95% CI 71.1% to 97.3%), accuracy = 23.4%, LR+ = 1.05 (95% CI 0.95 to 1.16), LR− = 0.58 (95% CI 0.14 to 2.38), prevalence = 15.3%*

Study details and design	Participant details	Intervention/comparators	Outcomes/analyses	Results
	Other relevant participant information: 189 were premenopausal and 23 were postmenopausal. 89 (42%) had a symptomatic vaginal discharge at the time of the examination **Result of last smear:** 48 (23%) had ASCUS, 142 (67%) had LSIL, 22 (10%) had HSIL **hrHPV test:** NR	**Comparator:** Conventional colposcopy. The cervix was divided into quadrants for examination Unmagnified visual inspection with acetic acid (not a relevant comparator for this review) was also studied **Reference standard:** Histology result from one pathologist; a team served as consultants for problem cases. Biopsies were taken at all positive areas and at the 2, 4, 8 and 10 o'clock positions at the squamocolumnar junction. Biopsies were performed with a bronchoscopy biopsy instrument (with 2 mm jaws). Endocervical curettage was also performed on every patient		**Niris Imaging System alone** Histology Device / CIN2+ / <CIN2 / Total Niris alone – Abnormal: 18 / 72 / 90 Normal/indeterminate: 14 / 105 / 119 Total: 32 / 177 / 209 *Calculated by EAG*: *Sensitivity = 56.3% (95% CI 39.3% to 71.8%), specificity = 59.3% (95% CI 52.0% to 66.3%), PPV = 20.0% (95% CI 13.0% to 29.4%), NPV = 88.2% (95% CI 81.2% to 92.9%), accuracy = 58.9%, LR+ = 1.38 (95% CI 0.97 to 1.97), LR– = 0.74 (95% CI 0.49 to 1.11), prevalence = 15.3%* **Colposcopy alone** Histology Device / CIN2+ / <CIN2 / Total Colposcopy – High grade: 12 / 52 / 64 Normal/low grade: 20 / 125 / 145 Total: 32 / 177 / 209 *Calculated by EAG*: *Sensitivity = 37.5% (95% CI 22.9% to 54.7%), specificity = 70.6% (95% CI 63.5% to 76.8%), PPV = 18.8% (95% CI 11.1% to 30.0%), NPV = 86.2% (95% CI 79.7% to 90.9%), accuracy = 65.6%, LR+ = 1.28 (95% CI 0.77 to 2.11), LR– = 0.89 (95% CI 0.67 to 1.18), prevalence = 15.3%* **Adverse events:** NR as an outcome

ASCUS, atypical squamous cells with uncertain significance; NR, not reported; ROC, receiver operator characteristic.

Appendix 3 Quality assessment

STUDY ID: Louwers *et al.*, 2010[6]

DOMAIN 1: PATIENT SELECTION

Describe methods of patient selection: Women referred for colposcopy owing to an abnormal cervical cytology or for follow-up of a CIN1 or 2 lesion. Pregnant women, women who had been pregnant in the previous 3 months, who had had previous surgery on the cervix or pelvic radiotherapy were excluded

Was a consecutive or random sample of patients enrolled?	YES
Was a case–control design avoided?	YES
Did the study avoid inappropriate exclusions?	YES
Could the selection of patients have introduced bias?	*RISK OF BIAS: LOW*

Are there concerns that the included patients and setting do not match the review question?

APPLICABILITY CONCERNS: LOW

DOMAIN 2: INDEX TEST

Describe how the index test results were interpreted: All colposcopies were performed or supervised by expert colposcopists, according to the Dutch national colposcopy guidelines, using DySIS as a regular video colposcope. The colposcopic impression was digitally recorded by the colposcopist, with annotation of the most atypical location and predicted severity of the lesion (blinded to the DySIS analysis of the images). Once this was completed, the DySIS colour-coded map was overlaid on the image of the cervix. Test performance was determined for CIN2+, using the predetermined DySIS cut-off values used in the study by Soutter *et al*.[17] The colour-coded map was compared with the colposcopist's impression and punch biopsies were taken from all identified suspicious sites

Video colposcopy was performed using the DySIS technology, rather than conventional colposcopy (video colposcopy is rarely used in the NHS), which may have affected estimates of colposcopy accuracy. Since the model used in this study, another DySIS model has been launched (in summer 2011), designed to improve ergonomics, reduce the cost and floor print of the device (rather than resolution/accuracy)

Colposcopists had to perform at least 20 colposcopies with DySIS and supervising colposcopists at least five, before participating. All colposcopies were performed or supervised by expert colposcopists, according to the Dutch national colposcopy guidelines

Were the index test results interpreted without knowledge of the results of the reference standard?	YES
If a threshold was used, was it prespecified?	YES
Was the execution of the intervention technology as it would be in practice?	YES
Was the execution of the comparator technology as it would be in practice?	NO
Were the colposcopists undertaking the tests experienced in colposcopy (i.e. accredited and with at least 1 year's experience)?	YES

Were the colposcopists undertaking the new technologies given training/experience in the new technology?	YES
Were the same clinical data available when the new technology test results were interpreted as would be available when the test is used in practice (e.g. cytology/HPV test result)?	*UNCLEAR*[a]

a. [Note: Based on subsequent information from DySIS Medical, this should read 'YES'.]

Could methods used to conduct or interpret the index test have introduced bias?

DySIS RISK OF BIAS: *LOW*

COLPOSCOPY RISK OF BIAS: *LOW*

Are there concerns that the index test, its conduct, or interpretation differ from the review question?

DySIS APPLICABILITY CONCERNS: *UNCLEAR*[b]

COLPOSCOPY APPLICABILITY CONCERNS: *HIGH*

b. [Note: Based on subsequent information from DySIS Medical, this should read 'LOW'.]

DOMAIN 3: REFERENCE STANDARD

Describe the reference standard and how it was conducted and interpreted: Punch biopsies were taken from suspicious sites indicated by the colposcopist, the DySIS colour-coded map and one additional control biopsy was taken from an area of apparently normal cervical tissue on the opposite side of the lesion(s). If both the colposcopist and the DySIS colour-coded map evaluated the cervix as normal, one biopsy was taken from the transformation zone at the 12 o'clock position. No biopsies were taken if a loop electrosurgical excision procedure was performed immediately (see and treat). The biopsy sampling procedure was video recorded and later reviewed to check whether the tissue sample was collected from the annotated area. Histology reports were independently reviewed by another pathologist, with disagreements resolved by a third pathologist. The final diagnosis was determined by the majority decision

Is the reference standard likely to correctly classify the target condition?	YES
Were the reference standard results interpreted without knowledge of the results of the index test?	UNCLEAR[a]
Was the execution of the reference standard as it would be in practice?	YES

a. (Note: Based on subsequent information from DySIS Medical, this should read 'YES'.]

Could methods used to conduct or interpret the reference standard have introduced bias?

RISK OF BIAS: *UNCLEAR*[b]

Are there concerns the target condition as defined by the reference standard does not match the question?

APPLICABILITY CONCERNS: *LOW*

b. (Note: Based on subsequent information from DySIS Medical, this should read 'LOW'.]

DOMAIN 4: FLOW AND TIMING

Draw a flow chart for the study or describe any patients who did not receive the index test and/or reference standard or who were excluded from the 2 × 2 table: Of 275 women recruited, 36 were excluded owing to unsaved examination data (9), no colour-coded map available (9), no colposcopy undertaken after signing informed consent (3), no abnormal referral cytology (3), DSI colposcope did not start (7), no available histology (5). Therefore, the 2 × 2 table only included 239 of 275 eligible women. Although 13% of patients were excluded from the analysis, reasons for exclusion appear to be valid and not particularly biased towards either technology

Describe the time interval between index and reference standard and any actions taken: Biopsies were taken at the time of the index test, for use in the reference standard

Was there an appropriate interval between index test and reference standard?	YES
Did all patients receive the same reference standard?	YES
Were all patients included in the analysis?	NO

Bias: *Could the patient flow have introduced bias?*

RISK OF BIAS: *LOW*

ADDED QUALITY ASSESSMENT QUESTIONS:

1. Was a sample size calculation used? YES. A power calculation was performed; the study aimed to recruit 200 women; analyses were based on 239 women in the ITT analyses.
2. Were the data analysed by lesion, patient or both? PATIENT
3. Were results for all pre-specified outcomes reported? YES
4. Any other comments? The main concern is that video colposcopy was conducted using the DySIS equipment rather than conventional colposcopy, any differences in visualisation (e.g. owing to the different speculum) may reduce the accuracy of conventional colposcopy. In addition, it is unclear whether the same clinical data were available when test results were interpreted, as would be available in practice (e.g. cytology/HPV test result). In practice, the decision to biopsy is made using such data, in addition to colposcopic impression. [Note: Based on subsequent information from DySIS Medical, this is no longer a concern as the same clinical data were available when interpreting the results as would be available when the test is used in practice.]

STUDY ID: Soutter *et al.*, 2009[17]

DOMAIN 1: PATIENT SELECTION

Describe methods of patient selection: Women referred for colposcopy owing to an abnormal cervical smear or symptoms suggesting the possibility of cervical neoplasia. Pregnant women, women who had had previous pelvic radiotherapy and women for whom any prolongation of the examination was inadvisable were excluded. In addition, women with an inadequate or inflammatory smear were excluded

Was a consecutive or random sample of patients enrolled?	YES
Was a case–control design avoided?	YES
Did the study avoid inappropriate exclusions?	YES
Could the selection of patients have introduced bias?	*RISK OF BIAS*: *LOW*

Are there concerns that the included patients and setting do not match the review question?

APPLICABILITY CONCERNS: *LOW*

DOMAIN 2: INDEX TEST

Describe how the index test results were interpreted: Areas for biopsy were marked by the DySIS user with a coloured circle. The second colposcopist completed a colposcopy form and indicated the areas for biopsy on a diagram, the DySIS pseudocolour map (PCM) and the first colposcopist's chosen biopsy points were then turned off and the second colposcopist indicated the colposcopy biopsy points on the image with a different coloured circle. The PCM was then turned back on, making both sets of biopsy points visible. The DySIS user took biopsies from all the points identified by both colposcopists. It was assumed that normal practice would include taking biopsies from lesions thought to be CIN1 and from areas with DySIS CB values of 500–552 units. Test performance was determined for high-grade CIN or invasion, using a DySIS CB cut-off value of 553 (which was determined from the data from the training group)

A precommercial DySIS model (FPC-03) was used. This has a lower resolution imaging camera than the later model used in the study by Louwers *et al.*,[6] therefore, the image resolution and accuracy are lower. Since the model used in the study by Louwers *et al.*[6] another model has been launched (in summer 2011), designed to improve ergonomics, reduce the cost and floor print of the device. In addition, the cut-off value used (to determine high-grade CIN) was determined from the data from the training group. It is unclear whether this cut-off value would be used in practice. Colposcopic assessment was performed by a second colposcopist using a video monitor displaying the images of the cervix captured by DySIS

A training group of 82 eligible women were recruited from May to July 2004, prior to the recruitment of the test group from August 2004 to July 2005

All colposcopists were experienced practitioners. UK colposcopists were accredited by the British Society for Colposcopy and Cervical Pathology and had at least 2 years' experience in busy clinics. The Greek colposcopists were similarly experienced. Most colposcopists had >5 years' experience. Both colposcopists had access to the woman's history and reason for referral

The colposcopist undertaking the colposcopy assessment used a video monitor displaying the images of the cervix captured by DySIS, so was unable to direct the colposcopic examination or request enlarged images of specific lesions (although the authors cite a publication by Ferris *et al.*,[70] which has shown that diagnostic accuracy is maintained under such conditions). Colposcopy was described as unsatisfactory in 65 cases because the squamocolumnar junction was not clearly visible, which may not have been the case if standard colposcopic equipment (with standard speculae) had been used; these patients were not excluded from the analysis. Areas for biopsy were recorded on a diagram and then transcribed on to the image, which may have introduced error. The DySIS user, rather than the colposcopist undertaking the colposcopy assessment, undertook the biopsies

Were the index test results interpreted without knowledge of the results of the reference standard?	YES
If a threshold was used, was it prespecified?	YES
Was the execution of the intervention technology as it would be in practice?	NO
Was the execution of the comparator technology as it would be in practice?	NO
Were the colposcopists undertaking the tests experienced in colposcopy (i.e. accredited and with at least 1 year's experience)?	YES
Were the colposcopists undertaking the new technologies given training/experience in the new technology?	YES
Were the same clinical data available when the new technology test results were interpreted as would be available when the test is used in practice (e.g. cytology/HPV test result)?	YES

Could methods used to conduct or interpret the index test have introduced bias?

DySIS RISK OF BIAS: *LOW*

COLPOSCOPY RISK OF BIAS: *LOW*

Are there concerns that the index test, its conduct, or interpretation differ from the review question?

DySIS APPLICABILITY CONCERNS: *HIGH*

COLPOSCOPY APPLICABILITY CONCERNS: *HIGH*

DOMAIN 3: REFERENCE STANDARD

Describe the reference standard and how it was conducted and interpreted: Both colposcopists selected areas for biopsy and also selected sites that did not seem to contain CIN in order to reduce verification bias. Histology reports were evaluated independently by another histopathologist, with disagreements resolved by a third histopathologist (16.5% biopsies were referred for a third opinion). The final diagnosis was determined by the majority opinion. Histopathologists were unaware of the DySIS result

Is the reference standard likely to correctly classify the target condition?	YES
Were the reference standard results interpreted without knowledge of the results of the index test?	YES
Was the execution of the reference standard as it would be in practice?	YES

Could methods used to conduct or interpret the reference standard have introduced bias?

RISK OF BIAS: *LOW*

Are there concerns the target condition as defined by the reference standard does not match the question?

APPLICABILITY CONCERNS: *LOW*

DOMAIN 4: FLOW AND TIMING

Draw a flow chart for the study or describe any patients who did not receive the index test and/or reference standard or who were excluded from the 2x2 table: Of 447 women recruited to the test group, 139 were excluded owing to software problems in the initial months of the trial (15), no biopsy being taken (23), unsatisfactory view of the cervix, largely owing to the size and design of the speculae initially adapted for the instrument (45), not eligible (6), 5% acetic acid was used (1), data form lost (1), biopsy slides lost (5), blood or mucus obscuring part of the cervix (1), biopsies taken from the wrong point (3), and excessive movement preventing a reliable measurement (2), problems with the application of acetic acid, largely owing to a batch of faulty disposable nozzles (37). Therefore, the 2x2 table only included 308 of 447 eligible women

Describe the time interval between index and reference standard and any actions taken: Biopsies were taken at the time of the index test, for use in the reference standard

Was there an appropriate interval between index test and reference standard?	YES
Did all patients receive the same reference standard?	YES
Were all patients included in the analysis?	NO

Bias: *Could the patient flow have introduced bias?*

RISK OF BIAS: *HIGH*

ADDED QUALITY ASSESSMENT QUESTIONS:

1. Was a sample size calculation used? YES. A power calculation was used, based on a meta-analysis assessing the accuracy of colposcopy for diagnosing high-grade CIN; the study aimed to recruit 300 women to the test group; analyses were based on 308 women
2. Were the data analysed by lesion, patient or both? PATIENT
3. Were results for all pre-specified outcomes reported? YES
4. Any other comments? Main concerns largely stem from using a precommercial model of DySIS; a high number of eligible patients were excluded from the assessment (139/447; 31%) owing to problems with the DySIS software (15), unsatisfactory view of the cervix, largely owing to the size and design of the speculae initially adapted for the instrument (45), problems with the application of acetic acid, largely owing to a batch of faulty disposable nozzles (37), no biopsy being taken (23), biopsy slides lost (5), biopsies taken from the wrong point (3), etc. Another major concern is the use of DySIS technology for undertaking the conventional colposcopy assessment. Colposcopy was described as unsatisfactory in 65 cases because the squamocolumnar junction was not clearly visible, which may not have been the case if standard colposcopic equipment (with standard speculae) had been used; these patients were not excluded from the analysis.

STUDY ID: Flowers *et al.*, unpublished

AiC information has been removed.

STUDY ID: Gallwas *et al.*, 2011[33]

DOMAIN 1: PATIENT SELECTION

Describe methods of patient selection: Women referred for colposcopy with suspected CIN were eligible. Women aged <18 years, and pregnant women, were excluded

Was a consecutive or random sample of patients enrolled?	UNCLEAR
Was a case–control design avoided?	YES
Did the study avoid inappropriate exclusions?	YES

Could the selection of patients have introduced bias?

RISK OF BIAS: *UNCLEAR*

Are there concerns that the included patients and setting do not match the review question?

APPLICABILITY CONCERNS: *LOW*

DOMAIN 2: INDEX TEST

Describe how the index test results were interpreted: Two investigators, blinded to the colposcopic and final histological diagnosis, evaluated each Niris image independently using a scale from 0 (normal) to 6 (squamous carcinoma). Test performance was determined for CIN1+, CIN2+ and CIN3+. Niris images were not interpreted during the colposcopic examination

Were the index test results interpreted without knowledge of the results of the reference standard?	YES
If a threshold was used, was it prespecified?	YES
Was the execution of the intervention technology as it would be in practice?	NO
Was the execution of the comparator technology as it would be in practice?	UNCLEAR
Were the colposcopists undertaking the tests experienced in colposcopy (i.e. accredited and with at least 1 year's experience)?	UNCLEAR
Were the colposcopists undertaking the new technologies given training/experience in the new technology?	UNCLEAR
Were the same clinical data available when the new technology test results were interpreted as would be available when the test is used in practice (e.g. cytology/HPV test result)?	UNCLEAR

Could methods used to conduct or interpret the index test have introduced bias?

NIRIS RISK OF BIAS: *UNCLEAR*

COLPOSCOPY RISK OF BIAS: *UNCLEAR*

Are there concerns that the index test, its conduct, or interpretation differ from the review question?

NIRIS APPLICABILITY CONCERNS: *HIGH*

COLPOSCOPY APPLICABILITY CONCERNS: *UNCLEAR*

DOMAIN 3: REFERENCE STANDARD

Describe the reference standard and how it was conducted and interpreted: It was unclear whether colposcopy results may have influenced the biopsy results, although the Niris images were anonymised

Is the reference standard likely to correctly classify the target condition?	YES
Were the reference standard results interpreted without knowledge of the results of the index test?	YES
Was the execution of the reference standard as it would be in practice?	UNCLEAR

Could methods used to conduct or interpret the reference standard have introduced bias?

RISK OF BIAS: *LOW*

Are there concerns the target condition as defined by the reference standard does not match the question?

APPLICABILITY CONCERNS: *UNCLEAR*

DOMAIN 4: FLOW AND TIMING

Draw a flow chart for the study or describe any patients who did not receive the index test and/or reference standard or who were excluded from the 2 × 2 table: Biopsies were taken from suspicious areas only (so false-negatives would not be picked up). Analysis was performed by image (rather than by individual), and it was unclear whether all recruited patients contributed to the analysis

Describe the time interval between index and reference standard and any actions taken: Biopsy taken at time of index test for use in reference standard

Was there an appropriate interval between index test and reference standard?	YES
Did all patients receive the same reference standard?	NO
Were all patients included in the analysis?	UNCLEAR

Bias: *Could the patient flow have introduced bias?*

RISK OF BIAS: *HIGH*

ADDED QUALITY ASSESSMENT QUESTIONS:

1. Was a sample size calculation used?	UNCLEAR
2. Were the data analysed by image/lesion, patient or both?	IMAGE
3. Were results for all prespecified outcomes reported?	YES
4. Any other comments?	NO

STUDY ID: Liu *et al.*, 2010[32]

DOMAIN 1: PATIENT SELECTION

Describe methods of patient selection: Non-pregnant women ≥ 18 years who had abnormal cytology findings or who tested positive for hrHPV

Was a consecutive or random sample of patients enrolled?	UNCLEAR[a]
Was a case–control design avoided?	YES
Did the study avoid inappropriate exclusions?	YES

a. [Note: Based on subsequent information from Imalux Corporation, this should read 'YES'.]

Could the selection of patients have introduced bias?

RISK OF BIAS: *UNCLEAR*[b]

b. [Note: Based on subsequent information from Imalux Corporation, this should read 'LOW']

Are there concerns that the included patients and setting do not match the review question?

APPLICABILITY CONCERNS: *LOW*

DOMAIN 2: INDEX TEST

Describe how the index test results were interpreted: Results for both the Niris probe and colposcopy were recorded before performing biopsies. Test performance was determined using indeterminate and abnormal results as cut-offs for the Niris probe, and using low-grade and high-grade cut-offs for colposcopy. The cervix was divided into quadrants for examination

Were the index test results interpreted without knowledge of the results of the reference standard?	YES
If a threshold was used, was it prespecified?	YES
Was the execution of the intervention technology as it would be in practice?	NO
Was the execution of the comparator technology as it would be in practice?	YES
Were the colposcopists undertaking the tests experienced in colposcopy (i.e. accredited and with at least 1 year's experience)?	UNCLEAR[a]
Were the colposcopists undertaking the new technologies given training/experience in the new technology?	UNCLEAR[a]
Were the same clinical data available when the new technology test results were interpreted as would be available when the test is used in practice (e.g. cytology/HPV test result)?	UNCLEAR[a]

a. [Note: Based on subsequent information from Imalux Corporation, this should read 'YES'.]

Could methods used to conduct or interpret the index test have introduced bias?

NIRIS RISK OF BIAS: *UNCLEAR*[b]

COLPOSCOPY RISK OF BIAS: *UNCLEAR*[b]

b. [Note: Based on subsequent information from Imalux Corporation, this should read 'LOW'.]

Are there concerns that the index test, its conduct, or interpretation differ from the review question?

NIRIS APPLICABILITY CONCERNS: *HIGH*

COLPOSCOPY APPLICABILITYCONCERNS: *LOW*

DOMAIN 3: REFERENCE STANDARD

Describe the reference standard and how it was conducted and interpreted: Histology results were obtained from a team of pathologists. One gynaecological pathologist served as the final reference and quality control

Is the reference standard likely to correctly classify the target condition?	YES
Were the reference standard results interpreted without knowledge of the results of the index test?	UNCLEAR[a]
Was the execution of the reference standard as it would be in practice?	YES

a. [Note: Based on subsequent information from Imalux Corporation, this should read 'YES'.]

Could methods used to conduct or interpret the reference standard have introduced bias?

RISK OF BIAS: *UNCLEAR*[b]

b. [Note: Based on subsequent information from Imalux Corporation, this should read 'LOW'.]

Are there concerns the target condition as defined by the reference standard does not match the question?

APPLICABILITY CONCERNS: *LOW*

DOMAIN 4: FLOW AND TIMING

Draw a flow chart for the study or describe any patients who did not receive the index test and/or reference standard or who were excluded from the 2 × 2 table: Not reported (NR)

Describe the time interval between index test and reference standard and any actions taken: Biopsy taken at time of index test for use in reference standard

Was there an appropriate interval between index test and reference standard?	YES
Did all patients receive the same reference standard?	YES

Were all patients included in the analysis? UNCLEAR

Bias: *Could the patient flow have introduced bias?*

RISK OF BIAS: *UNCLEAR*

ADDED QUALITY ASSESSMENT QUESTIONS:

1. Was a sample size calculation used?	UNCLEAR
2. Were the data analysed by lesion, patient or both?	BOTH
3. Were results for all pre-specified outcomes reported?	NO. PPV and NPV results not reported
4. Any other comments?	Study conducted in China: unclear generalisability of results to a UK population.

STUDY ID: Escobar *et al.*, 2006[31]

DOMAIN 1: PATIENT SELECTION

Describe methods of patient selection: Women aged 18–80 years referred with abnormal cervical cytology (≥atypical squamous cells of undetermined significance) or with suspicious lesions of the uterine cervix were recruited. Exclusion criteria were previous hysterectomy, previous treatment for pre-invasive or invasive cervical cancer, pregnancy or being a prisoner

Was a consecutive or random sample of patients enrolled?	UNCLEAR
Was a case–control design avoided?	YES
Did the study avoid inappropriate exclusions?	YES
Could the selection of patients have introduced bias?	NO

RISK OF BIAS: *UNCLEAR*

Are there concerns that the included patients and setting do not match the review question?

APPLICABILITY CONCERNS: *LOW*

DOMAIN 2: INDEX TEST

Describe how the index test results were interpreted: Niris images were anonymised and graded as being normal, indeterminate or abnormal. No relevant details were reported for colposcopy, although observations were recorded by quadrant

Were the index test results interpreted without knowledge of the results of the reference standard?	YES
If a threshold was used, was it pre-specified?	YES
Was the execution of the intervention technology as it would be in practice?	NO
Was the execution of the comparator technology as it would be in practice?	YES
Were the colposcopists undertaking the tests experienced in colposcopy (i.e. accredited and with at least 1 year's experience)?	UNCLEAR
Were the colposcopists undertaking the new technologies given training/experience in the new technology?	UNCLEAR
Were the same clinical data available when the new technology test results were interpreted as would be available when the test is used in practice (e.g. cytology/HPV test result)?	YES

Could methods used to conduct or interpret the index test have introduced bias?

NIRIS RISK OF BIAS: *UNCLEAR*

COLPOSCOPY RISK OF BIAS: *UNCLEAR*

Are there concerns that the index test, its conduct, or interpretation differ from the review question?

NIRIS APPLICABILITY CONCERNS: *HIGH*

COLPOSCOPY APPLICABILITY CONCERNS: *LOW*

DOMAIN 3: REFERENCE STANDARD

Describe the reference standard and how it was conducted and interpreted: Biopsies were taken from each quadrant and specimens were read by one author, with a team of gynaecological pathologists serving as consultants for problem cases. Niris images were anonymised

Is the reference standard likely to correctly classify the target condition?	YES
Were the reference standard results interpreted without knowledge of the results of the index test?	YES
Was the execution of the reference standard as it would be in practice?	YES

Could methods used to conduct or interpret the reference standard have introduced bias?

RISK OF BIAS: *LOW*

Are there concerns the target condition as defined by the reference standard does not match the question?

APPLICABILITY CONCERNS: *LOW*

DOMAIN 4: FLOW AND TIMING

Draw a flow chart for the study or describe any patients who did not receive the index test and/or reference standard or who were excluded from the 2 × 2 table: A total of 220 patients were recruited, with eight being eliminated owing to being aged <18 years (1), heavy bleeding (2), normal cytology (1), recent cone biopsies (2), a blank form (1) and for 'unknown' reasons (1)

Biopsies were taken from each quadrant at 2, 4, 8 and 10 o'clock at the squamocolumnar junction

Describe the time interval between index and reference standard and any actions taken: Biopsy taken at time of index test for use in reference standard

Was there an appropriate interval between index test and reference standard?	YES
Did all patients receive the same reference standard?	YES
Were all patients included in the analysis?	NO

Bias: *Could the patient flow have introduced bias?*

RISK OF BIAS: *LOW*

ADDED QUALITY ASSESSMENT QUESTIONS:

1. Was a sample size calculation used?	YES
2. Were the data analysed by lesion, patient or both?	BOTH
3. Were results for all pre-specified outcomes reported?	YES
4. Any other comments?	NO

Appendix 4 Table of excluded studies with rationale

Study details	Reason for exclusion
Anonymous, 2000[71]	Intervention
Anonymous, 2002[72]	Intervention
Anonymous, 2004[73]	Not a study
Anonymous, 2006[74]	Not a study
Anonymous, 2006[75]	Intervention
Anonymous, 2010[76]	Duplicate record
Anonymous, 2010[76]	Duplicate record
Anonymous, 2011[77]	Not a study
Abdul, 2005[78]	Not compared against colposcopy
Abdul, 2006[79]	Not compared against colposcopy
Acosta-Mesa, 2009[80]	Intervention
Agrawal, 2001[81]	Intervention
Alush, 2010[82]	Intervention
Alvarez, 2007[83]	Intervention
Anastasiadou, 2008[84]	Intervention
Atkinson, 2005[85]	Intervention
Azar, 2009[86]	Intervention
Badizadegan, 2004[87]	Intervention
Balas, 2001[88]	No diagnostic or patient outcome reported
Balas, 2002[89]	No diagnostic or patient outcome reported
Balas, 2002[89]	Duplicate record
Balas, 2005[90]	Not a study
Balas, 2008[91]	Not a study
Balas, 2010[92]	No diagnostic or patient outcome reported
Balasubramani, 2009[93]	Not compared against colposcopy
Bazant-Hegemark, 2007[94]	Intervention
Bazant-Hegemark, 2007[94]	Duplicate record
Belinson, 2001[95]	Intervention
Belinson, 2010[96]	No diagnostic or patient outcome reported
Belinson[a]	No diagnostic or patient outcome reported
Belinson, 2009[97]	No diagnostic or patient outcome reported
Benavides, 2003[98]	Intervention

Study details	Reason for exclusion
Benavides, 2003[98]	Duplicate record
Bogaards, 2002[99]	Intervention
Brookner, 2003[100]	Intervention
Brown, 2004[101]	No diagnostic or patient outcome reported
Brown, 2000[102]	Not compared against colposcopy
Brown, 2005[103]	Not compared against colposcopy
Bush, 2001[104]	Not women referred with abnormal cytology
Cantor, 2006[105]	Not a comparative study
Cantor, 2011[106]	Intervention
Chance, 2005[107]	Intervention
Chang, 2002[108]	Intervention
Chang, 2002[109]	Intervention
Chang, 2002[109]	Duplicate record
Chang, 2005[110]	Intervention
Chang, 2005[111]	Intervention
Chang, 2009[112]	Intervention
Chang, 2010[113]	Intervention
Chang, 2011[114]	Intervention
Cheung, 2003[115]	Intervention
Claude, 2001[116]	Intervention
ClinicalTrials.gov[117]	Intervention
ClinicalTrials.gov[118]	Intervention
ClinicalTrials.gov[119]	Intervention
ClinicalTrials.gov[120]	Intervention
ClinicalTrials.gov[121]	Intervention
ClinicalTrials.gov[122]	Intervention
ClinicalTrials.gov[123]	Intervention
ClinicalTrials.gov[124]	Intervention
ClinicalTrials.gov[125]	Intervention
ClinicalTrials.gov[126]	Intervention
ClinicalTrials.gov[127]	Intervention
ClinicalTrials.gov[128]	Intervention
ClinicalTrials.gov[129]	Intervention
ClinicalTrials.gov[130]	Intervention
Collier, 2007[131]	Intervention
Coppolillo, 2009[132]	Not a study

Study details	Reason for exclusion
Dattamajumdar, 2001[133]	Intervention
Dattamajumdar, 2001[133]	Duplicate record
Dattamajumdar, 2001[134]	Intervention
Dattamajumdar, 2003[135]	Intervention
DeSantis, 2007[136]	Not compared against colposcopy
DeWeert, 2003[137]	Intervention
DeWeert, 2003[137]	Duplicate record
Dominik, 2010[138]	Intervention
Drezek, 2002[139]	Intervention
Drezek, 2002[139]	Duplicate record
Escobar, 2004[140]	No diagnostic or patient outcome reported
Escobar, 2005[141]	Not a study
Feldchtein, unpublished[b]	Not compared against colposcopy
Feldchtein, 2003[142]	Not compared against colposcopy
Feldchtein, 2003[142]	Duplicate record
Feldchtein, 2005[143]	Not a study
Ferris, 2001[144]	Not compared against colposcopy
Ferris, 2003[145]	Not a comparative study
Ferris, 2010[146]	Intervention
Freeberg, 2007[147]	Intervention
Fujii, 2010[148]	Intervention
Gage, 2008[149]	Not a study
Gallwas, unpublished[c]	Not compared against colposcopy
Gallwas, 2009[150]	Not compared against colposcopy
Gallwas, 2010[151]	Not compared against colposcopy
Gallwas, 2010[152]	Not compared against colposcopy
Gandhi, 2006[153]	Not women referred with abnormal cytology
Georgakoudi, 2001[154]	Intervention
Georgakoudi, 2001[154]	Intervention
Georgakoudi, 2002[155]	Intervention
Ghanate, 2011[156]	Intervention
Gladkova, 2004[157]	Intervention
Gudibande, 2011[158]	Intervention
Guided Therapeutics[159]	Not a study
Gustafsson, 2003[160]	Intervention
Gustafsson, 2003[160]	Duplicate record
Gustafsson, 2003[161]	Intervention

Study details	Reason for exclusion
Gustafsson, 2003[161]	Duplicate record
Harper, 2004[162]	No diagnostic or patient outcome reported
Hsiung, 2001[163]	Intervention
Huang, 1991[164]	Not women referred with abnormal cytology
Huang, 2008[165]	Intervention
Huh, 2004[166]	Intervention
Huh, 2005[167]	Intervention
Imalux[168]	Not a study
Imalux[169]	Not a study
Imalux[170]	Not a study
Imalux[171]	Not a study
Imalux[172]	Not a study
Imalux[173]	Not a study
Imalux[174]	Not a study
Jeronimo, 2006[175]	Intervention
Jeronimo, 2007[176]	Intervention
Johansson, 2008[177]	Not a study
Kang, 2008[178]	Not compared against colposcopy
Kang, 2008[179]	Not compared against colposcopy
Kang, 2010[180]	Not a study
Kang, 2011[181]	Not compared against colposcopy
Kanter, 2009[182]	Intervention
Knapp, 2004[183]	Intervention
Kuznetzova, 2000[184]	Not women referred with abnormal cytology
Kuznetzova, 2000[184]	Duplicate record
Lange, 2004[185]	Intervention
Lange, 2005[186]	Intervention
Lange, 2005[186]	Duplicate record
Lange, 2005[187]	Intervention
Lange, 2005[187]	Duplicate record
Lange, 2005[187]	Intervention
Lange, 2005[188]	Duplicate record
Ledford[189]	Not a study
Lee, 2007[190]	Intervention
Lee, 2007[191]	Intervention
Lee, 2007[192]	Intervention

Study details	Reason for exclusion
Lee, 2007[192]	Intervention
Lee, 2008[193]	Intervention
Li, 2005[194]	Intervention
Li, 2006[195]	Intervention
Li, 2006[195]	Duplicate record
Li, 2006[196]	Intervention
Li, 2006[196]	Duplicate record
Li, 2006[197]	Intervention
Li, 2007[198]	Intervention
Li, 2007[198]	Duplicate record
Li, 2008[199]	Intervention
Li, 2008[199]	Duplicate record
Li, 2009[200]	Intervention
Li, 2009[201]	Intervention
Loning, 2003[202]	Intervention
Luck, 2004[203]	Not a study
Lukic, 2009[204]	Intervention
MacKinnon, 2007[205]	Intervention
Malpica, 2001[206]	Not women referred with abnormal cytology
Malpica, 2001[207]	Duplicate record
Margariti, 2010[208]	Intervention
Marin, 2005[209]	Intervention
Marsa, 2004[210]	Not a study
Martinho, 2011[211]	Intervention
Massad, 2003[212]	Intervention
McLaren, 2003[213]	Intervention
Mehlhorn, 2010[214]	Intervention
Mikhail, 2004[215]	Intervention
Milbourne, 2005[216]	Intervention
Mirabal, 2002[217]	Intervention
Mirkovic, 2009[218]	Intervention
Mo, 2008[219]	Intervention
Mo, 2008[219]	Duplicate record
Mo, 2009[220]	Intervention
Mourant, 2005[221]	Intervention
Mourant, 2007[222]	Intervention
Mourant, 2009[223]	Intervention

Study details	Reason for exclusion
Mourant, 2009[224]	Intervention
Muller, 2002[225]	Intervention
Murali Krishna, 2006[226]	Not women referred with abnormal cytology
Muthuvelu, 2011[227]	Intervention
Nath, 2004[228]	Intervention
National Horizon Scanning Centre, 2010[7]	Not a study
Nordstrom, 2001[229]	Intervention
Nour El-Din, 2009[230]	Intervention
O'Connell, 2000[231]	Not women referred with abnormal cytology
Okimoto, 2001[232]	Intervention
Okimoto, 2001[232]	Duplicate record
Orfanoudaki, 2005[233]	Intervention
Papoutsoglou, 2008[234]	No diagnostic or patient outcome reported
Papoutsoglou, 2008[234]	Duplicate record
Park, 2008[235]	Intervention
Park, 2011[236]	Intervention
Park, 2010[237]	Intervention
Parker, 2000[238]	Intervention
Parker, 2002[239]	Intervention
Parker, 2005[240]	Not a study
Pfefer, 2005[241]	Intervention
Pfefer, 2005[241]	Duplicate record
Pitris, 2000[242]	Intervention
Pitris, 2000[243]	Intervention
Pogue, 2001[244]	Intervention
Porras, 2012[245]	Intervention
Pretorius, 2007[246]	Intervention
Qiang, 2000[247]	Intervention
Qu, 2001[248]	Intervention
Qu, 2001[248]	Duplicate record
Redden Weber, 2008[249]	Intervention
Robichaux, 2002[250]	Intervention
Robichaux, 2002[250]	Duplicate record
Robichaux-Viehoever, 2007[251]	Intervention
Sanad, 2011[252]	Intervention
Sapozhnikova, 2003[253]	No diagnostic or patient outcome reported
Sapozhnikova, 2005[254]	Intervention
Schomacker, 2006[255]	Intervention

Study details	Reason for exclusion
Sergeev, 1997[256]	Not a study
Shakhova, [date unknown][257]	Intervention
Shakhova, 2003[258]	Not compared against colposcopy
Shakhova, 2003[259]	Not compared against colposcopy
Shakhova, 2003[259]	Duplicate record
Shakhova, 2003[260]	Not women referred with abnormal cytology
Shinn, 2007[261]	Intervention
Sokolov, 2004[262]	Intervention
Srinivasan, 2009[263]	Intervention
Sung, 2003[264]	Intervention
Tan, 2009[265]	Intervention
Trokhanova, 2010[266]	Intervention
Tromberg, 2009[267]	Intervention
Utzinger, 2001[268]	Intervention
Van Raad, 2003[269]	Intervention
Van Raad, 2003[269]	Duplicate record
Van Raad, 2003[270]	Intervention
Van Raad, 2005[271]	Intervention
Van Raad, 2005[271]	Duplicate record
Van Raad, 2006[272]	Intervention
Van Raad, 2006[272]	Duplicate record
Vargas, 2009[273]	Not women referred with abnormal cytology
Vargis, 2010[274]	Intervention
Vargis, 2010[275]	Intervention
Vargis, 2010[276]	Intervention
Vargis, 2011[277]	Intervention
Vengadesan, 2001[278]	Not women referred with abnormal cytology
Vengadesan, 2002[279]	Not women referred with abnormal cytology
Vincent, 2008[280]	Not women referred with abnormal cytology
Vincent, 2009[281]	Not women referred with abnormal cytology
Weingandt, 2002[282]	Intervention
Werner, 2007[283]	Not compared against colposcopy
Wilkinson, 2010[284]	Not compared against colposcopy
Winter, 2010[285]	Not compared against colposcopy
Winter, 2010[286]	Not compared against colposcopy
Wu, 2003[287]	Intervention
Wu, 2003[287]	Duplicate record

Study details	Reason for exclusion
Wu, 2003[288]	Intervention
Wu, 2003[288]	Duplicate record
Wu, 2003[289]	Intervention
Wu, 2003[290]	Intervention
Wu, 2003[290]	Duplicate record
Wu, 2008[291]	Intervention
Wu, 2009[292]	Intervention
Wu, 2010[293]	Intervention
Wulan, unpublished[d]	Not compared against colposcopy
Wulan, 2008[294]	Not compared against colposcopy
Wulan, 2010[295]	Not compared against colposcopy
Yang, 2008[296]	Intervention
Yu, 2011[297]	Intervention
Zagaynova, 2004[298]	Not compared against colposcopy
Zagaynova, 2004[298]	Duplicate record
Zagaynova, 2008[299]	Not women referred with abnormal cytology
Zara, 2008[300]	Not a study
Zertuche, 2009[301]	Intervention
Zhang, 2010[302]	Intervention
Zhao, 2009[303]	Intervention
Zhao, 2010[304]	Intervention

a Belinson *et al*., Department of Preventive Medicine, Northwestern University, Chicago, IL, 2011.

b Feldchtein F, *et al*., Institute of Applied Physics of Russian Academy of Sciences, Nizhny Novgorod, Russia, 2003.

c Gallwas J, *et al*., Department of Obstetrics and Gynecology, Ludwig Maximilians University Munich, Großhadern Medical Campus, Munich, Germany, 2003.

d Wulan N, *et al*., Peking University Shenzhen Hospital, Shenzhen, China (date of study not reported).

Appendix 5 Sensitivity analysis of the base case

TABLE 26 Base case for 25-year-old population

Reasons for referral	Borderline ± HPV			Mild ± HPV			Moderate			Severe		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	965.17	21.32695		999.32	21.32080		1144.33	21.33156		1839.20	21.32908	
DySIS alone	944.25	21.33399	Dominant	975.08	21.32849	Dominant	1113.10	21.33951	Dominant	1824.06	21.33415	Dominant
Colposcopy vs DySIS ± colposcopy												
Colposcopy	965.17	21.32695		999.32	21.32080		1144.33	21.33156		1839.20	21.32908	
DySIS + colposcopy	913.72	21.34142	Dominant	940.92	21.33651	Dominant	1073.04	21.34758	Dominant	1800.32	21.33957	Dominant

Reasons for referral	Possible invasion			Possible glandular neoplasia			3 × inadequate			Whole population		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	6553.69	21.21916		3295.20	21.30126		698.63	21.37129		**1163.85**	**21.32478**	
DySIS alone	6554.97	21.22054	936.51	3300.39	21.30241	4512.07	703.80	21.37167	13,614.43	**1141.70**	**21.33181**	**Dominant**
Colposcopy vs DySIS ± colposcopy												
Colposcopy	6553.69	21.21916		3295.20	21.30126		698.63	21.37129		**1163.85**	**21.32478**	
DySIS + colposcopy	6549.45	21.22196	Dominant	3298.06	21.30352	1263.24	702.46	21.37208	4831.73	**1110.09**	**21.33916**	**Dominant**

TABLE 27 Base case for 45-year-old population

Reasons for referral	Borderline ± HPV			Mild ± HPV			Moderate			Severe		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	1108.59	18.82101		1150.71	18.81143		1000.90	18.88313		1634.45	18.89695	
DySIS alone	1081.70	18.82948	Dominant	1118.01	18.82115	Dominant	963.15	18.89276	Dominant	1619.08	18.90193	Dominant
Colposcopy vs DySIS ± colposcopy												
Colposcopy	1108.59	18.82101		1150.71	18.81143		1000.90	18.88313		1634.45	18.89695	
DySIS + colposcopy	1047.91	18.83758	Dominant	1079.19	18.83029	Dominant	920.38	18.90184	Dominant	1596.20	18.90722	Dominant

Reasons for referral	Possible invasion			Possible glandular neoplasia			3 × inadequate			Whole population		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	6379.56	18.79176		3196.85	18.85120		641.23	18.90737		**1227.57**	**18.83484**	
DySIS alone	6380.67	18.79308	845.83	3199.83	18.85291	1750.91	643.86	18.90845	2447.07	**1199.32**	**18.84333**	**Dominant**
Colposcopy vs DySIS ± colposcopy												
Colposcopy	6379.56	18.79176		3196.85	18.85120		641.23	18.90737		**1227.57**	**18.83484**	
DySIS + colposcopy	6375.57	18.79446	Dominant	3196.22	18.85445	Dominant	640.79	18.90943	Dominant	**1164.59**	**18.85144**	**Dominant**

TABLE 28 Base case and duration of the HRQoL decrement as a result of cancer for stages 2–4 is 1 year

Reasons for referral	Borderline ± HPV			Mild ± HPV			Moderate			Severe		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	1188.55	20.40410		1223.09	20.39744		1106.85	20.45306		1754.00	20.46002	
DySIS alone	1163.45	20.41157	Dominant	1192.53	20.40593	Dominant	1071.80	20.46151	Dominant	1739.28	20.46472	Dominant
Colposcopy vs DySIS ± colposcopy												
Colposcopy	1188.55	20.40410		1223.09	20.39744		1106.85	20.45306		1754.00	20.46002	
DySIS + colposcopy	1131.10	20.41849	Dominant	1155.54	20.41364	Dominant	1031.45	20.46945	Dominant	1716.98	20.46970	Dominant

Reasons for referral	Possible invasion			Possible glandular neoplasia			3×inadequate			Whole population		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	6500.85	20.34764		3313.68	20.41413		753.02	20.47584		**1313.59**	**20.41449**	
DySIS alone	6501.71	20.34909	597.21	3316.53	20.41595	1563.64	755.20	20.47711	1720.37	**1287.18**	**20.42199**	**Dominant**
Colposcopy vs DySIS ± colposcopy												
Colposcopy	6500.85	20.34764		3313.68	20.41413		753.02	20.47584		**1313.59**	**20.41449**	
DySIS + colposcopy	6496.13	20.35057	Dominant	3312.33	20.41758	Dominant	751.27	20.47824	Dominant	**1254.00**	**20.42897**	**Dominant**

TABLE 29 Base case and duration of the HRQoL decrement as a result of cancer for stages 2–4 is 3 years

Reasons for referral	Borderline ± HPV			Mild ± HPV			Moderate			Severe		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	1188.55	20.40342		1223.09	20.39673		1106.85	20.45278		1754.00	20.45985	
DySIS alone	1163.45	20.41095	Dominant	1192.53	20.40528	Dominant	1071.80	20.46126	Dominant	1739.28	20.46456	Dominant
Colposcopy vs DySIS ± colposcopy												
Colposcopy	1188.55	20.40342		1223.09	20.39673		1106.85	20.45278		1754.00	20.45985	
DySIS + colposcopy	1131.10	20.41792	Dominant	1155.54	20.41304	Dominant	1031.45	20.46923	Dominant	1716.98	20.46956	Dominant

Reasons for referral	Possible invasion			Possible glandular neoplasia			3×inadequate			Whole population		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	6500.85	20.34747		3313.68	20.41386		753.02	20.47552		**1313.59**	**20.41392**	
DySIS alone	6501.71	20.34892	594.81	3316.53	20.41569	1554.12	755.20	20.47681	1703.00	**1287.18**	**20.42147**	**Dominant**
Colposcopy vs DySIS ± colposcopy												
Colposcopy	6500.85	20.34747		3313.68	20.41386		753.02	20.47552		**1313.59**	**20.41392**	
DySIS + colposcopy	6496.13	20.35041	Dominant	3312.33	20.41734	Dominant	751.27	20.47795	Dominant	**1254.00**	**20.42849**	**Dominant**

TABLE 30 Base case with cancer treatment costs 50% lower

Reasons for referral	Borderline ± HPV			Mild ± HPV			Moderate			Severe		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	966.40	20.40278		995.27	20.39607		938.97	20.45252		1234.26	20.45968	
DySIS alone	958.47	20.41037	Dominant	984.18	20.40468	Dominant	916.53	20.46103	Dominant	1223.92	20.46442	Dominant
Colposcopy vs DySIS ± colposcopy												
Colposcopy	966.40	20.40278		995.27	20.39607		938.97	20.45252		1234.26	20.45968	
DySIS + colposcopy	942.14	20.41738	Dominant	965.17	20.41249	Dominant	887.47	20.46903	Dominant	1205.84	20.46942	Dominant

Reasons for referral	Possible invasion			Possible glandular neoplasia			3×inadequate			Whole population		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	3584.46	20.34731		2002.37	20.41361		662.36	20.47523		**1032.17**	**20.41339**	
DySIS alone	3586.80	20.34877	1604.90	2008.15	20.41546	3139.49	667.92	20.47653	4291.62	**1021.32**	**20.42098**	**Dominant**
Colposcopy vs DySIS ± colposcopy												
Colposcopy	3584.46	20.34731		2002.37	20.41361		662.36	20.47523		**1032.17**	**20.41339**	
DySIS + colposcopy	3582.45	20.35026	Dominant	2006.21	20.41711	1097.27	666.59	20.47768	1726.47	**1002.56**	**20.42805**	**Dominant**

TABLE 31 Base case with cancer treatment costs 50% higher

Reasons for referral	Borderline ± HPV			Mild ± HPV			Moderate			Severe		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	1410.71	20.40278		1450.91	20.39607		1274.72	20.45252		2273.73	20.45968	
DySIS alone	1368.43	20.41037	Dominant	1400.88	20.40468	Dominant	1227.07	20.46103	Dominant	2254.65	20.46442	Dominant
Colposcopy vs DySIS ± colposcopy												
Colposcopy	1410.71	20.40278		1450.91	20.39607		1274.72	20.45252		2273.73	20.45968	
DySIS + colposcopy	1320.05	20.41738	Dominant	1345.91	20.41249	Dominant	1175.43	20.46903	Dominant	2228.13	20.46942	Dominant

Reasons for referral	Possible invasion			Possible glandular neoplasia			3×inadequate			Whole population		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	9417.23	20.34731		4625.00	20.41361		843.68	20.47523		**1595.01**	**20.41339**	
DySIS alone	9416.62	20.34877	Dominant	4624.91	20.41546	Dominant	842.49	20.47653	Dominant	**1553.04**	**20.42098**	**Dominant**
Colposcopy vs DySIS ± colposcopy												
Colposcopy	9417.23	20.34731		4625.00	20.41361		843.68	20.47523		**1595.01**	**20.41339**	
DySIS + colposcopy	9409.82	20.35026	Dominant	4618.45	20.41711	Dominant	835.96	20.47768	Dominant	**1505.44**	**20.42805**	**Dominant**

TABLE 32 Base case with HRQoL estimates of health states from the Sheffield model

Reasons for referral	Borderline ± HPV			Mild ± HPV			Moderate			Severe		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	1188.55	22.14086		1223.09	22.10561		1106.85	22.35851		1754.00	22.42003	
DySIS alone	1163.45	22.16328	Dominant	1192.53	22.13149	Dominant	1071.80	22.37952	Dominant	1739.28	22.42820	Dominant
Colposcopy vs DySIS ± colposcopy												
Colposcopy	1188.55	22.14086		1223.09	22.10561		1106.85	22.35851		1754.00	22.42003	
DySIS + colposcopy	1131.10	22.18218	Dominant	1155.54	22.15297	Dominant	1031.45	22.39710	Dominant	1716.98	22.43613	Dominant

Reasons for referral	Possible invasion			Possible glandular neoplasia			3 × inadequate			Whole population		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	6500.85	22.27015		3313.68	22.32172		753.02	22.37903		**1313.59**	**22.19236**	
DySIS alone	6501.71	22.27313	290.13	3316.53	22.32716	523.91	755.20	22.38439	408.14	**1287.18**	**22.21371**	**Dominant**
Colposcopy vs DySIS ± colposcopy												
Colposcopy	6500.85	22.27015		3313.68	22.32172		753.02	22.37903		**1313.59**	**22.19236**	
DySIS + colposcopy	6496.13	22.27571	Dominant	3312.33	22.33125	Dominant	751.27	22.38832	Dominant	**1254.00**	**22.23171**	**Dominant**

TABLE 33 Base case with QALY decrement associated with treatment biopsy increase by 200%

Reasons for referral	Borderline ± HPV			Mild ± HPV			Moderate			Severe		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	1188.55	20.40084		1223.09	20.39392		1106.85	20.44768		1754.00	20.45432	
DySIS alone	1163.45	20.40829	Dominant	1192.53	20.40238	Dominant	1071.80	20.45607	Dominant	1739.28	20.45899	Dominant
Colposcopy vs DySIS ± colposcopy												
Colposcopy	1188.55	20.40084		1223.09	20.39392		1106.85	20.44768		1754.00	20.45432	
DySIS + colposcopy	1131.10	20.41522	Dominant	1155.54	20.41010	Dominant	1031.45	20.46398	Dominant	1716.98	20.46396	Dominant

Reasons for referral	Possible invasion			Possible glandular neoplasia			3×inadequate			Whole population		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	6500.85	20.34205		3313.68	20.40901		753.02	20.47477		**1313.59**	**20.41055**	
DySIS alone	6501.71	20.34346	616.56	3316.53	20.41067	1712.79	755.20	20.47601	1764.17	**1287.18**	**20.41802**	**Dominant**
Colposcopy vs DySIS ± colposcopy												
Colposcopy	6500.85	20.34205		3313.68	20.40901		753.02	20.47477		**1313.59**	**20.41055**	
DySIS + colposcopy	6496.13	20.34491	Dominant	3312.33	20.41221	Dominant	751.27	20.47713	Dominant	**1254.00**	**20.42499**	**Dominant**

TABLE 34 Base case with QALY decrement associated with treatment biopsy increase by 500%

Reasons for referral	Borderline ± HPV			Mild ± HPV			Moderate			Severe		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	1188.55	20.39502		1223.09	20.38745		1106.85	20.43318		1754.00	20.438212	
DySIS alone	1163.45	20.40208	Dominant	1192.53	20.39550	Dominant	1071.80	20.44118	Dominant	1739.28	20.442729	Dominant
Colposcopy vs DySIS + colposcopy												
Colposcopy	1188.55	20.39502		1223.09	20.38745		1106.85	20.43318		1754.00	20.438212	
DySIS + colposcopy	1131.10	20.40872	Dominant	1155.54	20.40292	Dominant	1031.45	20.44883	Dominant	1716.98	20.447585	Dominant

Reasons for referral	Possible invasion			Possible glandular neoplasia			3 × inadequate			Whole population		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	6500.85	20.32628		3313.68	20.39519		753.02	20.47339		**1313.59**	**20.40203**	
DySIS alone	6501.71	20.32751	701.70	3316.53	20.39631	2537.73	755.20	20.47446	2044.382	**1287.18**	**20.40912**	**Dominant**
Colposcopy vs DySIS + colposcopy												
Colposcopy	6500.85	20.32628		3313.68	20.39519		753.02	20.47339		**1313.59**	**20.40203**	
DySIS + colposcopy	6496.13	20.32885	Dominant	3312.33	20.39749	Dominant	751.27	20.47546	Dominant	**1254.00**	**20.41584**	**Dominant**

TABLE 35 Base case with QALY decrement associated with treatment biopsy increase by 2000%

Reasons for referral	Borderline ± HPV			Mild ± HPV			Moderate			Severe		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	1188.55	20.36594		1223.09	20.35512		1106.85	20.36069		1754.00	20.35769	
DySIS alone	1163.45	20.37101	Dominant	1192.53	20.36110	Dominant	1071.80	20.36676	Dominant	1739.28	20.36140	Dominant
Colposcopy vs DySIS ± colposcopy												
Colposcopy	1188.55	20.36594		1223.09	20.35512		1106.85	20.36069		1754.00	20.35769	
DySIS + colposcopy	1131.10	20.37624	Dominant	1155.54	20.36705	Dominant	1031.45	20.37309	Dominant	1716.98	20.36570	Dominant

Reasons for referral	Possible invasion			Possible glandular neoplasia			3 × inadequate			Whole population		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	6500.85	20.24743		3313.68	20.32610		753.02	20.46650		**1313.59**	**20.35942**	
DySIS alone	6501.71	20.24781	2266.94	3316.53	20.32452	Dominated	755.20	20.46672	9932.82	**1287.18**	**20.36467**	**Dominant**
Colposcopy vs DySIS ± colposcopy												
Colposcopy	6500.85	20.24743		3313.68	20.32610		753.02	20.46650		**1313.59**	**20.35942**	
DySIS + colposcopy	6496.13	20.24858	Dominant	3312.33	20.32390	615.66	751.27	20.46715	Dominant	**1254.00**	**20.37008**	**Dominant**

TABLE 36 Base case with QALY decrement associated with cytological screening decreased by 50%

Reasons for referral	Borderline ± HPV			Mild ± HPV			Moderate			Severe		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	1188.55	20.40770		1223.09	20.40109		1106.85	20.45770		1754.00	20.46478	
DySIS alone	1163.45	20.41529	Dominant	1192.53	20.40971	Dominant	1071.80	20.46620	Dominant	1739.28	20.46951	Dominant
Colposcopy vs DySIS ± colposcopy												
Colposcopy	1188.55	20.40770		1223.09	20.40109		1106.85	20.45770		1754.00	20.46478	
DySIS + colposcopy	1131.10	20.42232	Dominant	1155.54	20.41752	Dominant	1031.45	20.47420	Dominant	1716.98	20.47452	Dominant

Reasons for referral	Possible invasion			Possible glandular neoplasia			3 × inadequate			Whole population		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	6500.85	20.35214		3313.68	20.41860		753.02	20.47977		**1313.59**	**20.41840**	
DySIS alone	6501.71	20.35361	590.30	3316.53	20.42046	1527.90	755.20	20.48107	1684.07	**1287.18**	**20.42599**	**Dominant**
Colposcopy vs DySIS ± colposcopy												
Colposcopy	6500.85	20.35214		3313.68	20.41860		753.02	20.47977		**1313.59**	**20.41840**	
DySIS + colposcopy	6496.13	20.35510	Dominant	3312.33	20.42214	Dominant	751.27	20.48223	Dominant	**1254.00**	**20.43306**	**Dominant**

TABLE 37 Base case with QALY decrement associated with cytological screening increased by 50%

Reasons for referral	Borderline ± HPV			Mild ± HPV			Moderate			Severe		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	1188.55	20.39786		1223.09	20.39105		1106.85	20.44733		1754.00	20.45459	
DySIS alone	1163.45	20.40544	Dominant	1192.53	20.39965	Dominant	1071.80	20.45585	Dominant	1739.28	20.45932	Dominant
Colposcopy vs DySIS ± colposcopy												
Colposcopy	1188.55	20.39786		1223.09	20.39105		1106.85	20.44733		1754.00	20.45459	
DySIS + colposcopy	1131.10	20.41245	Dominant	1155.54	20.40746	Dominant	1031.45	20.46385	Dominant	1716.98	20.46433	Dominant

Reasons for referral	Possible invasion			Possible glandular neoplasia			3 × inadequate			Whole population		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	6500.85	20.34248		3313.68	20.40863		753.02	20.47069		**1313.59**	**20.40838**	
DySIS alone	6501.71	20.34393	594.91	3316.53	20.41045	1563.18	755.20	20.47198	1690.12	**1287.18**	**20.41597**	**Dominant**
Colposcopy vs DySIS ± colposcopy												
Colposcopy	6500.85	20.34248		3313.68	20.40863		753.02	20.47069		**1313.59**	**20.40838**	
DySIS + colposcopy	6496.13	20.34542	Dominant	3312.33	20.41209	Dominant	751.27	20.47313	Dominant	**1254.00**	**20.42303**	**Dominant**

TABLE 38 Base case with alternative cost of colposcope £5000

Reasons for referral	Borderline ± HPV			Mild ± HPV			Moderate			Severe		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	1188.55	20.40278		1223.09	20.39607		1106.85	20.45252		1754.00	20.45968	
DySIS alone	1164.87	20.41037	Dominant	1193.97	20.40468	Dominant	1072.84	20.46103	Dominant	1740.22	20.46442	Dominant
Colposcopy vs DySIS ± colposcopy												
Colposcopy	1188.55	20.40278		1223.09	20.39607		1106.85	20.45252		1754.00	20.45968	
DySIS + colposcopy	1132.50	20.41738	Dominant	1156.97	20.41249	Dominant	1032.48	20.46903	Dominant	1717.91	20.46942	Dominant

Reasons for referral	Possible invasion			Possible glandular neoplasia			3 × inadequate			Whole population		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	6500.85	20.34731		3313.68	20.41361		753.02	20.47523		**1313.59**	**20.41339**	
DySIS alone	6502.64	20.34877	1231.93	3317.57	20.41546	2113.49	756.25	20.47653	2496.60	**1288.49**	**20.42098**	**Dominant**
Colposcopy vs DySIS ± colposcopy												
Colposcopy	6500.85	20.34731		3313.68	20.41361		753.02	20.47523		**1313.59**	**20.41339**	
DySIS + colposcopy	6497.07	20.35026	Dominant	3313.37	20.41711	Dominant	752.32	20.47768	Dominant	**1255.30**	**20.42805**	**Dominant**

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TABLE 39 Base case with alternative cost of colposcope £20,000

Reasons for referral	Borderline ± HPV			Mild ± HPV			Moderate			Severe		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	1188.55	20.40278		1223.09	20.39607		1106.85	20.45252		1754.00	20.45968	
DySIS alone	1160.62	20.41037	Dominant	1189.65	20.40468	Dominant	1069.70	20.46103	Dominant	1737.42	20.46442	Dominant
Colposcopy vs DySIS ± colposcopy												
Colposcopy	1188.55	20.40278		1223.09	20.39607		1106.85	20.45252		1754.00	20.45968	
DySIS + colposcopy	1128.29	20.41738	Dominant	1152.69	20.41249	Dominant	1029.40	20.46903	Dominant	1715.13	20.46942	Dominant

Reasons for referral	Possible invasion			Possible glandular neoplasia			3 × inadequate			Whole population		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	6500.85	20.34731		3313.68	20.41361		753.02	20.47523		**1313.59**	**20.41339**	
DySIS alone	6499.85	20.34877	Dominant	3314.44	20.41546	409.03	753.11	20.47653	68.06	**1284.55**	**20.42098**	**Dominant**
Colposcopy vs DySIS ± colposcopy												
Colposcopy	6500.85	20.34731		3313.68	20.41361		753.02	20.47523		**1313.59**	**20.41339**	
DySIS + colposcopy	6494.27	20.35026	Dominant	3310.24	20.41711	Dominant	749.18	20.47768	Dominant	**1251.40**	**20.42805**	**Dominant**

TABLE 40 Base case with QALY decrement associated with colposcopy decreased by 50%

Reasons for referral	Borderline ± HPV			Mild ± HPV			Moderate			Severe		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	1188.55	20.43451		1223.09	20.42871		1106.85	20.48101		1754.00	20.48289	
DySIS alone	1163.45	20.44167	Dominant	1192.53	20.43682	Dominant	1071.80	20.48776	Dominant	1739.28	20.48635	Dominant
Colposcopy vs DySIS ± colposcopy												
Colposcopy	1188.55	20.43451		1223.09	20.42871		1106.85	20.48101		1754.00	20.48289	
DySIS + colposcopy	1131.10	20.44834	Dominant	1155.54	20.44424	Dominant	1031.45	20.49394	Dominant	1716.98	20.48994	Dominant

Reasons for referral	Possible invasion			Possible glandular neoplasia			3 × inadequate			Whole population		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	6500.85	20.36794		3313.68	20.43582		753.02	20.49671		**1313.59**	**20.44380**	
DySIS alone	6501.71	20.36904	785.56	3316.53	20.43740	1805.23	755.20	20.49786	1891.44	**1287.18**	**20.45068**	**Dominant**
Colposcopy vs DySIS ± colposcopy												
Colposcopy	6500.85	20.36794		3313.68	20.43582		753.02	20.49671		**1313.59**	**20.44380**	
DySIS + colposcopy	6496.13	20.37013	Dominant	3312.33	20.43878	Dominant	751.27	20.49890	Dominant	**1254.00**	**20.45708**	**Dominant**

TABLE 41 Base case with QALY decrement associated with colposcopy increased by 50%

Reasons for referral	Borderline ± HPV			Mild ± HPV			Moderate			Severe		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	1188.55	20.37105		1223.09	20.36343		1106.85	20.42402		1754.00	20.43648	
DySIS alone	1163.45	20.37906	Dominant	1192.53	20.37253	Dominant	1071.80	20.43429	Dominant	1739.28	20.44248	Dominant
Colposcopy vs DySIS ± colposcopy												
Colposcopy	1188.55	20.37105		1223.09	20.36343		1106.85	20.42402		1754.00	20.43648	
DySIS + colposcopy	1131.10	20.38642	Dominant	1155.54	20.38074	Dominant	1031.45	20.44412	Dominant	1716.98	20.44890	Dominant

Reasons for referral	Possible invasion			Possible glandular neoplasia			3 × inadequate			Whole population		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	6500.85	20.32668		3313.68	20.39141		753.02	20.45375		**1313.59**	**20.38297**	
DySIS alone	6501.71	20.32850	475.73	3316.53	20.39352	1350.86	755.20	20.45519	1522.59	**1287.18**	**20.39128**	**Dominant**
Colposcopy vs DySIS ± colposcopy												
Colposcopy	6500.85	20.32668		3313.68	20.39141		753.02	20.45375		**1313.59**	**20.38297**	
DySIS + colposcopy	6496.13	20.33040	Dominant	3312.33	20.39545	Dominant	751.27	20.45645	Dominant	**1254.00**	**20.39902**	**Dominant**

TABLE 42 Base case with treatment probabilities from Gateshead

Reasons for referral	Borderline ± HPV			Mild ± HPV			Moderate			Severe		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	1176.04	20.40786		1198.08	20.40362		1179.92	20.44148		1892.24	20.43299	
DySIS alone	1161.60	20.41317	Dominant	1178.29	20.41010	Dominant	1140.94	20.45098	Dominant	1866.15	20.44091	Dominant
Colposcopy vs DySIS ± colposcopy												
Colposcopy	1176.04	20.40786		1198.08	20.40362		1179.92	20.44148		1892.24	20.43299	
DySIS + colposcopy	1143.04	20.41737	Dominant	1155.94	20.41509	Dominant	1095.63	20.46014	Dominant	1831.49	20.44924	Dominant

Reasons for referral	Possible invasion			Possible glandular neoplasia			3 × inadequate			Whole population		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	6556.62	20.33406		3473.10	20.34425		763.53	20.47453		**1328.27**	**20.41249**	
DySIS alone	6542.45	20.33909	Dominant	3449.50	20.36138	Dominant	765.23	20.47579	1347.56	**1307.50**	**20.41916**	**Dominant**
Colposcopy vs DySIS ± colposcopy												
Colposcopy	6556.62	20.33406		3473.10	20.34425		763.53	20.47453		**1328.27**	**20.41249**	
DySIS + colposcopy	6519.32	20.34465	Dominant	3417.91	20.37928	Dominant	761.26	20.47682	Dominant	**1282.26**	**20.42489**	**Dominant**

TABLE 43 Base case with cancer always identified

Reasons for referral	Borderline ± HPV			Mild ± HPV			Moderate			Severe		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	1188.05	20.40555		1222.74	20.39861		1105.71	20.45413		1751.13	20.46183	
DySIS alone	1163.10	20.41222	Dominant	1192.30	20.40635	Dominant	1070.99	20.46209	Dominant	1737.23	20.46593	Dominant
Colposcopy vs DySIS ± colposcopy												
Colposcopy	1188.05	20.40555		1222.74	20.39861		1105.71	20.45413		1751.13	20.46183	
DySIS + colposcopy	1130.90	20.41836	Dominant	1155.42	20.41335	Dominant	1031.00	20.46958	Dominant	1715.83	20.47026	Dominant

Reasons for referral	Possible invasion			Possible glandular neoplasia			3 × inadequate			Whole population		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	6499.02	20.34809		3312.84	20.41446		752.93	20.47607		**1312.75**	**20.41583**	
DySIS alone	6500.50	20.34930	1224.18	3315.96	20.41604	1980.62	755.14	20.47712	2113.36	**1286.59**	**20.42261**	**Dominant**
Colposcopy vs DySIS ± colposcopy												
Colposcopy	6499.02	20.34809		3312.84	20.41446		752.93	20.47607		**1312.75**	**20.41583**	
DySIS + colposcopy	6495.63	20.35052	Dominant	3312.09	20.41742	Dominant	751.24	20.47801	Dominant	**1253.67**	**20.42890**	**Dominant**

TABLE 44 Base case with all negative colposcopic or adjunct results considered clear

Reasons for referral	Borderline ± HPV			Mild ± HPV			Moderate			Severe		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	1331.49	20.36499		1381.48	20.35476		1221.53	20.42868		1838.92	20.43904	
DySIS alone	1265.29	20.38427	Dominant	1305.93	20.37600	Dominant	1148.18	20.44599	Dominant	1799.16	20.45025	Dominant
Colposcopy vs DySIS + colposcopy												
Colposcopy	1331.49	20.36499		1381.48	20.35476		1221.53	20.42868		1838.92	20.43904	
DySIS + colposcopy	1191.97	20.40209	Dominant	1223.83	20.39546	Dominant	1073.21	20.46119	Dominant	1752.36	20.4613	Dominant

Reasons for referral	Possible invasion			Possible glandular neoplasia			3 × inadequate			Whole population		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	6533.29	20.33907		3365.49	20.40032		772.31	20.46845		**1449.69**	**20.37859**	
DySIS alone	6525.37	20.34281	Dominant	3355.40	20.40571	Dominant	769.69	20.47158	Dominant	**1383.67**	**20.39707**	**Dominant**
Colposcopy vs DySIS + colposcopy												
Colposcopy	6533.29	20.33907		3365.49	20.40032		772.31	20.46845		**1449.69**	**20.37859**	
DySIS + colposcopy	6510.35	20.3467	Dominant	3340.27	20.41036	Dominant	761.23	20.47444	Dominant	**1311.40**	**20.41408**	**Dominant**

TABLE 45 Base case with true disease state defined as biopsy if available, otherwise colposcopy

Reasons for referral	Borderline ± HPV			Mild ± HPV			Moderate			Severe		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	1188.55	20.40278		1223.09	20.39607		1093.34	20.45297		1685.18	20.46132	
DySIS alone	1163.45	20.41037	Dominant	1192.53	20.40468	Dominant	1058.55	20.46145	Dominant	1670.33	20.46607	Dominant
Colposcopy vs DySIS ± colposcopy												
Colposcopy	1188.55	20.40278		1223.09	20.39607		1093.34	20.45297		1685.18	20.46132	
DySIS + colposcopy	1131.10	20.41738	Dominant	1155.54	20.41249	Dominant	1018.64	20.46938	Dominant	1648.01	20.47106	Dominant

Reasons for referral	Possible invasion			Possible glandular neoplasia			3 × inadequate			Whole population		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	7270.45	20.32908		2812.53	20.43029		617.79	20.49966		**1301.90**	**20.41373**	
DySIS alone	7271.47	20.33047	735.93	2816.00	20.43198	2061.22	623.12	20.49989	23,387.08	**1275.51**	**20.42132**	**Dominant**
Colposcopy vs DySIS ± colposcopy												
Colposcopy	7270.45	20.32908		2812.53	20.43029		617.79	20.49966		**1301.90**	**20.41373**	
DySIS + colposcopy	7266.16	20.33188	Dominant	2812.60	20.43347	22.04	622.44	20.50018	8950.63	**1242.38**	**20.42837**	**Dominant**

Appendix 6 Sensitivity analyses of the secondary analysis quality-adjusted life-year decrement of treatment biopsy 0.13 (from 0.005)

TABLE 46 Quality-adjusted life-year decrement of 0.13 (from 0.005) for 25-year-old population

Reasons for referral	Borderline ± HPV			Mild ± HPV			Moderate			Severe		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	965.17	21.28912		999.32	21.27800		1144.33	21.20452		1839.20	21.18469	
DySIS alone	944.25	21.29349	Dominant	975.08	21.28259	Dominant	1113.10	21.20844	Dominant	1824.06	21.18790	Dominant
Colposcopy vs DySIS ± colposcopy												
Colposcopy	965.17	21.28912		999.32	21.27800		1144.33	21.20452		1839.20	21.18469	
DySIS + colposcopy	913.72	21.29888	Dominant	940.92	21.28828	Dominant	1073.04	21.21374	Dominant	1800.32	21.19203	Dominant

Reasons for referral	Possible invasion			Possible glandular neoplasia			3 × inadequate			Whole population		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	6553.69	21.07859		3295.20	21.18107		698.63	21.36281		**1163.85**	**21.25966**	
DySIS alone	6554.97	21.07829	Dominated	3300.39	21.17764	Dominated	703.80	21.36201	Dominated	**1141.70**	**21.26380**	**Dominant**
Colposcopy vs DySIS ± colposcopy												
Colposcopy	6553.69	21.07859		3295.20	21.18107		698.63	21.36281		**1163.85**	**21.25966**	
DySIS + colposcopy	6549.45	21.07860	Dominant	3298.06	21.17571	Dominated	702.46	21.36165	Dominated	**1110.09**	**21.26902**	**Dominant**

TABLE 47 Quality-adjusted life-year decrement of 0.13 (from 0.005) for 45-year-old population

Reasons for referral	Borderline ± HPV			Mild ± HPV			Moderate			Severe		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	1108.59	18.77548		1150.71	18.76045		1000.90	18.75738		1634.45	18.75597	
DySIS alone	1081.70	18.78088	Dominant	1118.01	18.76690	Dominant	963.15	18.76366	Dominant	1619.08	18.75966	Dominant
Colposcopy vs DySIS ± colposcopy												
Colposcopy	1108.59	18.77548		1150.71	18.76045		1000.90	18.75738		1634.45	18.75597	
DySIS + colposcopy	1047.91	18.78673	Dominant	1079.19	18.77362	Dominant	920.38	18.77042	Dominant	1596.20	18.76404	Dominant

Reasons for referral	Possible invasion			Possible glandular neoplasia			3 × inadequate			Whole population		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	6379.56	18.65388		3196.85	18.73146		641.23	18.89816		**1227.57**	**18.76447**	
DySIS alone	6380.67	18.65391	36,489.08	3199.83	18.72868	Dominated	643.86	18.89808	Dominated	**1199.32**	**18.77001**	**Dominant**
Colposcopy vs DySIS ± colposcopy												
Colposcopy	6379.56	18.65388		3196.85	18.73146		641.23	18.89816		**1227.57**	**18.76447**	
DySIS + colposcopy	6375.57	18.65442	Dominant	3196.22	18.72724	148.27	640.79	18.89828	Dominant	**1164.59**	**18.77598**	**Dominant**

TABLE 48 Quality-adjusted life-year decrement of 0.13 (from 0.005) and duration of the HRQoL decrement as a result of cancer for stages 2–4 is 1 year

Reasons for referral	Borderline ± HPV			Mild ± HPV			Moderate			Severe		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	1188.55	20.35262		1223.09	20.34023		1106.85	20.32477		1754.00	20.31752	
DySIS alone	1163.45	20.35659	Dominant	1192.53	20.34505	Dominant	1071.80	20.32980	Dominant	1739.28	20.32080	Dominant
Colposcopy vs DySIS ± colposcopy												
Colposcopy	1188.55	20.35262		1223.09	20.34023		1106.85	20.32477		1754.00	20.31752	
DySIS + colposcopy	1131.10	20.36102	Dominant	1155.54	20.35015	Dominant	1031.45	20.33542	Dominant	1716.98	20.32479	Dominant

Reasons for referral	Possible invasion			Possible glandular neoplasia			3 × inadequate			Whole population		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	6500.85	20.20809		3313.68	20.29185		753.02	20.46363		**1313.59**	**20.33910**	
DySIS alone	6501.71	20.20803	Dominated	3316.53	20.28889	Dominated	755.20	20.46340	Dominated	**1287.18**	**20.34331**	**Dominant**
Colposcopy vs DySIS ± colposcopy												
Colposcopy	6500.85	20.20809		3313.68	20.29185		753.02	20.46363		**1313.59**	**20.33910**	
DySIS + colposcopy	6496.13	20.20851	Dominant	3312.33	20.28736	300.75	751.27	20.46353	17,532.97	**1254.00**	**20.34798**	**Dominant**

TABLE 49 Quality-adjusted life-year decrement of 0.13 (from 0.005) and duration of the HRQoL decrement as a result of cancer for stages 2–4 is 3 years

Reasons for referral	Borderline ± HPV			Mild ± HPV			Moderate			Severe		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	1188.55	20.35194		1223.09	20.33952		1106.85	20.32448		1754.00	20.31735	
DySIS alone	1163.45	20.35596	Dominant	1192.53	20.34440	Dominant	1071.80	20.32955	Dominant	1739.28	20.32064	Dominant
Colposcopy vs DySIS ± colposcopy												
Colposcopy	1188.55	20.35194		1223.09	20.33952		1106.85	20.32448		1754.00	20.31735	
DySIS + colposcopy	1131.10	20.36044	Dominant	1155.54	20.34956	Dominant	1031.45	20.33520	Dominant	1716.98	20.32464	Dominant

Reasons for referral	Possible invasion			Possible glandular neoplasia			3 × inadequate			Whole population		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	6500.85	20.20792		3313.68	20.29159		753.02	20.46332		**1313.59**	**20.33853**	
DySIS alone	6501.71	20.20787	Dominated	3316.53	20.28864	Dominated	755.20	20.46310	Dominated	**1287.18**	**20.34279**	**Dominant**
Colposcopy vs DySIS ± colposcopy												
Colposcopy	6500.85	20.20792		3313.68	20.29159		753.02	20.46332		**1313.59**	**20.33853**	
DySIS + colposcopy	6496.13	20.20835	Dominant	3312.33	20.28711	302.09	751.27	20.46324	22,885.94	**1254.00**	**20.34750**	**Dominant**

TABLE 50 Quality-adjusted life-year decrement of 0.13 (from 0.005) with cancer treatment costs 50% lower

Reasons for referral	Borderline ± HPV			Mild ± HPV			Moderate			Severe		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	966.40	20.35130		995.27	20.33886		938.97	20.32422		1234.26	20.31718	
DySIS alone	958.47	20.35538	Dominant	984.18	20.34380	Dominant	916.53	20.32932	Dominant	1223.92	20.32049	Dominant
Colposcopy vs DySIS ± colposcopy												
Colposcopy	966.40	20.35130		995.27	20.33886		938.97	20.32422		1234.26	20.31718	
DySIS + colposcopy	942.14	20.35991	Dominant	965.17	20.34901	Dominant	887.47	20.33499	Dominant	1205.84	20.32451	Dominant

Reasons for referral	Possible invasion			Possible glandular neoplasia			3 × inadequate			Whole population		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	3584.46	20.20776		2002.37	20.29134		662.36	20.46303		**1032.17**	**20.33799**	
DySIS alone	3586.80	20.20771	Dominated	2008.15	20.28840	Dominated	667.92	20.46282	Dominated	**1021.32**	**20.34230**	**Dominant**
Colposcopy vs DySIS ± colposcopy												
Colposcopy	3584.46	20.20776		2002.37	20.29134		662.36	20.46303		**1032.17**	**20.33799**	
DySIS + colposcopy	3582.45	20.20819	Dominant	2006.21	20.28688	Dominated	666.59	20.46297	Dominated	**1002.56**	**20.34705**	**Dominant**

TABLE 51 Quality-adjusted life-year decrement of 0.13 (from 0.005) with cancer treatment costs 50% higher

Reasons for referral	Borderline ± HPV			Mild ± HPV			Moderate			Severe		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	1410.71	20.35130		1450.91	20.33886		1274.72	20.32422		2273.73	20.31718	
DySIS alone	1368.43	20.35538	Dominant	1400.88	20.34380	Dominant	1227.07	20.32932	Dominant	2254.65	20.32049	Dominant
Colposcopy vs DySIS ± colposcopy												
Colposcopy	1410.71	20.35130		1450.91	20.33886		1274.72	20.32422		2273.73	20.31718	
DySIS + colposcopy	1320.05	20.35991	Dominant	1345.91	20.34901	Dominant	1175.43	20.33499	Dominant	2228.13	20.32451	Dominant

Reasons for referral	Possible invasion			Possible glandular neoplasia			3 × inadequate			Whole population		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	9417.23	20.20776		4625.00	20.29134		843.68	20.46303		**1595.01**	**20.33799**	
DySIS alone	9416.62	20.20771	13,147.26	4624.91	20.28840	30.60	842.49	20.46282	5739.69	**1553.04**	**20.34230**	**Dominant**
Colposcopy vs DySIS ± colposcopy												
Colposcopy	9417.23	20.20776		4625.00	20.29134		843.68	20.46303		**1595.01**	**20.33799**	
DySIS + colposcopy	9409.82	20.20819	Dominant	4618.45	20.28688	1467.59	835.96	20.46297	141,627.31	**1505.44**	**20.34705**	**Dominant**

TABLE 52 Quality-adjusted life-year decrement of 0.13 (from 0.005) with HRQoL estimates of health states from the Sheffield model

Reasons for referral	Borderline ± HPV			Mild ± HPV			Moderate			Severe		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	1188.55	22.08938		1223.09	22.04840		1106.85	22.23021		1754.00	22.27752	
DySIS alone	1163.45	22.10829	Dominant	1192.53	22.07061	Dominant	1071.80	22.24781	Dominant	1739.28	22.28427	Dominant
Colposcopy vs DySIS ± colposcopy												
Colposcopy	1188.55	22.08938		1223.09	22.04840		1106.85	22.23021		1754.00	22.27752	
DySIS + colposcopy	1131.10	22.12470	Dominant	1155.54	22.08948	Dominant	1031.45	22.26307	Dominant	1716.98	22.29122	Dominant

Reasons for referral	Possible invasion			Possible glandular neoplasia			3 × inadequate			Whole population		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	6500.85	22.13060		3313.68	22.19945		753.02	22.36683		**1313.59**	**22.11697**	
DySIS alone	6501.71	22.13207	586.37	3316.53	22.20010	4360.11	755.20	22.37068	567.32	**1287.18**	**22.13504**	**Dominant**
Colposcopy vs DySIS ± colposcopy												
Colposcopy	6500.85	22.13060		3313.68	22.19945		753.02	22.36683		**1313.59**	**22.11697**	
DySIS + colposcopy	6496.13	22.13365	Dominant	3312.33	22.20102	Dominant	751.27	22.37362	Dominant	**1254.00**	**22.15072**	**Dominant**

TABLE 53 Quality-adjusted life-year decrement of 0.13 (from 0.005) with QALY decrement associated with cytological screening decreased by 50%

Reasons for referral	Borderline ± HPV			Mild ± HPV			Moderate			Severe		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	1188.55	20.35623		1223.09	20.34388		1106.85	20.32940		1754.00	20.32227	
DySIS alone	1163.45	20.36031	Dominant	1192.53	20.34883	Dominant	1071.80	20.33449	Dominant	1739.28	20.32558	Dominant
Colposcopy vs DySIS ± colposcopy												
Colposcopy	1188.55	20.35623		1223.09	20.34388		1106.85	20.32940		1754.00	20.32227	
DySIS + colposcopy	1131.10	20.36484	Dominant	1155.54	20.35404	Dominant	1031.45	20.34016	Dominant	1716.98	20.32960	Dominant

Reasons for referral	Possible invasion			Possible glandular neoplasia			3 × inadequate			Whole population		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	6500.85	20.21259		3313.68	20.29633		753.02	20.46757		**1313.59**	**20.34300**	
DySIS alone	6501.71	20.21255	Dominated	3316.53	20.29341	Dominated	755.20	20.46737	Dominated	**1287.18**	**20.34732**	**Dominant**
Colposcopy vs DySIS ± colposcopy												
Colposcopy	6500.85	20.21259		3313.68	20.29633		753.02	20.46757		**1313.59**	**20.34300**	
DySIS + colposcopy	6496.13	20.21304	Dominant	3312.33	20.29191	305.75	751.27	20.46752	34,527.99	**1254.00**	**20.35207**	**Dominant**

TABLE 54 Quality-adjusted life-year decrement of 0.13 (from 0.005) with QALY decrement associated with cytological screening increased by 50%

Reasons for referral	Borderline ± HPV			Mild ± HPV			Moderate			Severe		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	1188.55	20.34638		1223.09	20.33383		1106.85	20.31904		1754.00	20.31209	
DySIS alone	1163.45	20.35045	Dominant	1192.53	20.33877	Dominant	1071.80	20.32414	Dominant	1739.28	20.31540	Dominant
Colposcopy vs DySIS ± colposcopy												
Colposcopy	1188.55	20.34638		1223.09	20.33383		1106.85	20.31904		1754.00	20.31209	
DySIS + colposcopy	1131.10	20.35497	Dominant	1155.54	20.34397	Dominant	1031.45	20.32982	Dominant	1716.98	20.31941	Dominant

Reasons for referral	Possible invasion			Possible glandular neoplasia			3 × inadequate			Whole population		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	6500.85	20.20293		3313.68	20.28635		753.02	20.45848		**1313.59**	**20.33298**	
DySIS alone	6501.71	20.20288	Dominated	3316.53	20.28340	Dominated	755.20	20.45827	Dominated	**1287.18**	**20.33729**	**Dominant**
Colposcopy vs DySIS ± colposcopy												
Colposcopy	6500.85	20.20293		3313.68	20.28635		753.02	20.45848		**1313.59**	**20.33298**	
DySIS + colposcopy	6496.13	20.20335	Dominant	3312.33	20.28186	300.99	751.27	20.45842	29,832.09	**1254.00**	**20.34204**	**Dominant**

TABLE 55 Quality-adjusted life-year decrement of 0.13 (from 0.005) with alternative cost of colposcope £5000

Reasons for referral	Borderline ± HPV			Mild ± HPV			Moderate			Severe		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	1188.55	20.35130		1223.09	20.33886		1106.85	20.32422		1754.00	20.31718	
DySIS alone	1164.87	20.35538	Dominant	1193.97	20.34380	Dominant	1072.84	20.32932	Dominant	1740.22	20.32049	Dominant
Colposcopy vs DySIS ± colposcopy												
Colposcopy	1188.55	20.35130		1223.09	20.33886		1106.85	20.32422		1754.00	20.31718	
DySIS + colposcopy	1132.50	20.35991	Dominant	1156.97	20.34901	Dominant	1032.48	20.33499	Dominant	1717.91	20.32451	Dominant

Reasons for referral	Possible invasion			Possible glandular neoplasia			3 × inadequate			Whole population		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	6500.85	20.20776		3313.68	20.29134		753.02	20.46303		**1313.59**	**20.33799**	
DySIS alone	6502.64	20.20771	Dominated	3317.57	20.28840	Dominated	756.25	20.46282	Dominated	**1288.49**	**20.34230**	**Dominant**
Colposcopy vs DySIS ± colposcopy												
Colposcopy	6500.85	20.20776		3313.68	20.29134		753.02	20.46303		**1313.59**	**20.33799**	
DySIS + colposcopy	6497.07	20.20819	Dominant	3313.37	20.28688	69.02	752.32	20.46297	12,799.20	**1255.30**	**20.34705**	**Dominant**

TABLE 56 Quality-adjusted life-year decrement of 0.13 (from 0.005) with alternative cost of colposcope £20,000

Reasons for referral	Borderline ± HPV			Mild ± HPV			Moderate			Severe		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	1188.55	20.35130		1223.09	20.33886		1106.85	20.32422		1754.00	20.31718	
DySIS alone	1160.62	20.35538	Dominant	1189.65	20.34380	Dominant	1069.70	20.32932	Dominant	1737.42	20.32049	Dominant
Colposcopy vs DySIS ± colposcopy												
Colposcopy	1188.55	20.35130		1223.09	20.33886		1106.85	20.32422		1754.00	20.31718	
DySIS + colposcopy	1128.29	20.35991	Dominant	1152.69	20.34901	Dominant	1029.40	20.33499	Dominant	1715.13	20.32451	Dominant

Reasons for referral	Possible invasion			Possible glandular neoplasia			3 × inadequate			Whole population		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	6500.85	20.20776		3313.68	20.29134		753.02	20.46303		**1313.59**	**20.33799**	
DySIS alone	6499.85	20.20771	21,491.18	3314.44	20.28840	Dominated	753.11	20.46282	Dominated	**1284.55**	**20.34230**	**Dominant**
Colposcopy vs DySIS ± colposcopy												
Colposcopy	6500.85	20.20776		3313.68	20.29134		753.02	20.46303		**1313.59**	**20.33799**	
DySIS + colposcopy	6494.27	20.20819	Dominant	3310.24	20.28688	772.00	749.18	20.46297	70,427.79	**1251.40**	**20.34705**	**Dominant**

TABLE 57 Quality-adjusted life-year decrement of 0.13 (from 0.005) with QALY decrement associated with colposcopy decreased by 50%

Reasons for referral	Borderline ± HPV			Mild ± HPV			Moderate			Severe		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	1188.55	20.38304		1223.09	20.37150		1106.85	20.35272		1754.00	20.34039	
DySIS alone	1163.45	20.38668	Dominant	1192.53	20.37594	Dominant	1071.80	20.35605	Dominant	1739.28	20.34243	Dominant
Colposcopy vs DySIS ± colposcopy												
Colposcopy	1188.55	20.38304		1223.09	20.37150		1106.85	20.35272		1754.00	20.34039	
DySIS + colposcopy	1131.10	20.39087	Dominant	1155.54	20.38076	Dominant	1031.45	20.35990	Dominant	1716.98	20.34502	Dominant

Reasons for referral	Possible invasion			Possible glandular neoplasia			3 × inadequate			Whole population		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	6500.85	20.22839		3313.68	20.31355		753.02	20.48451		**1313.59**	**20.36841**	
DySIS alone	6501.71	20.22798	Dominated	3316.53	20.31034	Dominated	755.20	20.48416	Dominated	**1287.18**	**20.37200**	**Dominant**
Colposcopy vs DySIS ± colposcopy												
Colposcopy	6500.85	20.22839		3313.68	20.31355		753.02	20.48451		**1313.59**	**20.36841**	
DySIS + colposcopy	6496.13	20.22806	14,476.70	3312.33	20.30855	270.47	751.27	20.48420	5662.25	**1254.00**	**20.37608**	**Dominant**

TABLE 58 Quality-adjusted life-year decrement of 0.13 (from 0.005) with QALY decrement associated with colposcopy increased by 50%

Reasons for referral	Borderline ± HPV			Mild ± HPV			Moderate			Severe		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	1188.55	20.31957		1223.09	20.30622		1106.85	20.29572		1754.00	20.29398	
DySIS alone	1163.45	20.32408	Dominant	1192.53	20.31166	Dominant	1071.80	20.30258	Dominant	1739.28	20.29855	Dominant
Colposcopy vs DySIS ± colposcopy												
Colposcopy	1188.55	20.31957		1223.09	20.30622		1106.85	20.29572		1754.00	20.29398	
DySIS + colposcopy	1131.10	20.32895	Dominant	1155.54	20.31725	Dominant	1031.45	20.31008	Dominant	1716.98	20.30399	Dominant

Reasons for referral	Possible invasion			Possible glandular neoplasia			3 × inadequate			Whole population		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	6500.85	20.18713		3313.68	20.26914		753.02	20.44155		**1313.59**	**20.30758**	
DySIS alone	6501.71	20.18744	2772.74	3316.53	20.26646	Dominated	755.20	20.44148	Dominated	**1287.18**	**20.31260**	**Dominant**
Colposcopy vs DySIS ± colposcopy												
Colposcopy	6500.85	20.18713		3313.68	20.26914		753.02	20.44155		**1313.59**	**20.30758**	
DySIS + colposcopy	6496.13	20.18833	Dominant	3312.33	20.26522	345.32	751.27	20.44175	Dominant	**1254.00**	**20.31802**	**Dominant**

TABLE 59 Quality-adjusted life-year decrement of 0.13 (from 0.005) with treatment probabilities from Gateshead

Reasons for referral	Borderline ± HPV			Mild ± HPV			Moderate			Severe		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	1176.04	20.34959		1198.08	20.33859		1179.92	20.31207		1892.24	20.29118	
DySIS alone	1161.60	20.35107	Dominant	1178.29	20.34033	Dominant	1140.94	20.31817	Dominant	1866.15	20.29766	Dominant
Colposcopy vs DySIS ± colposcopy												
Colposcopy	1176.04	20.34959		1198.08	20.33859		1179.92	20.31207		1892.24	20.29118	
DySIS + colposcopy	1143.04	20.35277	Dominant	1155.94	20.34222	Dominant	1095.63	20.32496	Dominant	1831.49	20.30490	Dominant

Reasons for referral	Possible invasion			Possible glandular neoplasia			3 × inadequate			Whole population		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	6556.62	20.19955		3473.10	20.25160		763.53	20.46013		**1328.27**	**20.33200**	
DySIS alone	6542.45	20.20223	Dominant	3449.50	20.26111	Dominant	765.23	20.45981	Dominated	**1307.50**	**20.33485**	**Dominant**
Colposcopy vs DySIS ± colposcopy												
Colposcopy	6556.62	20.19955		3473.10	20.25160		763.53	20.46013		**1328.27**	**20.33200**	
DySIS + colposcopy	6519.32	20.20622	Dominant	3417.91	20.27379	Dominant	761.26	20.45982	7266.53	**1282.26**	**20.33805**	**Dominant**

TABLE 60 Quality-adjusted life-year decrement of 0.13 (from 0.005) with cancer always identified

Reasons for referral	Borderline ± HPV			Mild ± HPV			Moderate			Severe		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	1188.05	20.35402		1222.74	20.34135		1105.71	20.32581		1751.13	20.31930	
DySIS alone	1163.10	20.35720	Dominant	1192.30	20.34544	Dominant	1070.99	20.33036	Dominant	1737.23	20.32198	Dominant
Colposcopy vs DySIS ± colposcopy												
Colposcopy	1188.05	20.35402		1222.74	20.34135		1105.71	20.32581		1751.13	20.31930	
DySIS + colposcopy	1130.90	20.36087	Dominant	1155.42	20.34985	Dominant	1031.00	20.33553	Dominant	1715.83	20.32533	Dominant

Reasons for referral	Possible invasion			Possible glandular neoplasia			3 × inadequate			Whole population		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	6499.02	20.20852		3312.84	20.29217		752.93	20.46385		**1303.14**	**20.34162**	
DySIS alone	6500.50	20.20823	Dominated	3315.96	20.28898	Dominated	755.14	20.46340	Dominated	**1286.59**	**20.34390**	**Dominant**
Colposcopy vs DySIS ± colposcopy												
Colposcopy	6499.02	20.20852		3312.84	20.29217		752.93	20.46385		**1290.73**	**20.34303**	
DySIS + colposcopy	6495.63	20.20845	42,845.11	3312.09	20.28719	149.75	751.24	20.46329	3062.97	**1253.67**	**20.34790**	**Dominant**

TABLE 61 Quality-adjusted life-year decrement of 0.13 (from 0.005) with all negative colposcopic or adjunct results considered clear

Reasons for referral	Borderline ± HPV			Mild ± HPV			Moderate			Severe		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	1331.49	20.32144		1381.48	20.30697		1221.53	20.30439		1838.92	20.29915	
DySIS alone	1265.29	20.33565	Dominant	1305.93	20.32281	Dominant	1148.18	20.31707	Dominant	1799.16	20.30828	Dominant
Colposcopy vs DySIS + colposcopy												
Colposcopy	1331.49	20.32144		1381.48	20.30697		1221.53	20.30439		1838.92	20.29915	
DySIS + colposcopy	1191.97	20.34962	Dominant	1223.83	20.33813	Dominant	1073.21	20.32900	Dominant	1752.36	20.31785	Dominant

Reasons for referral	Possible invasion			Possible glandular neoplasia			3 × inadequate			Whole population		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	6533.29	20.20065		3365.49	20.28351		772.31	20.45835		**1449.69**	**20.31045**	
DySIS alone	6525.37	20.20268	Dominant	3355.40	20.28309	Dominant	769.69	20.45963	Dominant	**1383.67**	**20.32419**	**Dominant**
Colposcopy vs DySIS + colposcopy												
Colposcopy	6533.29	20.20065		3365.49	20.28351		772.31	20.45835		**1449.69**	**20.31045**	
DySIS + colposcopy	6510.35	20.20540	Dominant	3340.27	20.28389	Dominant	761.23	20.46122	Dominant	**1311.40**	**20.33764**	**Dominant**

TABLE 62 Quality-adjusted life-year decrement of 0.13 (from 0.005) with true disease defined as biopsy if available, otherwise colposcopy

Reasons for referral	Borderline ± HPV			Mild ± HPV			Moderate			Severe		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	1188.55	20.40278		1223.09	20.39607		1093.34	20.45297		1685.18	20.46132	
DySIS alone	1163.45	20.41037	Dominant	1192.53	20.40468	Dominant	1058.55	20.46145	Dominant	1670.33	20.46607	Dominant
Colposcopy vs DySIS ± colposcopy												
Colposcopy	1188.55	20.40278		1223.09	20.39607		1093.34	20.45297		1685.18	20.46132	
DySIS + colposcopy	1131.10	20.41738	Dominant	1155.54	20.41249	Dominant	1018.64	20.46938	Dominant	1648.01	20.47106	Dominant

Reasons for referral	Possible invasion			Possible glandular neoplasia			3 × inadequate			Whole population		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	7270.45	20.32908		2812.53	20.43029		617.79	20.49966		**1301.90**	**20.41373**	
DySIS alone	7271.47	20.33047	735.93	2816.00	20.43198	2061.22	623.12	20.49989	23,387.08	**1275.51**	**20.42132**	**Dominant**
Colposcopy vs DySIS ± colposcopy												
Colposcopy	7270.45	20.32908		2812.53	20.43029		617.79	20.49966		**1301.90**	**20.41373**	
DySIS + colposcopy	7266.16	20.33188	Dominant	2812.60	20.43347	22.04	622.44	20.50018	8950.63	**1242.38**	**20.42837**	**Dominant**

Appendix 7 Secondary analysis cost of treatment biopsy £2758 sensitivity analyses

TABLE 63 Cost of treatment biopsy for 25-year-old population

Reason for referral	Borderline ± HPV			Mild ± HPV			Moderate			Severe		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	1723.48	21.32695		1857.27	21.32080		3691.15	21.33156		4733.95	21.32908	
DySIS alone	1756.21	21.33399	4649.03	1895.25	21.32849	4934.90	3740.53	21.33951	6213.92	4755.95	21.33415	4340.73
Colposcopy vs DySIS ± colposcopy												
Colposcopy	1723.48	21.32695		1857.27	21.32080		3691.15	21.33156		4733.95	21.32908	
DySIS + colposcopy	1766.36	21.34142	2964.54	1907.90	21.33651	3221.52	3756.03	21.34758	4050.39	4758.08	21.33958	2299.72

Reason for referral	Possible invasion			Possible glandular neoplasia			3 × inadequate			Whole population		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	9371.80	21.21916		5704.63	21.30126		868.66	21.37129		**2469.31**	**21.32478**	
DySIS alone	9406.55	21.22054	25,241.70	5801.71	21.30241	84,345.22	897.43	21.37167	75,833.03	**2505.07**	**21.33181**	**5086.47**
Colposcopy vs DySIS ± colposcopy												
Colposcopy	9371.80	21.21916		5704.63	21.30126		868.66	21.37129		**2469.31**	**21.32478**	
DySIS + colposcopy	9423.37	21.22196	18,416.40	5860.35	21.30352	68,694.37	911.68	21.37208	54,285.09	**2516.20**	**21.33916**	**3259.53**

TABLE 64 Cost of treatment biopsy for 45-year-old population

Reason for referral	Borderline ± HPV			Mild ± HPV			Moderate			Severe		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	2021.28	18.82101		2172.59	18.81143		3521.97	18.88313		4460.79	18.89695	
DySIS alone	2055.89	18.82948	4086.59	2205.65	18.82115	3398.39	3551.32	18.89276	3048.44	4471.12	18.90193	2076.05
Colposcopy vs DySIS ± colposcopy												
Colposcopy	2021.28	18.82101		2172.59	18.81143		3521.97	18.88313		4460.79	18.89695	
DySIS + colposcopy	2067.40	18.83759	2781.87	2215.32	18.83029	2265.52	3555.05	18.90184	1768.43	4466.50	18.90722	556.69

Reason for referral	Possible invasion			Possible glandular neoplasia			3 × inadequate			Whole population		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	9143.74	18.79176		5597.39	18.85120		825.87	18.90737		**2638.27**	**18.83484**	
DySIS alone	9170.64	18.79308	20,428.26	5690.15	18.85291	54,398.26	851.76	18.90845	24,022.33	**2669.10**	**18.84333**	**3632.78**
Colposcopy vs DySIS ± colposcopy												
Colposcopy	9143.74	18.79176		5597.39	18.85120		825.87	18.90737		**2638.27**	**18.83484**	
DySIS + colposcopy	9182.90	18.79446	14,526.06	5746.32	18.85445	45,903.94	864.27	18.90943	18,682.14	**2677.41**	**18.85144**	**2357.86**

TABLE 65 Cost of treatment biopsy and duration of the HRQoL decrement as a result of cancer for stages 2–4 is 1 year

Reason for referral	Borderline ± HPV			Mild ± HPV			Moderate			Severe		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	2220.53	20.40410		2370.05	20.39744		3678.84	20.45306		4610.74	20.46002	
DySIS alone	2265.75	20.41157	6047.71	2412.97	20.40593	5054.98	3712.21	20.46151	3951.50	4624.56	20.46472	2939.74
Colposcopy vs DySIS ± colposcopy												
Colposcopy	2220.53	20.40410		2370.05	20.39744		3678.84	20.45306		4610.74	20.46002	
DySIS + colposcopy	2283.34	20.41850	4362.10	2428.21	20.41364	3591.42	3718.48	20.46945	2418.51	4622.12	20.46970	1175.42

Reason for referral	Possible invasion			Possible glandular neoplasia			3 × inadequate			Whole population		
	Costs (£)		QALYs	Costs (£)	QALYs	ICER	Costs (£)		QALYs	ICER		Costs (£)
Colposcopy vs DySIS alone												
Colposcopy	9298.48	20.34764		5764.91	20.41413		997.66	20.47584		**2825.02**	**20.41449**	
DySIS alone	9329.51	20.34909	21,445.51	5863.56	20.41595	54,206.49	1029.99	20.47711	25,430.58	**2864.43**	**20.42199**	**5256.60**
Colposcopy vs DySIS ± colposcopy												
Colposcopy	9298.48	20.34764		5764.91	20.41413		997.66	20.47584		**2825.02**	**20.41449**	
DySIS + colposcopy	9344.17	20.35057	15,596.09	5923.06	20.41758	45,716.23	1046.11	20.47824	20,151.15	**2877.68**	**20.42897**	**3636.86**

TABLE 66 Cost of treatment biopsy and duration of the HRQoL decrement as a result of cancer for stages 2–4 is 3 years

Reason for referral	Borderline ± HPV			Mild ± HPV			Moderate			Severe		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	2220.53	20.40342		2370.05	20.39673		3678.84	20.45278		4610.74	20.45985	
DySIS alone	2265.75	20.41095	6003.59	2412.97	20.40528	5019.09	3712.21	20.46126	3935.65	4624.56	20.46456	2930.27
Colposcopy vs DySIS ± colposcopy												
Colposcopy	2220.53	20.40342		2370.05	20.39673		3678.84	20.45278		4610.74	20.45985	
DySIS + colposcopy	2283.34	20.41792	4330.54	2428.21	20.41304	3566.06	3718.48	20.46923	2409.32	4622.12	20.46956	1171.83

Reason for referral	Possible invasion			Possible glandular neoplasia			3 × inadequate			Whole population		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	9298.48	20.34747		5764.91	20.41386		997.66	20.47552		**2825.02**	**20.41392**	
DySIS alone	9329.51	20.34893	21,359.44	5863.56	20.41569	53,876.46	1029.99	20.47681	25,173.73	**2864.43**	**20.42147**	**5222.68**
Colposcopy vs DySIS ± colposcopy												
Colposcopy	9298.48	20.34747		5764.91	20.41386		997.66	20.47552		**2825.02**	**20.41392**	
DySIS + colposcopy	9344.17	20.35041	15,539.27	5923.06	20.41734	45,454.06	1046.11	20.47795	19,958.02	**2877.68**	**20.42849**	**3613.77**

TABLE 67 Cost of treatment biopsy with cancer treatment costs 50% lower

Reason for referral	Borderline ± HPV			Mild ± HPV			Moderate			Severe		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	1998.37	20.40278		2142.23	20.39607		3510.96	20.45252		4091.00	20.45968	
DySIS alone	2060.77	20.41037	8227.65	2204.61	20.40468	7247.73	3556.94	20.46103	5401.77	4109.20	20.46442	3845.42
Colposcopy vs DySIS ± colposcopy												
Colposcopy	1998.37	20.40278		2142.23	20.39607		3510.96	20.45252		4091.00	20.45968	
DySIS + colposcopy	2094.38	20.41738	6575.11	2237.84	20.41249	5823.62	3574.50	20.46903	3848.01	4110.97	20.46942	2050.80

Reason for referral	Possible invasion			Possible glandular neoplasia			3 × inadequate			Whole population		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	6382.09	20.34731		4453.59	20.41361		907.01	20.47523		**2543.60**	**20.41339**	
DySIS alone	6414.60	20.34877	22,292.01	4555.18	20.41546	55,166.14	942.71	20.47653	27,543.13	**2598.57**	**20.42098**	**7241.77**
Colposcopy vs DySIS ± colposcopy												
Colposcopy	6382.09	20.34731		4453.59	20.41361		907.01	20.47523		**2543.60**	**20.41339**	
DySIS + colposcopy	6430.48	20.35026	16,401.87	4616.93	20.41711	46,695.93	961.42	20.47768	22,219.55	**2626.24**	**20.42805**	**5637.90**

TABLE 68 Cost of treatment biopsy with cancer treatment costs 50% higher

Reason for referral	Borderline ± HPV			Mild ± HPV			Moderate			Severe		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	2442.68	20.40278		2597.87	20.39607		3846.71	20.45252		5130.48	20.45968	
DySIS alone	2470.73	20.41037	3698.31	2621.32	20.40468	2724.34	3867.48	20.46103	2440.17	5139.93	20.46442	1997.56
Colposcopy vs DySIS ± colposcopy												
Colposcopy	2442.68	20.40278		2597.87	20.39607		3846.71	20.45252		5130.48	20.45968	
DySIS + colposcopy	2472.29	20.41738	2027.86	2618.59	20.41249	1261.80	3862.46	20.46903	953.60	5133.26	20.46942	286.18

Reason for referral	Possible invasion			Possible glandular neoplasia			3 × inadequate			Whole population		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	12,214.86	20.34731		7076.22	20.41361		1088.32	20.47523		**3106.44**	**20.41339**	
DySIS alone	12,244.42	20.34877	20,267.40	7171.94	20.41546	51,977.84	1117.28	20.47653	22,334.06	**3130.29**	**20.42098**	**3141.03**
Colposcopy vs DySIS ± colposcopy												
Colposcopy	12,214.86	20.34731		7076.22	20.41361		1088.32	20.47523		**3106.44**	**20.41339**	
DySIS + colposcopy	12,257.85	20.35026	14,571.32	7229.18	20.41711	43,728.11	1130.80	20.47768	17,342.52	**3129.12**	**20.42805**	**1547.06**

TABLE 69 Cost of treatment biopsy with HRQoL estimates of health states from the Sheffield model

Reason for referral	Borderline ± HPV			Mild ± HPV			Moderate			Severe		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	2220.53	22.14086		2370.05	22.10561		3678.84	22.35851		4610.74	22.42003	
DySIS alone	2265.75	22.16328	2017.18	2412.97	22.13149	1658.17	3712.21	22.37952	1588.22	4624.56	22.42820	1691.57
Colposcopy vs DySIS ± colposcopy												
Colposcopy	2220.53	22.14086		2370.05	22.10561		3678.84	22.35851		4610.74	22.42003	
DySIS + colposcopy	2283.34	22.18218	1520.27	2428.21	22.15297	1228.25	3718.48	22.39710	1027.18	4622.12	22.43613	706.36

Reason for referral	Possible invasion			Possible glandular neoplasia			3 × inadequate			Whole population		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	9298.48	22.27015		5764.91	22.32172		997.66	22.37903		**2825.02**	**22.19236**	
DySIS alone	9329.51	22.27313	10,418.25	5863.56	22.32716	18,162.19	1029.99	22.38439	6033.13	**2864.43**	**22.21371**	**1845.69**
Colposcopy vs DySIS ± colposcopy												
Colposcopy	9298.48	22.27015		5764.91	22.32172		997.66	22.37903		**2825.02**	**22.19236**	
DySIS + colposcopy	9344.17	22.27572	8211.19	5923.06	22.33125	16,598.66	1046.11	22.38832	5215.15	**2877.68**	**22.23171**	**1338.35**

TABLE 70 Cost of treatment biopsy with QALY decrement associated with cytological screening decreased by 50%

Reason for referral	Borderline ± HPV			Mild ± HPV			Moderate			Severe		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	2220.53	20.40770		2370.05	20.40109		3678.84	20.45770		4610.74	20.46478	
DySIS alone	2265.75	20.41529	5959.10	2412.97	20.40971	4983.70	3712.21	20.46620	3922.88	4624.56	20.46951	2920.16
Colposcopy vs DySIS ± colposcopy												
Colposcopy	2220.53	20.40770		2370.05	20.40109		3678.84	20.45770		4610.74	20.46478	
DySIS + colposcopy	2283.34	20.42232	4298.72	2428.21	20.41752	3540.99	3718.48	20.47420	2401.97	4622.12	20.47452	1168.14

Reason for referral	Possible invasion			Possible glandular neoplasia			3 × inadequate			Whole population		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	9298.48	20.35214		5764.91	20.41860		997.66	20.47977		**2825.02**	**20.41840**	
DySIS alone	9329.51	20.35361	21,197.31	5863.56	20.42046	52,967.35	1029.99	20.48107	24,893.96	**2864.43**	**20.42599**	**5189.10**
Colposcopy vs DySIS ± colposcopy												
Colposcopy	9298.48	20.35214		5764.91	20.41860		997.66	20.47977		**2825.02**	**20.41840**	
DySIS + colposcopy	9344.17	20.35510	15,437.49	5923.06	20.42214	44,764.23	1046.11	20.48223	19,748.98	**2877.68**	**20.43306**	**3590.93**

TABLE 71 Cost of treatment biopsy with QALY decrement associated with cytological screening increased by 50%

Reason for referral	Borderline ± HPV			Mild ± HPV			Moderate			Severe		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	2220.53	20.39786		2370.05	20.39105		3678.84	20.44733		4610.74	20.45459	
DySIS alone	2265.75	20.40544	5966.87	2412.97	20.39965	4988.37	3712.21	20.45585	3919.05	4624.56	20.45932	2922.82
Colposcopy vs DySIS ± colposcopy												
Colposcopy	2220.53	20.39786		2370.05	20.39105		3678.84	20.44733		4610.74	20.45459	
DySIS + colposcopy	2283.34	20.41245	4304.25	2428.21	20.40746	3544.43	3718.48	20.46385	2399.65	4622.12	20.46433	1168.85

Reason for referral	Possible invasion			Possible glandular neoplasia			3 × inadequate			Whole population		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	9298.48	20.34248		5764.91	20.40863		997.66	20.47069		**2825.02**	**20.40838**	
DySIS alone	9329.51	20.34393	21,362.74	5863.56	20.41045	54,190.58	1029.99	20.47198	24,983.39	**2864.43**	**20.41597**	**5193.71**
Colposcopy vs DySIS ± colposcopy												
Colposcopy	9298.48	20.34248		5764.91	20.40863		997.66	20.47069		**2825.02**	**20.40838**	
DySIS + colposcopy	9344.17	20.34542	15,536.01	5923.06	20.41209	45,668.86	1046.11	20.47313	19,813.20	**2877.68**	**20.42303**	**3594.03**

TABLE 72 Cost of treatment biopsy with alternative cost of colposcope £5000

Reason for referral	Borderline ± HPV			Mild ± HPV			Moderate			Severe		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	2220.53	20.40278		2370.05	20.39607		3678.84	20.45252		4610.74	20.45968	
DySIS alone	2267.17	20.41037	6149.67	2414.41	20.40468	5153.68	3713.26	20.46103	4043.97	4625.49	20.46442	3118.42
Colposcopy vs DySIS ± colposcopy												
Colposcopy	2220.53	20.40278		2370.05	20.39607		3678.84	20.45252		4610.74	20.45968	
DySIS + colposcopy	2284.74	20.41738	4397.51	2429.64	20.41249	3629.62	3719.51	20.46903	2463.01	4623.04	20.46942	1263.58

Reason for referral	Possible invasion			Possible glandular neoplasia			3 × inadequate			Whole population		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	9298.48	20.34731		5764.91	20.41361		997.66	20.47523		**2825.02**	**20.41339**	
DySIS alone	9330.44	20.34877	21,919.04	5864.60	20.41546	54,140.14	1031.04	20.47653	25,748.11	**2865.74**	**20.42098**	**5364.44**
Colposcopy vs DySIS ± colposcopy												
Colposcopy	9298.48	20.34731		5764.91	20.41361		997.66	20.47523		**2825.02**	**20.41339**	
DySIS + colposcopy	9345.10	20.35026	15,802.44	5924.10	20.41711	45,510.68	1047.16	20.47768	20,208.36	**2878.98**	**20.42805**	**3681.14**

TABLE 73 Cost of treatment biopsy with alternative cost of colposcope £20,000

Reason for referral	Borderline ± HPV			Mild ± HPV			Moderate			Severe		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	2220.53	20.40278		2370.05	20.39607		3678.84	20.45252		4610.74	20.45968	
DySIS alone	2262.92	20.41037	5589.60	2410.08	20.40468	4650.74	3710.12	20.46103	3674.95	4622.70	20.46442	2527.62
Colposcopy vs DySIS ± colposcopy												
Colposcopy	2220.53	20.40278		2370.05	20.39607		3678.84	20.45252		4610.74	20.45968	
DySIS + colposcopy	2280.53	20.41738	4109.45	2425.36	20.41249	3368.88	3716.42	20.46903	2276.41	4620.27	20.46942	978.31

Reason for referral	Possible invasion			Possible glandular neoplasia			3 × inadequate			Whole population		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	9298.48	20.34731		5764.91	20.41361		997.66	20.47523		**2825.02**	**20.41339**	
DySIS alone	9327.65	20.34877	20,001.03	5861.46	20.41546	52,435.68	1027.89	20.47653	23,319.57	**2861.80**	**20.42098**	**4845.32**
Colposcopy vs DySIS ± colposcopy												
Colposcopy	9298.48	20.34731		5764.91	20.41361		997.66	20.47523		**2825.02**	**20.41339**	
DySIS + colposcopy	9342.30	20.35026	14,854.91	5920.97	20.41711	44,614.69	1044.02	20.47768	18,926.39	**2875.08**	**20.42805**	**3415.17**

TABLE 74 Cost of treatment biopsy with QALY decrement associated with colposcopy decreased by 50%

Reason for referral	Borderline ± HPV			Mild ± HPV			Moderate			Severe		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	2220.53	20.43451		2370.05	20.42871		3678.84	20.48101		4610.74	20.48289	
DySIS alone	2265.75	20.44167	6320.28	2412.97	20.43682	5291.36	3712.21	20.48776	4946.71	4624.56	20.48635	3993.59
Colposcopy vs DySIS ± colposcopy												
Colposcopy	2220.53	20.43451		2370.05	20.42871		3678.84	20.48101		4610.74	20.48289	
DySIS + colposcopy	2283.34	20.44834	4541.70	2428.21	20.44424	3745.32	3718.48	20.49394	3067.38	4622.12	20.48994	1614.09

Reason for referral	Possible invasion			Possible glandular neoplasia			3 × inadequate			Whole population		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	9298.48	20.36794		5764.91	20.43582		997.66	20.49671		**2825.02**	**20.44380**	
DySIS alone	9329.51	20.36904	28,209.16	5863.56	20.43740	62,581.76	1029.99	20.49786	27,959.29	**2864.43**	**20.45068**	**5730.70**
Colposcopy vs DySIS ± colposcopy												
Colposcopy	9298.48	20.36794		5764.91	20.43582		997.66	20.49671		**2825.02**	**20.44380**	
DySIS + colposcopy	9344.17	20.37013	20,875.54	5923.06	20.43878	53,500.94	1046.11	20.49890	22,064.94	**2877.68**	**20.45708**	**3967.38**

TABLE 75 Cost of treatment biopsy with QALY decrement associated with colposcopy increased by 50%

Reason for referral	Borderline ± HPV			Mild ± HPV			Moderate			Severe		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	2220.53	20.37105		2370.05	20.36343		3678.84	20.42402		4610.74	20.43648	
DySIS alone	2265.75	20.37906	5643.92	2412.97	20.37253	4714.02	3712.21	20.43429	3247.56	4624.56	20.44248	2303.19
Colposcopy vs DySIS ± colposcopy												
Colposcopy	2220.53	20.37105		2370.05	20.36343		3678.84	20.42402		4610.74	20.43648	
DySIS + colposcopy	2283.34	20.38643	4085.40	2428.21	20.38074	3360.89	3718.48	20.44412	1972.22	4622.12	20.44890	915.70

Reason for referral	Possible invasion			Possible glandular neoplasia			3 × inadequate			Whole population		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	9298.48	20.32668		5764.91	20.39141		997.66	20.45375		**2825.02**	**20.38297**	
DySIS alone	9329.51	20.32850	17,083.27	5863.56	20.39352	46,829.97	1029.99	20.45519	22,506.97	**2864.43**	**20.39128**	**4744.88**
Colposcopy vs DySIS ± colposcopy												
Colposcopy	9298.48	20.32668		5764.91	20.39141		997.66	20.45375		**2825.02**	**20.38297**	
DySIS + colposcopy	9344.17	20.33040	12,309.06	5923.06	20.39545	39,146.97	1046.11	20.45645	17,925.59	**2877.68**	**20.39902**	**3282.32**

TABLE 76 Cost of treatment biopsy with treatment probabilities from Gateshead

Reason for referral	Borderline ± HPV			Mild ± HPV			Moderate			Severe		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	2344.13	20.40786		2501.85	20.40362		3774.17	20.44148		4735.03	20.43299	
DySIS alone	2406.51	20.41317	11,740.57	2577.08	20.41010	11,609.51	3803.29	20.45098	3066.64	4737.87	20.44091	359.30
Colposcopy vs DySIS ± colposcopy												
Colposcopy	2344.13	20.40786		2501.85	20.40362		3774.17	20.44148		4735.03	20.43299	
DySIS + colposcopy	2438.18	20.41737	9882.75	2616.72	20.41509	10,017.40	3805.45	20.46014	1676.68	4725.20	20.44924	Dominant

Reason for referral	Possible invasion			Possible glandular neoplasia			3 × inadequate			Whole population		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	9253.20	20.33406		5330.31	20.34425		1052.14	20.47453		**2941.87**	**20.41249**	
DySIS alone	9286.06	20.33909	6540.84	5459.63	20.36138	7547.05	1085.49	20.47579	26,495.64	**2997.72**	**20.41916**	**8378.21**
Colposcopy vs DySIS ± colposcopy												
Colposcopy	9253.20	20.33406		5330.31	20.34425		1052.14	20.47453		**2941.87**	**20.41249**	
DySIS + colposcopy	9294.45	20.34465	3897.52	5532.60	20.37928	5773.97	1102.06	20.47682	21,790.27	**3023.33**	**20.42489**	**6568.11**

TABLE 77 Cost of treatment biopsy with cancer always identified

Reason for referral	Borderline ± HPV			Mild ± HPV			Moderate			Severe		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	2221.08	20.40555		2370.70	20.39861		3678.21	20.45413		4608.40	20.46183	
DySIS alone	2266.11	20.41222	6749.50	2413.39	20.40635	5519.82	3711.74	20.46209	4213.18	4622.87	20.46593	3531.34
Colposcopy vs DySIS ± colposcopy												
Colposcopy	2221.08	20.40555		2370.70	20.39861		3678.21	20.45413		4608.40	20.46183	
DySIS + colposcopy	2283.51	20.41836	4872.34	2428.43	20.41335	3917.57	3718.20	20.46958	2588.26	4621.17	20.47026	1515.18

Reason for referral	Possible invasion			Possible glandular neoplasia			3 × inadequate			Whole population		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	9296.81	20.34809		5764.35	20.41446		997.93	20.47607		**2842.42**	**20.41840**	
DySIS alone	9328.42	20.34930	26,099.63	5863.19	20.41604	62,582.88	1030.17	20.47712	30,825.32	**2864.43**	**20.42261**	**5229.01**
Colposcopy vs DySIS ± colposcopy												
Colposcopy	9296.81	20.34809		5764.35	20.41446		997.93	20.47607		**2849.12**	**20.42077**	
DySIS + colposcopy	9343.73	20.35052	19,305.95	5922.93	20.41742	53,574.33	1046.21	20.47801	24,889.36	**2877.66**	**20.42890**	**3507.81**

TABLE 78 Cost of treatment biopsy with all negative colposcopic or adjunct results considered clear

Reasons for referral	Borderline ± HPV			Mild ± HPV			Moderate			Severe		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	2204.69	20.36499		2339.50	20.35476		3713.20	20.42868		4643.19	20.43904	
DySIS alone	2239.91	20.38427	1826.91	2372.16	20.37600	1537.90	3732.69	20.44599	1126.154	4645.14	20.45025	174.50
Colposcopy vs DySIS ± colposcopy												
Colposcopy	2204.69	20.36499		2339.50	20.35476		3713.20	20.42868		4643.19	20.43904	
DySIS + colposcopy	2243.94	20.40209	1057.91	2373.17	20.39546	827.42	3723.36	20.46119	312.5898	4628.19	20.46130	Dominant

Reasons for referral	Possible invasion			Possible glandular neoplasia			3 × inadequate			Whole population		
	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER	Costs (£)	QALYs	ICER
Colposcopy vs DySIS alone												
Colposcopy	9308.20	20.33907		5707.29	20.40032		974.75	20.46845		**2815.76**	**20.37859**	
DySIS alone	9334.62	20.34281	7070.18	5813.66	20.40571	19,727.18	1009.26	20.47158	11,020.69	**2844.60**	**20.39707**	**1560.92**
Colposcopy vs DySIS ± colposcopy												
Colposcopy	9308.20	20.33907		5707.29	20.40032		974.75	20.46845		**2815.76**	**20.37859**	
DySIS + colposcopy	9342.94	20.34670	4556.72	5875.66	20.41036	16,765.66	1026.28	20.47444	8607.67	**2843.89**	**20.41408**	**792.58**

Appendix 8 Protocol (submitted 22 September 2011)

EVIDENCE ASSESSMENT AND ANALYSIS REPORT COMMISSIONED BY THE NIHR HTA PROGRAMME ON BEHALF OF THE NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE – PROTOCOL

1. Title of the project:

Adjunctive colposcopy technologies for examination of the uterine cervix – Dysis, LuViva Advanced Cervical Scan, Niris Imaging System and APX 100

2. Name of External Assessment Group (EAG) and project leads

CRD/CHE Technology Assessment Group (Centre for Reviews and Dissemination/Centre for Health Economics), University of York

Ros Wade Research Fellow
Centre for Reviews and Dissemination
University of York, Heslington, York
YO10 5DD
Tel: (01904) 321051
Fax: (01904) 321041
Email: ros.wade@york.ac.uk

Eldon Spackman Research Fellow Centre for Health Economics
University of York, Heslington, York
YO10 5DD
Tel: (01904) 321422
Fax: (01904) 321402
Email: eldon.spackman@york.ac.uk

3. Plain English summary

2,828 women were diagnosed with cervical cancer in the UK in 2007, making it the eleventh most common cancer in women, and accounting for around 2% of all cancers among women. Women will develop changes in the cervix many years before any progression to cancer. These pre-malignant changes are called high grade cervical intraepithelial neoplasia (CIN). Women may also get low grade CIN which is not precancerous but can cause changes at cervical screening.

Women in England between the ages of 25 and 64 are invited for regular cervical screening every three to five years under the NHS Cervical Screening Programme in order to detect abnormalities of the cervical cells. Screening is conducted using liquid based cytology (LBC) where a sample of cells is brushed from the cervix. If the test identifies abnormal cells they are described as 'dyskaryosis'. These abnormalities can range from borderline changes to severe dyskaryosis.

Women with an abnormal result from their LBC test, or repeated inadequate or borderline results, are referred for a colposcopy examination. With the introduction of HPV triage guidelines in 2011/2012, patients with borderline or mild abnormalities who also test positive for high risk human papillomavirus (HPV) should be referred for colposcopy, whilst those who test negative for high risk HPV should be returned to routine recall for cervical screening.

A colposcope (a binocular with a bright light) enables the cervix to be magnified and clearly seen; any abnormal area can be biopsied for histological analysis to diagnose CIN or invasive cervical cancer. There were 155,414 referrals for colposcopy in 2009–2010 in England; 78.6% of these were as a result of cervical screening and 17.5% were referred with symptoms, 3.9% were referred for reasons not otherwise specified. There were 453,947 appointments at colposcopy clinics in England in 2009–2010.

Colposcopy involves a significant amount of subjective assessment. The DySIS digital video colposcope (DySIS Medical), the LuViva Advanced Cervical Scan (Guided Therapeutics), the Niris Imaging System (Imalux Corporation) and the APX 100 device (Zilico Ltd) have been developed for use as an adjunct to colposcopy to improve its accuracy.

The DySIS system maps the whitening effect following application of acetic acid (aceto-whitening) to the cervix, to assist the clinician in selecting areas for biopsy and treatment. Aceto-whitening is highly correlated with the altered structure and functionality of abnormal cervical epithelium. The LuViva Advanced Cervical Scan has been designed to detect changes in cervical cells by shining light on the cervix and measuring the patterns of light reflected. The Niris Imaging System directs near infra-red light at the cervix; the intensity of light reflected back is a function of tissue structure and content, allowing differentiation of normal and abnormal tissue. The APX 100 device has been designed to measure the resistivity of cervical cells to distinguish between normal and abnormal tissue.

The main purpose of this project is to assess the benefits, adverse effects and cost-effectiveness of the DySIS digital video colposcope (DySIS Medical), the LuViva Advanced Cervical Scan (Guided Therapeutics), the Niris Imaging System (Imalux Corporation) and the APX 100 device (Zilico Ltd) used as an adjunct to colposcopy for patients referred for colposcopy through the NHS Cervical Screening Programme.

4. Decision problem

4.1. Objectives

The aim of the project is to determine the clinical and cost-effectiveness of adjunctive colposcopy technologies for examination of the uterine cervix for patients referred for colposcopy through the NHS Cervical Screening Programme; the technologies under consideration are DySIS, LuViva Advanced Cervical Scan, Niris Imaging System and APX 100. The clinical outcomes to be considered are diagnostic test accuracy outcomes (e.g. sensitivity and specificity), adverse effects and patient experience.

4.2. Interventions

DySIS (developed by DySIS Medical)

The Dynamic Spectral Imaging System (DySIS) or Dynamic Spectral Imaging colposcope, is a digital image analysing system, for detecting cancerous and precancerous cervical tissue. DySIS maps the whitening effect following application of acetic acid (aceto-whitening) on the epithelium of the cervix, to assist the clinician in selecting areas for biopsy and treatment. It does this by producing a quantitative measurement of the rate, extent, and duration of aceto-whitening, which is highly correlated with the altered structure and functionality of abnormal epithelial cells of the cervix. The dynamic map produced can be overlaid on a colour image to assist in determining the presence and grade of any neoplastic lesion. DySIS is designed to work in conjunction with a bespoke DySIS speculum.

DySIS consists of an optical head with a white light-emitting diode for uniform illumination, magnification optics coupled to a digital colour charged-coupled device camera for image capture, and a computer and control electronics unit with a thin film transistor monitor for image and data display. Linear polarisers are used in both the imaging and illumination pathways to reduce surface reflection (which might obscure the acetowhitening effect). The optical head does not come into contact with the tissue and magnifies images between 10 and 27 times.[1] It is mounted on a mechanical arm to position and stabilise it, and locked onto an extension shaft attached to the speculum, to ensure a stable field-of-view during image acquisition. For this reason, the speculum used with DySIS is different from the standard specula used in colposcopy and gynaecology practice.

DySIS has a CE mark and the cost in the UK ranges from £18,000 to £22,000. This is around twice the cost of a standard colposcope. Costs for specula are £3.50 per examination.[2]

LuViva Advanced Cervical Scan (developed by Guided Therapeutics)

LuViva distinguishes between normal and diseased tissue by detecting biochemical and morphological changes at the cellular level. This is done using optical spectroscopy; light is directed at the cervix and the resulting fluorescence and reflectance spectra are collected and analysed. LuViva consists of a base unit with a results display, and a single-use guide which is placed on the surface of the cervix.[3]

LuViva costs £11,500 and the single-use guide costs £17.25 per patient.[2] It is expected to receive a CE mark by the end of 2011 and should be available in the UK in early 2012.

Niris Imaging System (developed by Imalux Corporation)

The Niris Imaging System utilises optical coherence tomography and is designed to work in conjunction with a standard speculum. Its imaging console produces near infra-red light which is directed at the cervix. Optical light is backscattered from the tissue, collected by a detachable fibre-optic probe, and combined with an internal reference signal, to produce a high spatial resolution two-dimensional image of the superficial tissue microstructure. The intensity of light reflected back is a function of tissue structure and content, allowing differentiation of normal and abnormal tissue.

The system includes built-in *protocols* for image comparison with automated calculations for intensity and distance, with raw data also reported. Images can be monitored over time, allowing side-by-side comparisons of a patient's results from two time periods (images are exportable to an ancillary monitor).

Niris probes have a limited useful life of around 200 patient procedures but can be processed for re-use. A probe sheath is used to provide physical stability and help prevent cross-contamination.

The Niris Imaging System costs $49,500 (around £31,000) plus taxes and shipping. The probe costs $2,700 (around £1700) and a disposable sheath costs $30 (around £19).[2] The device is expected to receive a CE mark and become available in the UK in October, 2011.

APX 100 (developed by Zilico Ltd)

The APX 100 handset device, designed to work in conjunction with a standard speculum, measures the resistivity (via electrical impedance spectroscopy) of cervical epithelial cells to distinguish between normal and abnormal tissue. The degree of impedance seen is related to tissue structure; normal, pre-cancerous, and cancerous cervical tissue has different structures.

The handset takes readings by direct contact (using a disposable sleeve) with the cervix. A base station charges the handset and collects data (which can then be transferred to a computer). Results from each reading site are compared with reference spectra, derived from models of different cervical tissues, to calculate the probability of high grade neoplasia. The exact location for biopsy is determined by using the device in a second, single-point, operating mode. In this mode the device will immediately

indicate when it has been placed onto high-grade CIN and a biopsy can be taken or the patient offered immediate treatment.[2]

Zilico aim to use data from a recent trial to obtain a CE mark and expects to launch the APX 100 by the end of 2011. The device costs £2000 and single-use, disposable sleeves cost £20.[2]

4.3. Comparator technologies

Standard colposcopy, with directed biopsy/treatment when necessary, is the current usual management for women referred with abnormal cytology results. A colposcope is a binocular field microscope used to examine the cervix following sequential application of saline, 3–5% acetic acid, and sometimes Lugol's iodine to identify any epithelial changes or capillary vessel patterns suggestive of disease. Histological examination of any biopsied tissue, which is the gold standard for diagnosis of cervical intraepithelial neoplasia (CIN) or invasive cervical cancer, is then undertaken. The initial outcome of colposcopy is classified as being adequate, where the whole of the transformation zone (and any lesions) can be viewed, or inadequate, where full visualisation is not possible, and where further investigation may be required. The skills of the colposcopist relate to training, experience, and the volume of patients seen. Colposcopy involves a significant amount of subjective assessment – results from the same patient may vary when assessed by different colposcopists.[4] Details of referral cytology results, other clinical information, the type of management available, and the number of biopsies taken are also relevant when interpreting the results of colposcopy.

A meta-analysis of nine studies published in 1998 estimated the sensitivity and specificity of colposcopy as being 96% and 48% respectively in detecting CIN2+, and 85% and 69% respectively when differentiating between normal/low-grade CIN and high-grade CIN/cancer,[5] although most studies appeared to be subject to bias.[6] More recently, better quality studies have reported a sensitivity of around 57% for detecting CIN2+[7] and around 56% for detecting CIN3+.[8]

A standard colposcope costs between £6000–£12,000 and a disposable speculum costs £2.[2]

4.4. Population and relevant subgroups

2,828 women were diagnosed with cervical cancer in the UK in 2007, making it the eleventh most common cancer in women, and accounting for around 2% of all cancers among women. Cervical cancer is the most common cancer in females aged under 35; 702 women aged under 35 were diagnosed with cervical cancer in the UK in 2007.[9] Women will develop changes in the cervix many years before any progression to cancer. These pre-malignant changes are high grade CIN. Women may also get low grade CIN, which is not precancerous, but can cause changes at cervical screening.

Infection with certain genotypes of human papillomavirus (HPV), in particular HPV 16 and HPV 18, have been shown to be associated with the development of cervical cancer and CIN; almost all cervical cancers contain high risk HPV DNA. However, most HPV infections will not progress to CIN; the cell changes associated with HPV will regress to normal. Certain risk factors are associated with the progression of HPV infection to CIN, including the HPV genotype, early age at first intercourse, long duration of the most recent sexual relationship and cigarette smoking.[9]

Women in England between the ages of 25 and 64 are invited for regular cervical screening every three years (if aged between 25 and 49 years) or every five years (if aged between 50 and 64 years) under the NHS Cervical Screening Programme.[10] Most screening is conducted using liquid based cytology; a sample of exfoliated cells is brushed from the transformation zone of the cervix for assessment in a pathology laboratory. Cytological assessment is performed to detect nuclear abnormalities, which are described as dyskaryotic. The degree of dyskaryosis can range from mild to severe, or borderline changes may be seen.

Just under 3.3 million women aged between 25 and 64 attended for cervical screening in 2009–2010; the percentage of eligible women who were recorded as screened at least once in the previous 5 years was

78.9%. Approximately 3.7 million samples were examined in 2009–2010, of which 3.4 million (92.9%) were submitted by GPs and NHS community clinics (suggesting that they were part of the NHS Cervical Screening Programme).[11]

2.9% of tests did not have a result, owing to an inadequate sample. This figure has dropped significantly (from approximately 9%) since the introduction of liquid based cytology. Women with an inadequate sample should be recalled for a repeat test; if women have three consecutive inadequate results, they should be referred for colposcopy.

The table below presents a summary of cytology test results and management options for patients with an adequate test result, submitted by GPs and NHS community clinics. However, the management of patients will change with the introduction of new guidelines for HPV triage, due to be implemented in 2011/2012.[12] These are discussed further below.

Result	Definition	Action*	Proportion (2009–2010)**
Negative	No nuclear abnormalities	Place on routine recall	93.2%
Borderline changes	Nuclear changes that are not normal are present. Unsure whether the changes are dyskaryosis	Repeat the test in 6 months. Most will have reverted to normal. After 3 consecutive normal results, return to normal recall. If abnormality persists (3 times) or worsens, refer for colposcopy. If in a ten year period there are 3 borderline or more severe results, refer for colposcopy	3.8%
Mild dyskaryosis	Nuclear abnormalities that are indicative of low grade CIN	Refer for colposcopy (although it remains acceptable to repeat the test in 6 months instead – most will have reverted to normal after 6 months). Refer to colposcopy if changes persist on 2 occasions	1.9%
Moderate dyskaryosis	Nuclear abnormalities reflecting probable CIN2	Refer for colposcopy	0.5%
Severe dyskaryosis	Nuclear abnormalities reflecting probable CIN3	Refer for colposcopy	0.6%

*Recommendations taken from Colposcopy and Programme Management[10]

**Figures taken from Cervical Screening Programme England 2009–10[11]

There were 155,414 referrals for colposcopy in 2009–2010; 78.6% of these were as a result of screening and 17.5% were clinically indicated, 3.9% were referred for reasons not otherwise specified. Of women referred for colposcopy via the NHS Cervical Screening Programme, 58.8% were referred for borderline changes or mild dyskaryosis; 12.3% were referred for moderate dyskaryosis and 15.8% were referred for severe dyskaryosis or worse. There were a total of 453,947 appointments at colposcopy clinics in 2009–2010; 41.9% of which were new appointments, 7.9% were return appointments for treatment and 50.2% were follow-up appointments.[11]

27% of appointments were not attended; 2.6% were cancelled by the patient on the day, 10.2% were cancelled in advance, 10.5% were not attended with no advance warning and 3.7% were cancelled by the clinic.[11]

Overall, 63.5% of women attending for colposcopy had some treatment or procedure at their first attendance, the most common treatment or procedure at first attendance was diagnostic biopsy, carried out at 45.5% of first attendances. The most common procedure at first attendance for women referred for low-grade abnormalities was diagnostic biopsy, whilst the most common procedure at first attendance for women referred for high-grade abnormalities was excision. The majority of those women presenting with

high-grade abnormalities who had either no treatment, or only diagnostic biopsy at first attendance, are likely to have received therapeutic treatment at a subsequent attendance.[11]

New guidelines due to be implemented in 2011/2012 state that samples from women with low grade abnormalities (borderline changes or mild dyskaryosis on cytology) should be tested for high risk HPV for triage for referral for colposcopy.[12] The test is performed on the liquid based cytology sample already obtained as part of the NHS Cervical Screening Programme. Women who test positive for high risk HPV should be referred for colposcopy, whilst women who test negative for high risk HPV should be returned to routine recall.

The patient group of interest for this assessment is women referred for colposcopy through the NHS Cervical Screening Programme. Women referred because of symptoms indicative of cervical cancer (e.g. post-coital bleeding or appearance suggestive of cancer) are not of relevance to this assessment. Where possible, separate analyses will be performed according to cytology findings. These technologies may be more appropriate for patients with borderline changes, or mild or moderate dyskaryosis, since more severe abnormalities are easier to detect with standard colposcopy.

4.5. Place of the intervention in the care pathway

Women with an abnormal cytology result, or repeated inadequate or borderline cytology results, are referred for colposcopy. According to the new HPV triage guidelines due to be implemented in 2011/2012 women with a borderline or mild dyskaryosis result should only be referred for colposcopy if they also test positive for high risk HPV. Colposcopy is used to visualise the cervix; if any abnormal area is identified a biopsy is taken and sent for histological analysis. Colposcopy clinics are usually located within gynaecology or genitourinary medicine departments of general hospitals, although some colposcopy may take place in primary care in the future.

DySIS, LuViva Advanced Cervical Scan, Niris Imaging System and APX 100 are used as an adjunct to standard colposcopy.

5. Report methods for assessing the outcomes arising from the use of the interventions

A systematic review of the evidence on the adjunctive colposcopy technologies; DySIS, LuViva Advanced Cervical Scan, Niris Imaging System and APX 100, compared with standard colposcopy will be conducted. The review will be conducted following the general principles recommended in CRD's guidance[13] and the PRISMA statement.[14]

Inclusion and exclusion criteria

The titles and abstracts of records identified by the search strategy will be examined for relevance by two reviewers independently. Full papers of any potentially relevant records will be obtained where possible and screened by two reviewers independently. The relevance of each study to the review and the decision to include/exclude studies will be made according to the inclusion criteria detailed below. Any disagreements will be resolved by consensus.

Participants

Studies of women referred for colposcopy because of an abnormal cytology result will be eligible for inclusion. Studies that also include women referred for colposcopy because of symptoms indicative of cervical cancer (e.g. post-coital bleeding) or women referred for colposcopy for follow-up of CIN will be eligible for inclusion. Studies that only include women referred for colposcopy because of symptoms indicative of cervical cancer or for follow-up of CIN will be excluded.

Interventions/comparators

Studies comparing DySIS (DySIS Medical), LuViva Advanced Cervical Scan (Guided Therapeutics), Niris Imaging System (Imalux Corporation) or APX 100 (Zilico Ltd) with standard colposcopy will be eligible for inclusion. Comparisons of any of these interventions plus colposcopy compared with colposcopy alone are also eligible for inclusion.

Outcomes

The clinical outcomes of interest are diagnostic test accuracy outcomes (e.g. sensitivity and specificity), adverse effects and patient experience. In the unlikely event that other patient health outcomes are reported (e.g. morbidity and mortality from cancer or treatment), these will also be included in the assessment.

Study designs

Comparative studies will be eligible for inclusion, including diagnostic test accuracy studies and controlled trials.

Literature searching

Searches of the literature will be conducted in order to identify studies and other relevant literature in the following key areas.

Extensive searches of the literature relating to the specified technologies (DySIS, LuViva Advanced Cervical Scan, Niris Imaging System and APX 100).

Additional supplementary searches will be carried out as necessary. Searches for studies for cost and quality of life data will also be included, as determined by the model.

Electronic sources will be searched for primary studies. These sources will include MEDLINE, EMBASE, CINAHL, HMIC, ISI Science Citation Index and the Cochrane Library (including the Cochrane Database of Systematic Reviews (CDSR), the Database of Abstracts of Reviews of Effects (DARE), the Health Technology Assessment (HTA) Database, the NHS Economic Evaluation Database (NHS EED) and CENTRAL).

Ongoing and unpublished studies will be searched for using appropriate sources, including controlled trials.com and other web-based resources.

Where necessary, relevant reviews and guidelines will be identified through searching additional resources, including Clinical Evidence, National Institute for Health and Clinical Excellence (NICE) website, NHS Evidence – National Library of Guidelines, SIGN Guidelines, the Guidelines International Network website.

The searches will combine terms for cervix with terms for the technologies being assessed. For the technologies we will use both generic terms (e.g. colposcopy) and terms for specific products (e.g. DySIS).

Search terms will be identified by scanning key papers identified during the review, through discussion with the review team and clinical experts, and by using database thesauri. Reference lists of included papers will be assessed and the abstracts of relevant conferences will be searched, where possible, for additional relevant studies. Searches will be limited by date, according to the date of development of the new technologies. No limits relating to language or study design will be applied to the searches.

Data extraction strategy

Data relating to both study characteristics and results will be extracted by one reviewer using a standardised data extraction form and independently checked by another. Discrepancies will be resolved by discussion, with involvement of a third reviewer when necessary. If time constraints allow, attempts will be made to contact authors for any missing data. Data from multiple publications of the same study will be extracted as a single study.

Quality assessment strategy

The quality of the included studies will be assessed using standard checklists[13] adapted as necessary to incorporate topic-specific quality issues. The methodological quality of diagnostic test accuracy studies will be assessed using the QUADAS tool.[15]

The assessment will be performed by one reviewer, and independently checked by another. Discrepancies will be resolved by discussion, with involvement of a third reviewer when necessary.

The results of the quality assessment will be tabulated and the more important methodological problems will be discussed in terms of their potential effect on the results of the included studies. In addition, if data allow, quality components will be used in sensitivity analyses.

Methods of analysis/synthesis

In the initial analysis/synthesis of data, the results of data extraction will be presented in structured tables and as a narrative summary, grouped by participant and intervention characteristics. Where possible, data will be presented separately for the specific subgroups of interest (participants with borderline changes, or mild or moderate dyskaryosis), and/or other relevant participant characteristics (e.g. women known to be more challenging in colposcopy such as pregnant women or post-menopausal women). Where sufficient clinically and statistically homogenous data are available, data will be pooled using appropriate meta-analytic techniques. Clinical, methodological and statistical heterogeneity will be investigated.

6. Report methods for synthesising evidence of cost-effectiveness

6.1. Identifying and systematically reviewing published cost-effectiveness studies

Searches for economic evaluations will be undertaken in the databases listed in section 5. These sources will be used to identify any studies of the cost-effectiveness of DySIS (DySIS Medical), LuViva Advanced Cervical Scan (Guided Technologies), Niris Imaging System (Imalux Corporation) or APX 100 (Zilico Ltd), against colposcopy or each other. A broad range of study designs will be considered in the assessment of cost-effectiveness including economic evaluations conducted alongside randomised or non randomised trials, modelling studies and analyses of administrative data sets. The review will focus on full economic evaluations that compare two or more options and consider both costs and consequences (including cost-effectiveness and cost–benefit analyses). To gain an insight into the modelling methods we will also consider cost-effectiveness studies examining screening for cervical cancer. These studies will not be subject to a formal assessment but will be used, if necessary, to assist in the overall development of a new analytical model with the aim of identifying important structural assumptions, parameter estimates and highlighting key areas of uncertainty.

The quality of the studies identified will be assessed according to the criteria for economic evaluation detailed in the methodological guidance developed by NICE.[16] This information will be tabulated and summarised within the report. In particular, information will be extracted on the comparators, study population, main analytic approaches, primary outcome measures, quality of life estimates, costs, estimates of incremental cost-effectiveness and approaches to quantifying decision uncertainty.

In a brief review of the literature no cost-effectiveness modelling has been undertaken on diagnostics that identify CIN. Multiple modelling efforts have been undertaken to determine the cost-effectiveness of screening or HPV vaccination in the UK.[17–21] Since both screening and vaccination occur upstream from diagnosis of CIN much of the previously published model structure and many of the inputs may be useful in our current modelling efforts. It is possible that a previously developed model can be adapted for the current study. The usefulness of previous models will be judged based on:

1. appropriateness for the decision problem being considered in this assessment
2. relevance of outputs for decision making (i.e. need to be able to estimate long-term NHS costs and QALYs)
3. ability to reproduce the model or to collaborate with model developers.

6.2. Evaluation of costs, quality of life and cost-effectiveness

A decision model will be developed (as above, probably based on an existing model) to estimate the cost-effectiveness of DySIS, LuViva Advanced Cervical Scan, Niris Imaging System, APX 100 and standard colposcopy for patients referred for colposcopy through the NHS Cervical Screening Programme. The perspective will be that of the NHS and Personal Social Services (PSS), health outcomes will be expressed in terms of quality-adjusted life years (QALYs) and both costs and health outcomes will be discounted at a rate of 3.5% per annum in accordance with methodological guidance developed by NICE.[16]

DySIS, LuViva Advanced Cervical Scan, Niris Imaging System and APX 100 aim to improve the accuracy of colposcopy, resulting in the improved identification of cancerous and precancerous cervical tissue.

The model will attempt to establish a link between diagnostic test accuracy and final health outcomes. This will involve consideration of how each technology impacts on the identification of cancerous and precancerous cervical tissue and linking this identification to treatment or monitoring options and their effect on disease progression. The model will also include the impact of the technologies on unnecessary biopsies and excisions which may increase the risk of preterm labour, pain, bleeding and discharge.

Resource utilisation and costs will be estimated for DySIS, LuViva Advanced Cervical Scan, Niris Imaging System, APX 100 and standard colposcopy. These costs will include the costs of the diagnostic tests which will be dependent on capital costs of the equipment, consumables, annual maintenance costs and staff costs (including any training costs) as well as the costs of procedures occurring as a result of the tests, for example biopsies and excisions. It will be important to consider patient throughput and its impact on the cost per patient for the diagnostic tests. The diagnostic test's accuracy will also influence throughput as a large number of false positives will unnecessarily increase follow-up. Data for the cost analysis will be drawn from routine NHS sources[22] and discussions with individual hospitals and manufacturers of the technologies considered.

Further details of the model structure and data to be used to populate it will have to await the findings of the systematic searches of the literature. However, it is expected that particular consideration will be given to the following key variables:

- sensitivity and specificity of the different technologies
- resource utilisation and costs for the different technologies
- links to long-term outcomes
- adherence to colposcopy and follow-up
- 'see and treat' rates,

The specific objectives of the cost-effectiveness analysis are:

- To use an economic model to estimate the cost-effectiveness of DySIS, LuViva Advanced Cervical Scan, Niris Imaging System, APX 100 and standard colposcopy for diagnosis of patients referred for colposcopy through the NHS Cervical Screening Programme. Health outcomes will be in terms of QALYs and the perspective taken will be the NHS and PSS.
- To populate the model using the most appropriate data identified from published literature and other sources.
- To characterise the uncertainty in the data used to populate the model and present the resulting uncertainty in the results to decision makers. A probabilistic model will be developed which requires that, where possible, uncertainty in inputs are reflected through the use of appropriate distributions.

Using Monte Carlo simulation, this parameter uncertainty will be translated into uncertainty in the overall results. This will be presented graphically using cost-effectiveness acceptability curves which show the probability that an intervention is cost-effective for a given cost-effectiveness threshold (cost per QALY).

- To use sensitivity analyses to examine alternative assumptions in the data and to see how sensitive the results are to different assumptions.

7. Handling information from the companies

Any 'commercial in confidence' data provided by the manufacturers (DySIS Medical, Guided Therapeutics, Imalux Corporation and Zilico Ltd) and specified as such will be highlighted in blue and underlined in the assessment report. Any 'academic in confidence' data provided by the manufacturers will be highlighted in yellow and underlined in the assessment report.

8. Competing interests of authors

None of the authors has any conflicts of interest.

9. Timetable/milestones

Milestone	Date to be completed
Submission of final protocol	19/09/11
Submission of progress report	14/11/11
Submission of draft Diagnostic Assessment Report	11/01/12
Submission of Diagnostic Assessment Report	08/02/12

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